Ricardo A. Munoz
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Carol G. Vetterly
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Editors

Critical Care of Children with Heart Disease

Basic Medical and Surgical Concepts

Second Edition

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To my wife Lina, my sons Rafael and Ricardo (Ricky) and my grandsons Daniel and Julian.

Ricardo A. Munoz

To Laurinda Odete, my dear mother. And to my lovely family.

Eduardo M. da Cruz

To my husband, daughter and mother, for their endless support and patience.

Carol G. Vetterly

The Editors would also like to dedicate this book to all those caregivers who commit to care for children and young adults with critical congenital and acquired heart disease.

We would like to express our sincere gratitude and appreciation for our illustrators, Steven P. Goldberg and Angelo Rutty, who created the exceptional surgical figures throughout the text. Their outstanding talents and contributions helped to make the book a valuable educational tool.

Ricardo A. Munoz
Victor O. Morell
Carol G. Vetterly
Eduardo M. da Cruz

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Chapter 1
The Transition from Fetal to Postnatal Life: Normal and Abnormal Hearts

Bettina F. Cuneo

Abstract At no other time in life does the human cardiovascular system undergo changes as profound as those changes that occur at birth. The circulation switches from one that is in parallel to one that is in series, systemic afterload increases suddenly, and pulmonary afterload decreases. The fetal shunts – the patent ductus arteriosus (PDA) and the patent foramen ovale (PFO) – close. The infant with a cardiovascular anomaly dependent on the parallel circulation and the fetal shunts will not survive the transition to stable postnatal life without intervention. This chapter will first review the prenatal hemodynamics and flow patterns in the normal and abnormal fetal heart. Second, it will describe the circulatory changes accompanying birth and explain the consequences of the extrauterine life to the neonate with cardiac anomalies.

1.1 Introduction

With recent advances in fetal imaging techniques, including ultrasound and MRI, it is now possible to examine the circulation in the developing human fetus. Doppler interrogation of flow patterns as early as 8–9 weeks provides clues to the developing cardiovascular system including maturation of diastolic function, the important role of the atria in fetal cardiac output, effects of structural noncardiac or chromosomal anomalies, and how gestational age affects the placental and venous flows [1–8]. Recognizing how cardiovascular development differs in the abnormal heart can advance the understanding of the natural history of congenital heart disease and may, in the future, provide an opportunity for intervention, even in the first trimester.

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1.2 Circulation in the Fetus with a Normal Heart

1.2.1 Cardiac Output

The distribution of the normal fetal cardiac output is seen in Fig. 1.1. Because of the two fetal shunts (the PFO and the ductus arteriosus or DA), the fetal circulation operates in

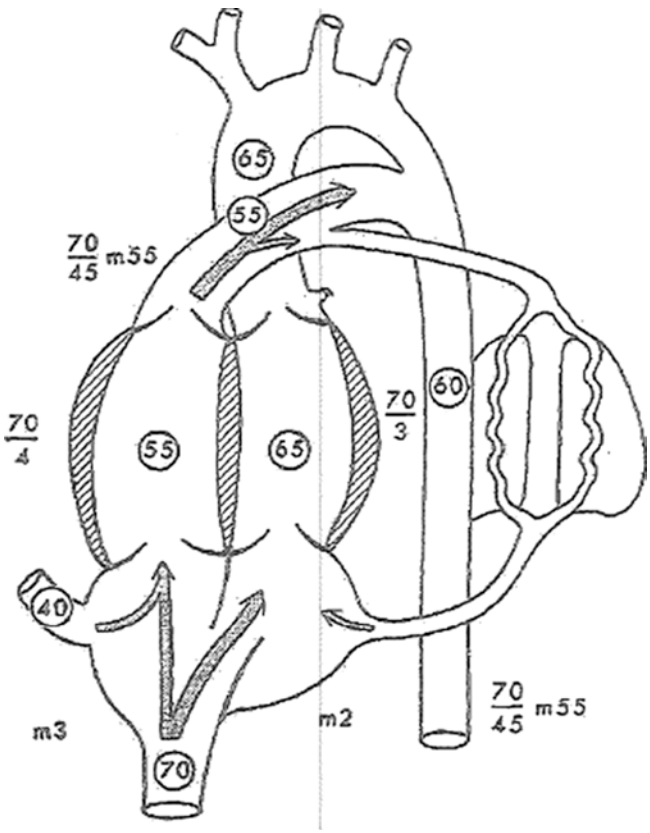

Fig. 1.1 Oxygen saturation, mean, systolic and diastolic pressure patterns in the normal human fetal heart

R. A. Munoz et al. (eds.), *Critical Care of Children with Heart Disease*, https://doi.org/10.1007/978-3-030-21870-6_1

parallel. This means that the combined cardiac output does not change if one of the ventricles is absent or dysfunctional. Put differently, the cardiac output of each ventricle is not equal, but "combined." The percentage that each ventricle contributes to the combined cardiac output is governed by preload, contractility heart rate, and afterload. The first three components of cardiac output are similar between the right ventricle (RV) and the left ventricle (LV), but afterload differs considerably. The RV faces the lungs and the placenta. The lungs have high resistance because they are unexpanded and fluid-filled and the placenta has a very low resistance. Therefore, in early gestation, only about 4% of the combined cardiac output enters the lungs. Later in gestation, this number doubles, related to decreased pulmonary vascular impedance and increased cross-sectional area of the pulmonary arterioles [9, 10]. In comparison to the limited flow to the pulmonary circulation, ~ 42% of the combined ventricular output passes from the RV to the descending aorta thru the PDA and then to the low-resistance highly compliant placenta through the umbilical artery (Fig. 1.2a). Unlike the low resistance faced by the RV, the LV faces increased afterload because it ejects into the coronary arteries, the upper body, and the fetal brain, which have high resistance and poor compliance.

As gestation progresses, RV and LV stroke volume (amount of blood ejected per heart beat) and the combined cardiac output in the human fetus increase from about 40 ml/minute at 15 weeks [11] to 1470–1900 ml/minute near term [11, 12]. For reasons listed above, the RV stroke volume exceeds LV stroke volume by about 28% throughout gestation [13].

1.2.2 Blood Flow and Oxygen Delivery in the Normal Fetus

The circulation in the normal fetus is shown in Fig. 1.2. Blood is oxygenated in the placenta and returns to the fetus through the umbilical vein, which divides into the ductus venosus (DV) and a right umbilical vein (Fig. 1.2b). Approximately 20–30% of umbilical venous blood enters the DV, which then drains into the proximal inferior vena cava (IVC). Blood from the DV and left hepatic vein enters the left side of the IVC. The right umbilical vein, carrying about 70% of the blood volume from the placenta, joins the portal vein, which supplies the right lobe of the liver [14]. Umbilical venous blood is well saturated (PO2 = 30–35 mmHg, O2 saturation 80%). Blood flow volume increases linearly with fetal weigh [15, 16]. In the first trimester, umbilical venous flow is pulsatile, but by 13 weeks it is continuous [17].

In the proximal IVC, highly oxygenated DV blood is diverted to the left atrium (LA) by the crista dividens. Less oxygenated blood from the IVC blood passes into the right atrium (RA) [18, 19]. In the low-risk fetus, flow in the DV remains relatively constant during gestation, but in response to hypoxia, the IVC dilates and carries a greater proportion of flow at an increased velocity [20–23] (Fig. 1.3a). Normally flow in the DV is antegrade during ventricular and atrial systole, but in the fetus with impending heart failure, there is reversal of the a-wave during atrial systole (Fig. 1.3b, c).

As seen in Fig. 1.2, oxygenated blood from the DV mixes with the pulmonary venous return in the LA and then passes through the LV to the aorta. This provides highly oxygenated blood (PO2 25 mmHg, 65% saturation) to the coronary

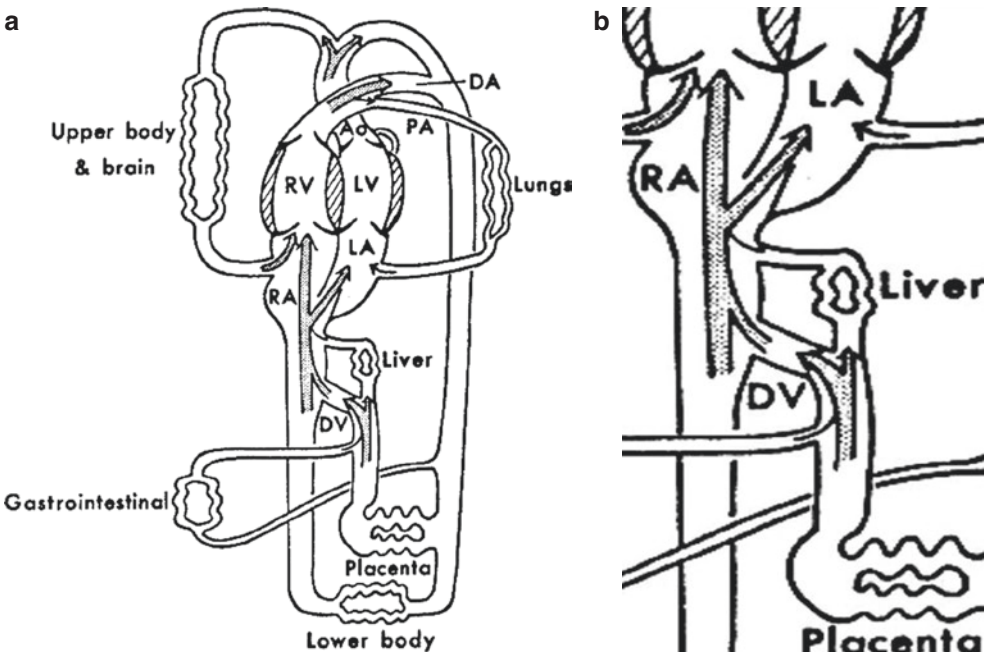

Fig. 1.2 Blood flow in the normal human fetus. (**a**) The entire circulatory system. (**b**) Close-up of the fetal venous systems

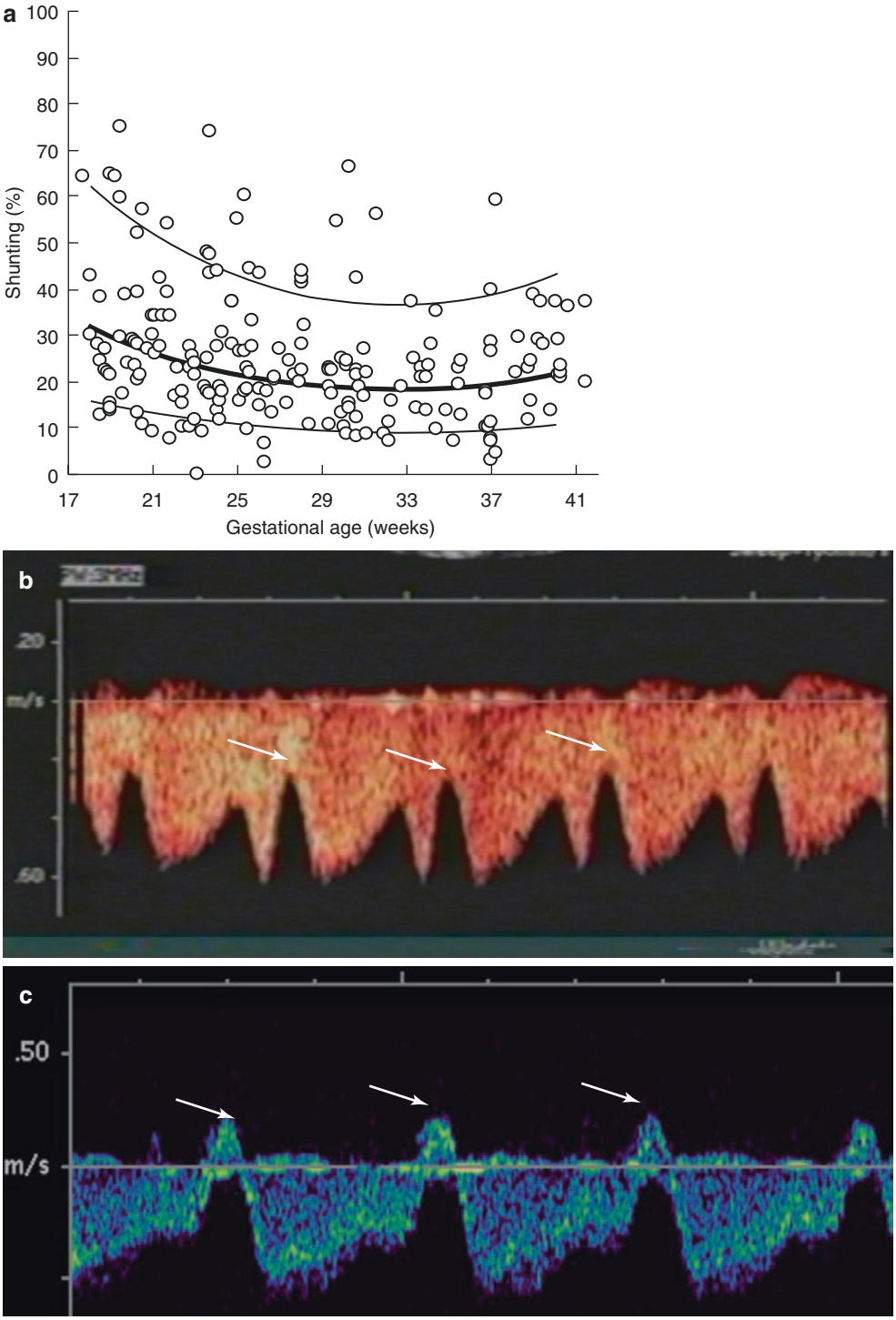

Fig. 1.3 The ductus venosus (DV). (**a**) Blood flow vs. gestational age in the DV across gestation. (**b**) Normal blood flow in the DV showing absent reverse flow during atrial systole (arrows). (**c**) Abnormal blood flow in a fetus with hydrops (not shown) with reverse flow during atrial systole (arrows), indicating abnormal ventricular compliance. (Kiserud et al. [23])

arteries and the fetal brain. Less oxygenated blood (PO2 17–20 mmHg, 55% saturation) from the superior and inferior vena cava passes through the right heart. About 4–5% of the blood volume enters the lungs from the RV, but the majority is shunted across the DA to reach the fetal body and placenta. Because the resistance is lower in the placenta than in the fetal body, the placenta receives 40–50% of the fetal combined ventricular output.

1.3 The Fetal Myocardium and Cardiac Function

Contraction of the fetal heart relies on the interaction between the contractile units, composed of the sarcomere and the contractile proteins myosin, troponin, and tropomyosin, the sarcoplasmic reticulum, and the β-adrenergic

stimulation. Contractility depends on multiple factors including the number of sarcomeres, the contractile protein isoforms, the number of calcium-binding sites in the sarcoplasmic reticulum (which regulates calcium uptake and release), and the density of β-adrenergic receptors and sympathetic nerve endings.

The fetal heart has key differences from the adult heart. First, the fetal heart has fewer contractile units, sarcomeres, and β-adrenergic receptors and a higher percentage (60%) of noncontractile elements [24, 25]. Second, calcium uptake from the sarcoplasmic reticulum and calcium release from troponin occur much more slowly than in the adult heart due to a poorly developed T tubular system [26]. Other factors affecting cardiac output are not related to the immature myocardium per se but the noncompliant lungs and rigid chest wall which mechanically limit diastolic filling [27].

Because of the limitations of the immature myocardium and the constraints of the fetal chest, at the same muscle length, the fetal myocardium develops less active tension and can generate less force [25]. Clinically, this means the fetal myocardium has a limited ability to increase stroke volume in response to a need for increased cardiac output. In fact, the primary way the fetus can increase cardiac output is by increasing heart rate. The fetal heart operates high on the Starling curve, which means it responds poorly to increases in afterload and preload [28]. Perhaps due to histological differences, the RV is less able to respond to increases in end-diastolic volume (preload) compared to the LV [29, 30]. This may be one of the reasons that hydrops develops so quickly in the fetal circulation with extra-cardiac vascular malformations that increase the preload to the right heart.

As gestation progresses, contractility of the fetal heart increases due to several factors. First, the density of myocardial β-adrenergic receptors increases. Second, the sarcoplasmic reticulum becomes more efficient in distributing calcium to troponin-binding sites [26]. Third, the concentration of adult myosin isoforms and myofibrillar numbers increases, resulting in an increased velocity of sarcomere shortening [31, 32]. Lastly, thyroid hormone, which mediates fetal cardiac contractility and regulates the growth of cardiomyocytes, increases linearly with gestational age [33].

1.4 Circulation in the Fetus with an Abnormal Heart

1.4.1 Basic Principles

Structural and functional cardiac anomalies result in abnormal flow patterns within the fetal circulation [34]. The PFO and DA allow redistribution of blood flow from the abnormal ventricle or great vessel to the unaffected cardiac chamber. Because blood flow is redistributed in fetuses with cardiac anomalies, oxygen delivery is altered. These physiological changes have both in utero and postnatal consequences, including a high proportion of congenital heart disease (CHD) fetuses with growth restriction [35]. However, except for myocardial dysfunction, prolonged arrhythmias, or valvar insufficiency, most CHD situations are well tolerated in utero because of the unique parallel fetal circulation, which allows redistribution of cardiac output.

1.4.2 The Fetus with Obstructed Systemic Blood Flow

Mild LV outflow obstructive defects such as aortic stenosis or coarctation of the aorta result in little or no significant change in cardiac output or oxygen delivery (Fig. 1.4). On the other hand, hypoplastic left heart syndrome (HLHS) with mitral and aortic atresia (Fig. 1.5a) can cause profound alterations in blood flow and oxygen delivery, fetal growth, and brain maturation [36]. Critical aortic stenosis has features of HLHS, but changes in oxygen delivery and flow patterns are not as profound (Fig. 1.4b)

The hemodynamic response to aortic obstruction depends on the severity of the obstruction, when in gestation obstruction occurs, and how quickly the obstruction develops. As previously discussed, the LV does not respond well to sudden increases in afterload, but if the obstruction is mild or develops gradually, the LV can maintain cardiac output by hypertrophy (Fig. 1.6a). However, increased LV mass occurs at the expense of decreased ventricular compliance and increased end-diastolic filling pressure which place the fetus at risk for heart failure. Alternately, if LV obstruction progresses rapidly, LV stroke volume decreases, and the heart dilates and becomes severely dysfunctional. Endocardial fibroelastosis, seen as echo-bright tissue, is often seen in this condition (Fig. 1.6b). The consequence of severe LV dysfunction is absent antegrade flow to the fetal brain. At this point, flow to the fetal brain and the coronary arteries is supplied by the lower oxygenated blood from the DA, and retrograde flow is seen in the aortic arch (Fig. 1.6c). Since the O_2 concentration of blood supplied to the fetal brain from the RV (and the DA) is lower than the O_2 concentration from the LV (and aorta), the fetal brain receives less O_2. To compensate for the lower oxygen delivery to the cerebral circulation, autoregulatory mechanisms in the fetus increase flow in the DV, reduce cerebral vascular resistance, and increase umbilical artery (UA) resistance to improve cerebral perfusion [37–42]. This results in increased diastolic flow velocity and a lower pulsatility index in the middle cerebral artery (MCA)

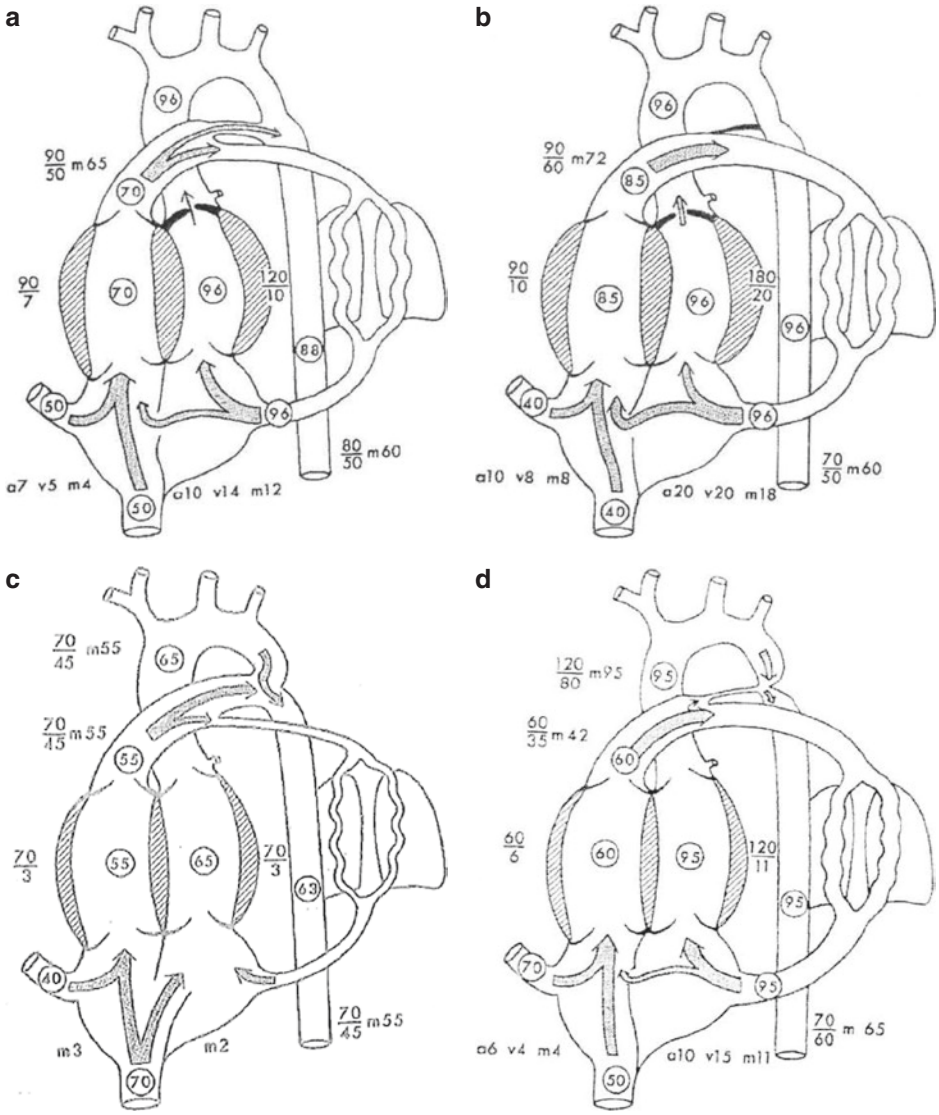

Fig. 1.4 Pre- and postnatal circulation in the fetus (**a**) and neonate with coarctation of the aorta (**b**). Note in (**b**), the increase in LA pressure and end-diastolic LV pressure in the neonate as a result of increased pulmonary venous return and pulmonary venous congestion because of decreased LV compliance, increased LV systolic because of increased systemic vascular resistance, and higher PO2 in blood flow entering the lungs. Pre- and postnatal circulation of the fetus (**c**) and neonate (**d**) with coarctation of the aorta. As with aortic stenosis, with coarctation, the LV pressure increases after birth, but the pressure in the DA does not increase. This results in a pressure difference between the right arm and either leg as the ductus is closing. If the ductus remains open, there is a right-to-left shunt across the DA resulting in low O_2 saturations in the infant's legs compared to his right arm (unless there is an anomalous origin of the right subclavian artery distal to the coarctation. This physiology is the rationale for four extremity pulse oximeter screening to detect congenital heart defects with ductal-dependent blood flow

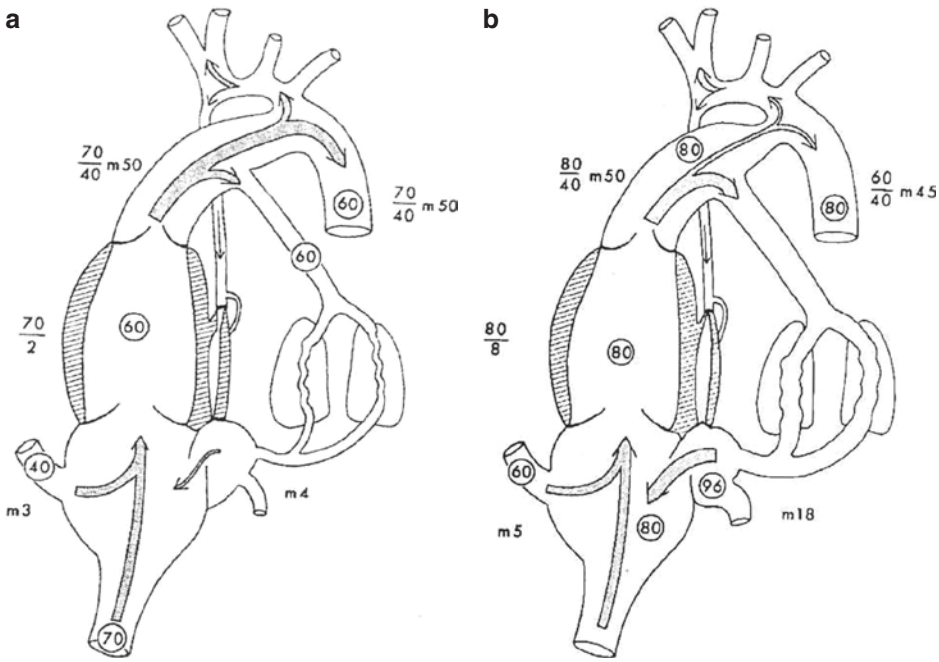

Fig. 1.5 Pre- and postnatal circulation of the fetus (**a**) and newborn (**b**) with hypoplastic left heart syndrome (HLHS)

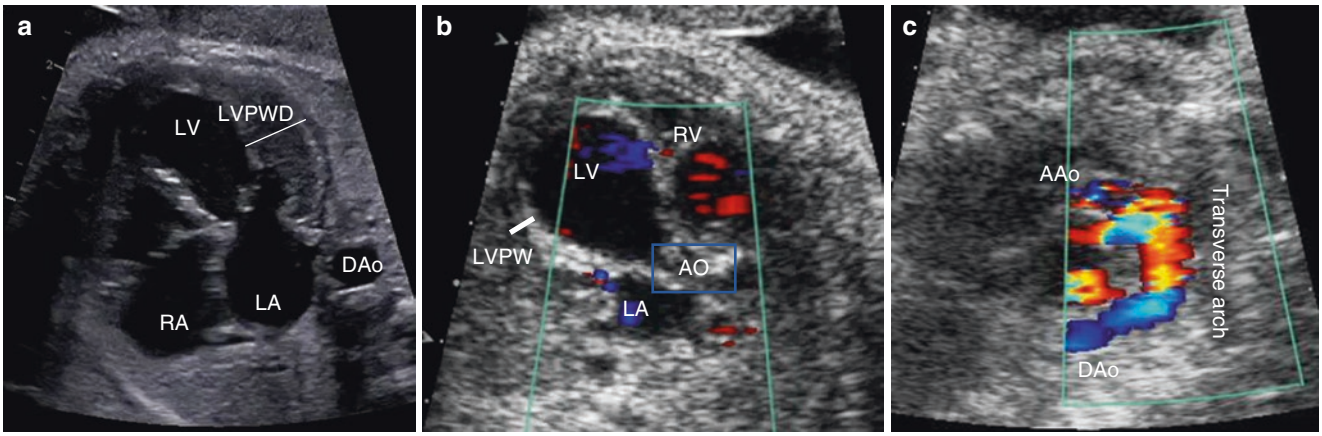

Fig. 1.6 Fetal echocardiography images of critical aortic stenosis. (**a**) This fetus has developed severe ventricular hypertrophy due to slow progression of aortic stenosis. (**b**) Another fetus with aortic stenosis that either was more severe or developed in earlier gestation resulting in endocardial fibroelastosis and a hypoplastic left ventricle. (**c**) Retrograde flow in the transverse aortic arch. In this fetus, there is inadequate antegrade flow through the aorta due to severely depressed LV function, so the cerebral circulation is supplied retrograde from the PDA. This is a hallmark of a ductal-dependent systemic outflow lesion

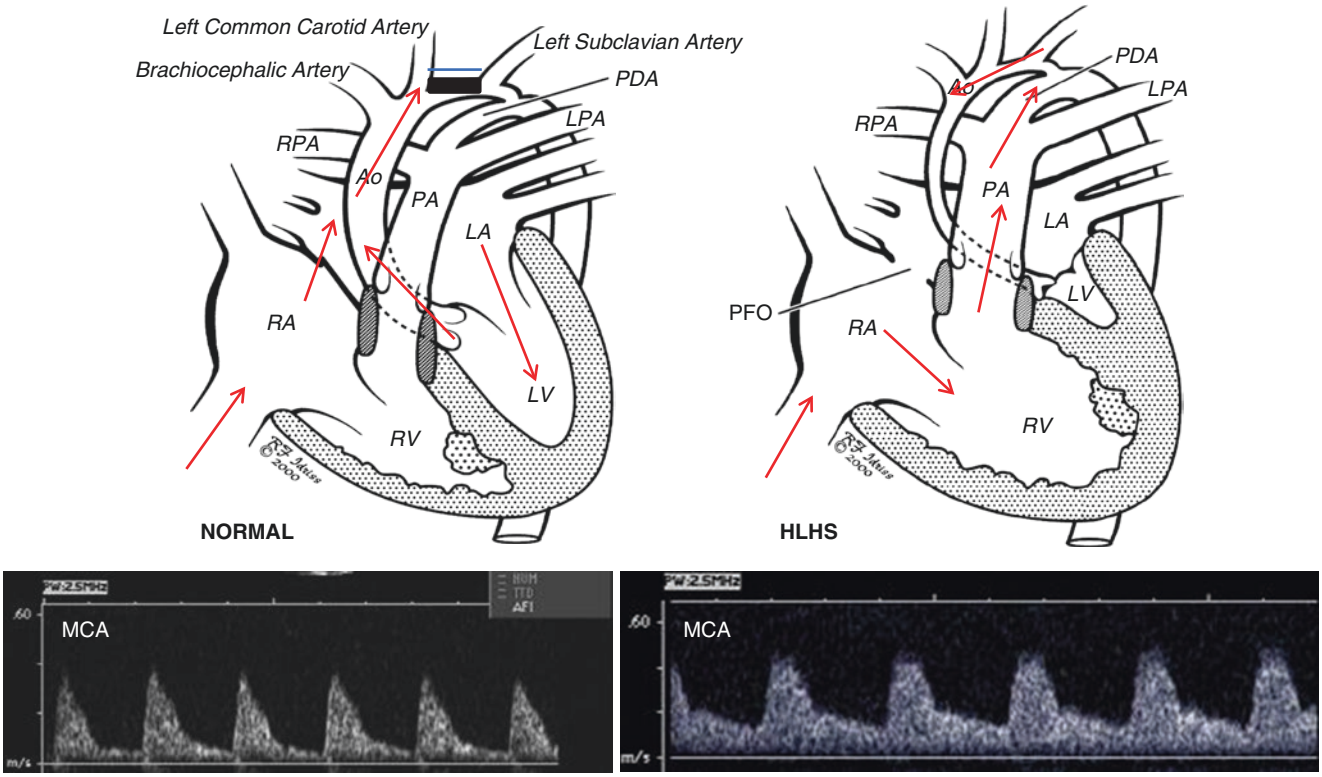

Fig. 1.7 Blood flow patterns in the normal fetus and the fetus with hypoplastic left heart syndrome (HLHS) explaining Doppler flow in the middle cerebral artery. In the normal fetus, there is an adequate volume of well-oxygenated blood so diastolic flow is reduced and the pulsatility index is high. In the fetus with HLHS, there is a decreased volume of cerebral blood flow which is less well oxygenated, so the cerebral vasculature dilates and the pulsatility index falls

[43] (Fig. 1.7). In the fetus with mild aortic stenosis or coarctation of the aorta, transverse arch flow can still be antegrade and PFO flow still right to left. In these milder cases, cerebral vascular resistance is intermediate between the normal fetus and the fetus with aortic atresia or severe aortic stenosis [41, 42] (Fig. 1.8). Unlike infants with aortic atresia, infants with coarctation of the aorta do not have small head circumferences [36]. The differences in UA and MCA pulsatility indices between the normal fetus and the fetus with HLHS are shown in Fig. 1.9.

The fetus with a structurally or functionally abnormal left heart survives because the combined fetal cardiac output is

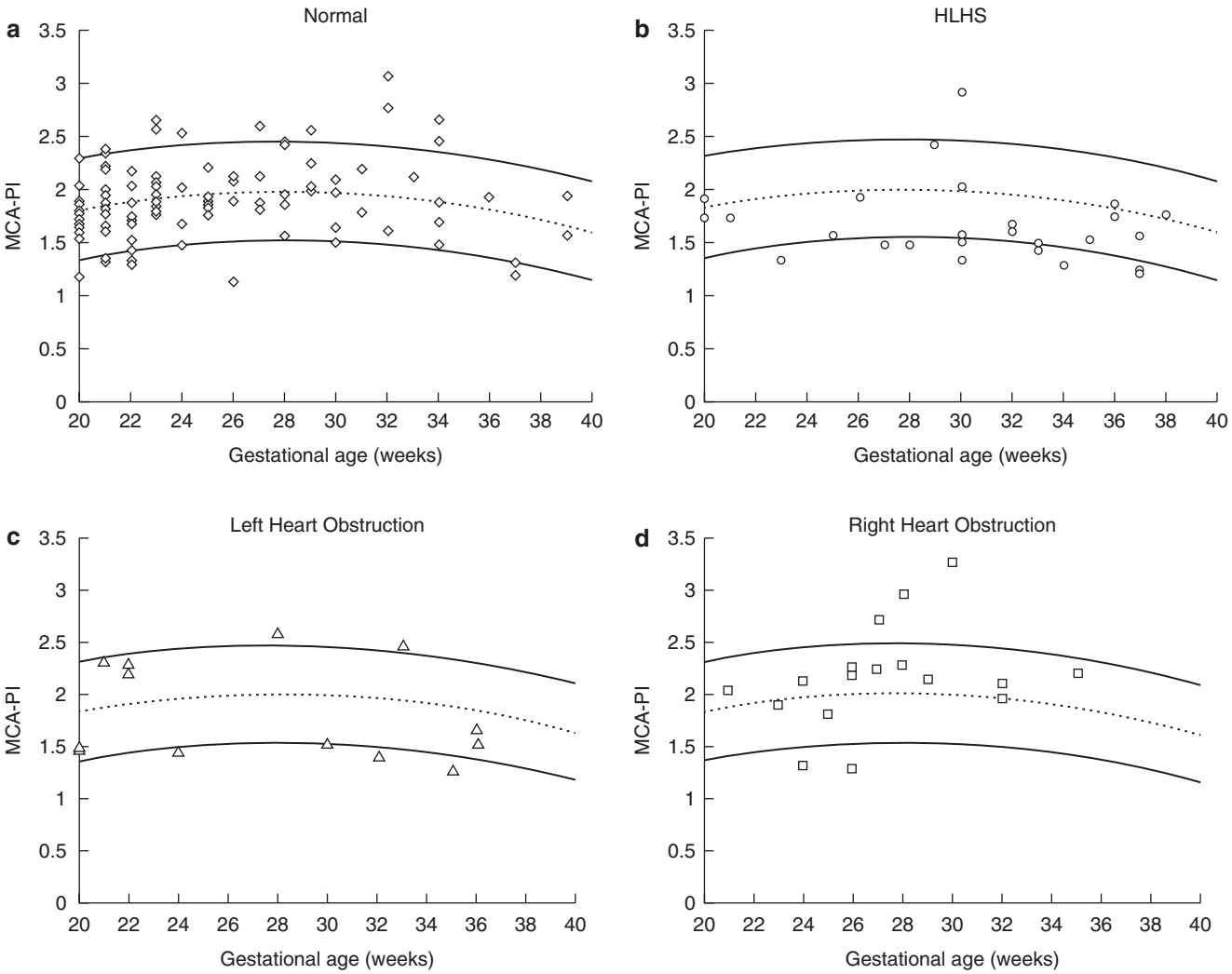

Fig. 1.8 A graph of middle cerebral PI (reflection of cerebral vasodilation) vs. gestational age in fetuses with (**a**) a structurally normal heart, (**b**) hypoplastic left heart, (**c**) left outflow (LVOT) obstruction, and (**d**) right outflow obstruction. The PI of HLHS fetuses is lower than normal, while that of the LOVT obstruction is intermediate. (Kaltman [42])

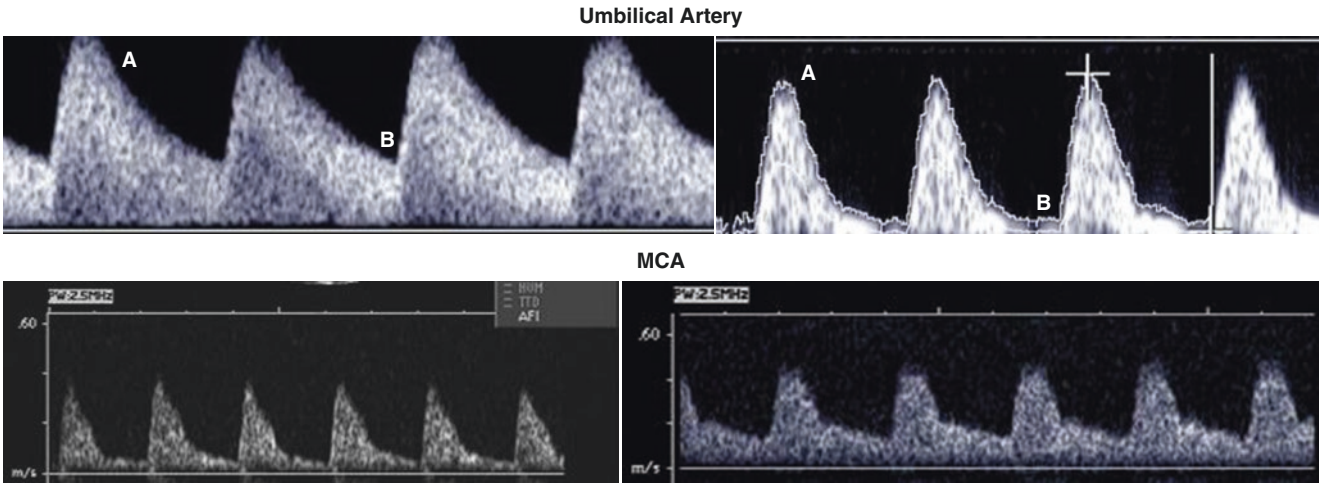

Fig. 1.9 The UA and MCA PI in fetuses with normal hearts and those who have brain sparing like HLHS. PI = A–B/mean. In the normal circulation, UA PI is high and the MCA PI is low. Alternatively, the UA PI in the fetus with brain sparing is low and UA PI of the MA is high. (Doppler wave forms from Figueras F et al. AJOG 2011)

maintained by the parallel circulation. However, a vicious cycle develops with this anatomy. High left atrial (LA) pressure secondary to mitral stenosis or mitral atresia restricts right-to-left shunting across the PFO. Ultimately, the shunt reverses to become left to right, resulting in diminished blood flow to the left heart and decreased growth of the mitral valve, LV, and aorta. Another serious consequence of the reverse atrial shunt is that preferential streaming of highly oxygenated blood from the DV to the left heart and coronary and cerebral circulation no longer occurs. Rather, highly oxygenated blood from the DV mixes with less oxygenated blood from the SVC and pulmonary veins (through the left-to-right shunt). More highly oxygenated blood then enters the lungs and the descending aorta, rather than the fetal brain. The effects of increased PO_2 on the lungs are vasodilation and early growth of the vascular smooth muscle.

In summary, the flow patterns resulting from different types of LV obstruction in utero can anticipate the postnatal circulation and type of resuscitation needed after birth. Reverse systolic flow in the transverse aortic arch signifies decreased LV output either from aortic atresia or severe LV dysfunction and predicts a ductal-dependent postnatal circulation [44]. Antegrade flow across the transverse aortic arch suggests the left ventricle can sustain the postnatal circulation. In the fetus with HLHS, critical PFO obstruction is characterized by abnormal pulmonary venous flow patterns in utero [45] and can predict the need for immediate LA decompression after birth and before palliative surgery or heart transplantation [46] (Fig. 1.10).

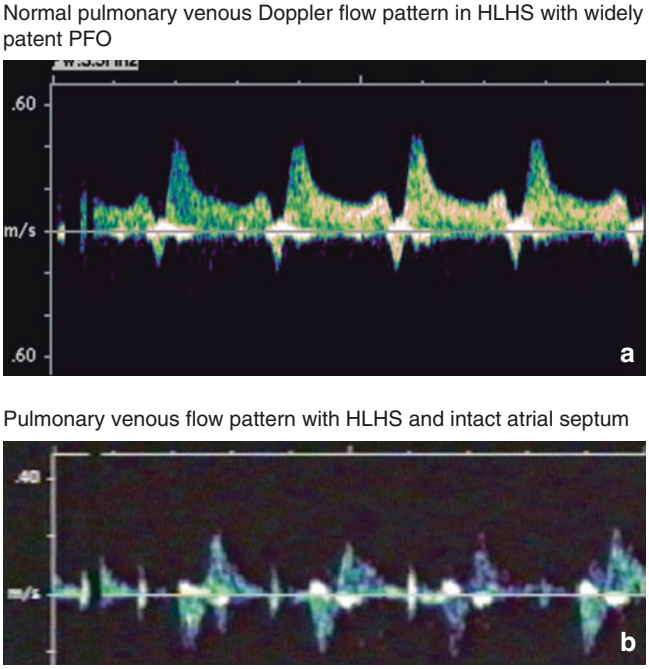

Fig. 1.10 Flow patterns in the pulmonary veins of fetuses with HLHS and (**a**) widely patent PFO or (**b**) highly restrictive PFO

1.4.3 The Fetus with Obstructed Pulmonary Blood Flow

The anatomic spectrum of right-sided obstructive lesions ranges from mild isolated valvar pulmonary stenosis to pulmonary atresia with intact ventricular septum and tricuspid atresia, but the end result of all is reduced pulmonary blood flow (Figs. 1.11 and 1.12). Obstruction can be anatomic due to hypoplasia of the pulmonary outflow tract and the RV ventricle, stenosis of the pulmonary valve, or pulmonary atresia, or it can be functional. Functional pulmonary atresia occurs when the RV dysfunction precludes antegrade flow, and instead, flow to the lungs is retrograde though a DA which is shunting not right to left but left to right. Functional pulmonary atresia can be seen in Uhl's anomaly, Ebstein's anomaly of the tricuspid valve, and severe tricuspid valve dysplasia (Fig. 1.13).

As with left-sided obstructive lesions, combined cardiac output remains unchanged in the fetus with severe right-sided obstructive lesions. If the pulmonary valve stenosis is mild to moderate and develops gradually, the RV hypertrophies. In critical pulmonary stenosis, the RV can generate over 100 mmHg. However, the cost is tricuspid valve dysfunction (insufficiency), decreased RV compliance, and increased RV filling pressures. At some point, the balance of the cardiac output shifts to the LV. Because of the parallel circulation, most right-sided obstructive lesions are well tolerated in fetal life. On the other hand, the right-sided defects with severe tricuspid or pulmonary insufficiency, as is seen with Ebstein's anomaly, tricuspid valve dysplasia, and tetralogy of Fallot with absent pulmonary valve, are at increased risk of heart failure, hydrops, and fetal demise.

The fetal blood flow patterns in right-sided obstructive lesions depend upon the degree and site of obstruction and if a ventricular septal defect (VSD) is present. The more proximal the obstruction (tricuspid valve vs. pulmonary valve), the more abnormal the flow pattern will be. The course of the circulation in the fetus with pulmonary atresia with intact ventricular septum is shown in Fig. 1.11. Most of the systemic venous blood preferentially crosses the PFO to the LA and LV. The PFO allows the RA to be successfully decompressed and heart failure does not develop. Preferential flow to the left heart occurs because the tricuspid valve is small, filling pressure in the RV is high, and compliance is low. As a consequence of decreased flow to the right heart, the DA only carries about 8% of the combined cardiac output. This is reflected in its small size relative to the aortic isthmus, which carries the majority of the cardiac output. Besides being smaller than normal, the ductus is tortuous and arises from the underside of the aorta. This situation is tolerated in utero.

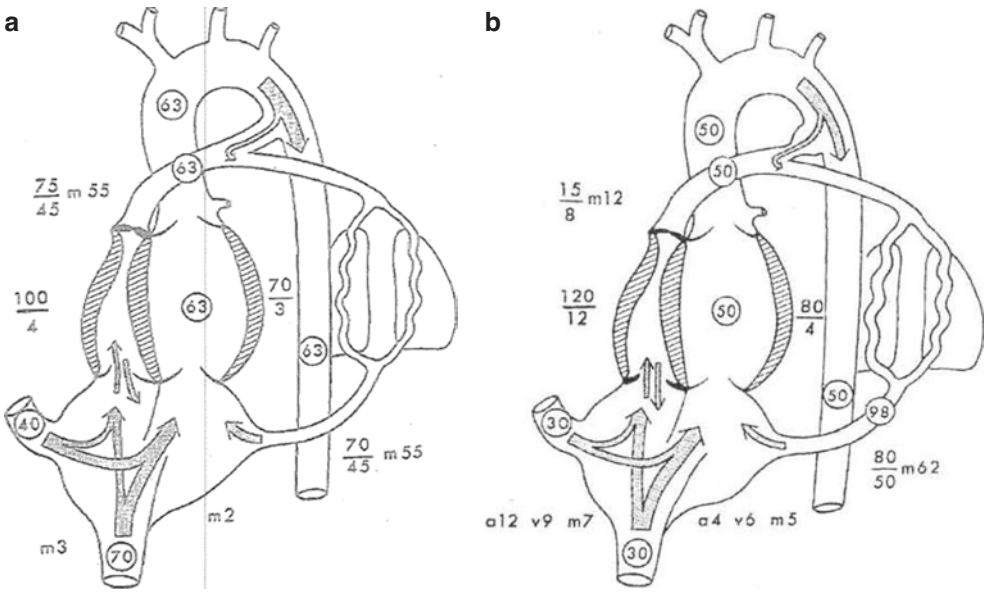

Fig. 1.11 Pre- and postnatal circulation with pulmonary atresia and intact ventricular septum in the fetus (**a**) and neonate (**b**). Note that after birth, pulmonary blood flow remains ductal dependent, RV pressures rise, and oxygen content is lower in the cerebral circulation than during fetal life

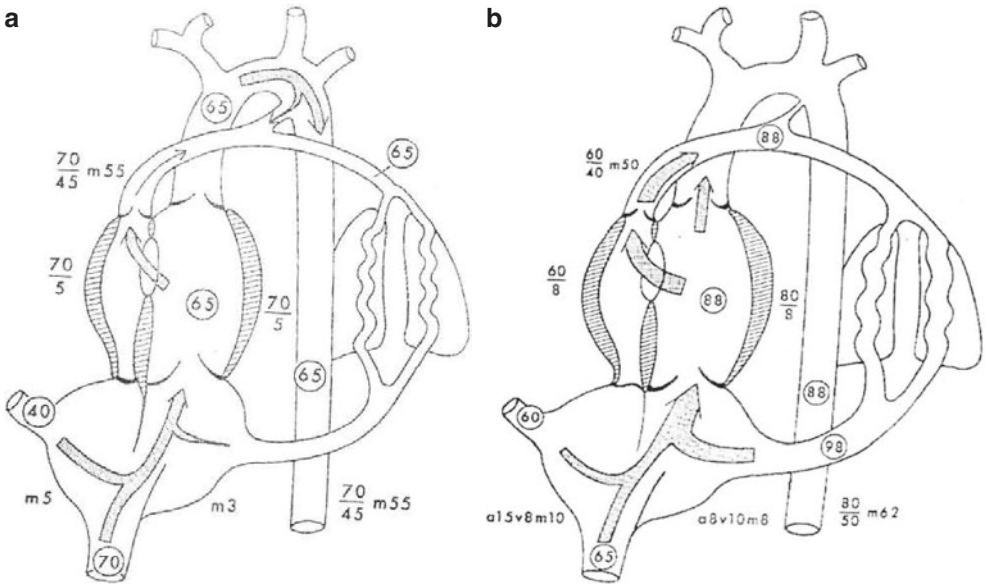

Fig. 1.12 In contrast to pulmonary atresia with intact ventricular septum, tricuspid atresia is usually accompanied by a VSD which allows enlargement of the RV and antegrade pulmonary artery flow. After birth, the obligatory right-to-left shunt across the PFO increases improving the delivery of more oxygenated blood to the cerebral circulation than seen in Fig. 1.11

Oxygen delivery to the pulmonary, but not the systemic, circulation is influenced by the presence of a VSD with tricuspid atresia and hypoplastic right heart. All systemic and pulmonary venous blood enter the LV (from the systemic veins across the PFO) meaning that the entire combined ventricular output enters the ascending aorta. This means the PO_2 of the cerebral circulation will be lower than normal. The effect of lower oxygen delivery to the brain of the fetus with tricuspid atresia and VSD is not as marked as it is in HLHS. In fact head circumferences are usually normal in the former. Additionally, studies have reported either a normal or slightly increased CVR with right heart obstruction [40–42]. It may be that lower oxygen saturation of the cerebral blood flow is compensated by increased cerebral blood flow volume. On the other hand, the PO_2 of the pulmonary circulation will also be higher than normal, whether flow to the pulmonary arteries is supplied antegrade (through a VSD from the LV to the RV) or from a left-to-right shunt across the DA. Higher oxygen content in the pulmonary circulation may decrease arteriolar vasoconstriction and enhance the development of vascular smooth muscle. These changes can result in pulmonary hypertension after birth.

1.4.4 The Fetus with Severe Tricuspid Valve Insufficiency

Although anatomically different, blood flow patterns and oxygenation of the fetus with Ebstein's anomaly or tricuspid

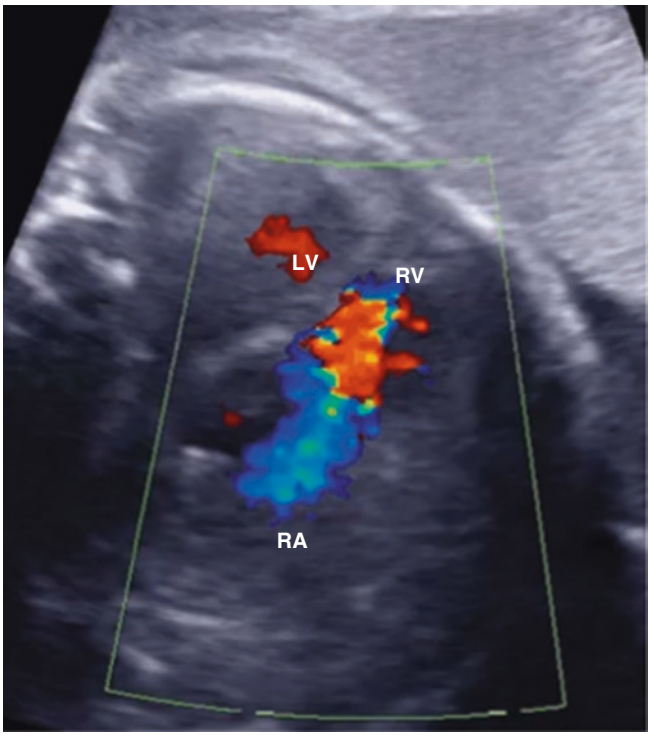

Fig. 1.13 Fetal echocardiogram showing four-chamber color flow Doppler of the severe tricuspid insufficiency arising from the displaced Ebstein's anomaly of the tricuspid valve in the right ventricle (RV) and entering the dilated right atrium (RA). LV left ventricle

valve dysplasia are very similar. These defects are two of the most severe cardiac anomalies and have a very high perinatal loss rate [47]. The major feature of these defects is severe tricuspid insufficiency through an anatomically abnormal valve. It is the consequences of severe and long-standing tricuspid insufficiency that create such a lethal anomaly with such poor outcomes.

With each heartbeat, the regurgitant volume (blood going back into the RA rather than into the RV and PA) increases. Thus, antegrade flow across the pulmonary valve decreases, and flow to the LA across the PFO increases. If the PFO is small, pressure in the already volume-overloaded RA and RV will increase, and heart failure will rapidly develop. Cardiac output can further be diminished by the dilated RV that may compress the LV and restrict its filling. Therefore, the LV cannot compensate for the RV, and the combined cardiac output falls. Other consequences of severe tricuspid insufficiency are severe cardiomegaly and thinning of the RV. The considerable enlargement of the RA and RV can cause pulmonary hypoplasia. The RV can become as thin as the atrial wall and may not be able to generate sufficient pressure during systole to open the pulmonary valve. This results in functional pulmonary atresia. Just as in anatomic pulmonary atresia, pulmonary blood flow is completely dependent on the DA. In the most severe cases, the pulmonary valve is stuck in a semi-open position resulting in pulmonary insufficiency and a "circular shunt." The circular shunt exacerbates the volume loading of the RV and the compression of the LV. The resulting low cardiac output reduces placental blood flow which in turn impairs oxygen and nutrient delivery to the fetus. Mixing of relatively desaturated right atrial and right ventricular blood with pulmonary venous blood in the left atrium reduces the PO_2 of the cerebral circulation. It is no wonder that there is a high incidence of demise in these fetuses; in fact, the mortality in fetal Ebstein's anomaly and tricuspid valve dysplasia has not changed considerably in the past three decades [48, 49]. Although many hemodynamic variables have been suggested as indicative of a poor prognosis, a cardiothoracic ratio of >66%, functional pulmonary atresia, hydrops, and decreased LV function are associated with a poor outcome [49, 50].

1.4.5 D-Transposition of the Great Arteries

D-transposition of the great arteries (D-TGA) is characterized by atrioventricular concordance and ventriculo-arterial discordance (Fig. 1.14a). Since there is atrioventricular concordance, the preferential streaming of oxygenated blood through the ductus venosus and the right-to-left shunt across the PFO continues to occur. However, because of the ventriculo-arterial discordance, the more highly oxygenated blood enters the pulmonary artery from the LV rather than the aorta. In other words, the PO_2 of blood entering the fetal lungs is about 20% higher, and the PO_2 of blood supplying the fetal brain is about 20% lower than in the fetus with a structurally normal heart. The decreased oxygen content of blood in the cerebral circulation results in cerebral vasodilation and a "brain-sparing" effect. This is the same compensatory mechanism that occurs in HLHS [41, 42, 51] and may be the reason that, like infants with HLHS, neonates with D-TGV have smaller head sizes than normal.

The increased oxygen content of the pulmonary arterial blood results in relaxation of the arteriolar smooth muscle and pulmonary vasodilation. This has two consequences: First, increased flow volume and higher oxygen saturation early in pregnancy can result in premature maturation of the arterioles and ultimately postnatal pulmonary hypertension. Second, the increased pulmonary blood flow is at the expense of the PDA. Normally 85% of RV output enters the PDA, but in D-TGV the combination of pulmonary vasodilation and higher PDA impendence reduces flow to the PDA. In addition, the ductus is known to constrict in the presence of increased oxygen. We have previously mentioned that PO_2 in the pulmonary artery (and hence the PDA) is higher than in the normal circulation. The more mature the fetus, the greater the vasoconstrictor response to oxygen [52, 53]. The combi-

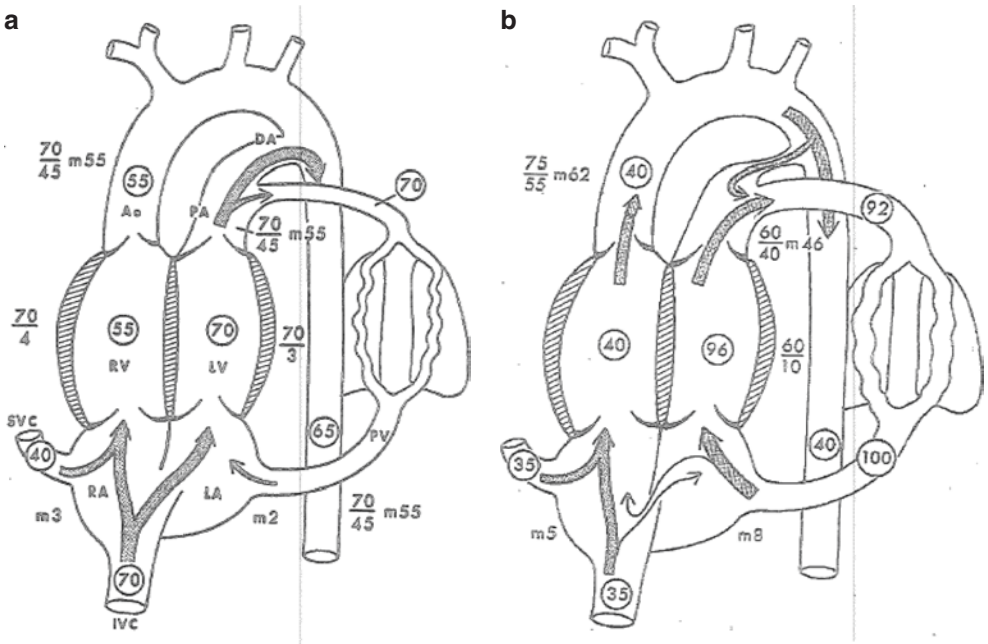

Fig. 1.14 Pre- and postnatal circulation of the fetus (**a**) and newborn (**b**) transposition of the great vessels. After birth, the circulations are in series and without inadequate mixing; especially at the atrial level, the fetus becomes hypoxic and acidotic. Fetuses with D-transposition benefit from delivery in a cardiac center of excellence where a balloon atrial septostomy can be readily performed

nation of anatomically restricted blood flow with higher PO_2 content may predispose to PDA constriction and contribute to the development of pulmonary hypertension. It is not known why some, but not all, fetuses with D-TGV develop pulmonary hypertension. One hypothesis is that the ductus venosus dilates so more highly oxygenated blood travels to the left heart [54].

The hemodynamics of TGA are affected by the size of the PFO. Because of increased pulmonary blood flow, there is increased pulmonary venous return that raises left atrial pressure, which restricts the right-to-left shunt and promotes premature constriction or even closure of the PFO. This may be the reason why about 50% of newborns require balloon atrial septostomy for stabilization prior to the arterial switch operation [55].

1.5 Postnatal Circulation

1.5.1 The Fetus with a Structurally and Functionally Normal Heart

There are four major cardiovascular adaptations after birth [56]: (1) the placenta is removed from the fetal circulation; (2) the infant begins to breathe, and the lungs become the respiratory organ; (3) the pulmonary circulation is separated from the systemic circulation and the PFO and PDA close; and, (4) over a longer period of time, the myocardium performance improves.

With the clamping of the umbilical cord, the placenta is removed from the circulation. Rather than pumping to the low-resistance placenta, the heart suddenly faces the much higher systemic vascular resistance. This can be detrimental if LV function is impaired from structural or functional defects or if cardiac output cannot be increased by an increase in heart rate. Loss of the placenta also affects the ductus venosus, and the systemic venous return to the IVC decreases from 40% to approximately 20%. With less flow, the ductus venosus constricts and closes a few hours to days after birth.

The second major adaptation occurs with the infant's first breath. Expansion of the lungs and breathing room air stimulates pulmonary stretch receptors and causes vasodilation of the pulmonary vascularity. Pulmonary vascular impedance plummets, and, with the combination of increased alveolar surface area and decreased impedance, pulmonary blood flow increases. Ventilation with oxygen further decreases pulmonary vascularity after birth. The combination of ventilation and oxygenation maximizes pulmonary blood flow. Treatment with the pulmonary vasodilators prostaglandin and nitric oxide will further increase pulmonary blood flow [57].

The result of increased pulmonary blood flow is increased pulmonary venous return to the LA and equalization of atrial pressures. These changes promote closure of the PFO [57]. The increase in blood oxygenation which occurs with breathing decreases the endogenous production of prostaglandin, and the PDA begins to close. At the same time, flow to the PDA lessens because pulmonary vascular resistance falls and systemic vascular resistance rises. With the constriction and closure of the fetal shunts, the circulation changes from one that is in parallel to one that is in series. This means cardiac output is now defined as the volume of blood ejected by each ventricle, rather than the combined cardiac output of the fetal circulation.

In addition to the change in circulation, the cardiac output of both ventricles increases by several mechanisms. First, preload to the LV is increased due to the greater amount of pulmonary vascular venous return. Second, afterload to the RV is decreased because of the fall in pulmonary vascular resistance with inflation of the lungs. Mechanical changes in the fetal thorax also increase cardiac output: After delivery and ventilation, high intrapleural pressure which has inhibited filling of the ventricles drops. As a result, biventricular compliance improves allowing greater filling of the ventricles [27].

Lastly, in addition to changes in preload and afterload, histological changes in response to cortisol and thyroid hormone and β-adrenergic receptors promote increased cardiac output by increased contractility [58, 59].

1.5.2 The Infant with Obstructed Systemic Blood Flow

Defects in this category include valvar aortic stenosis, coarctation of the aorta, and hypoplastic left heart syndrome. The clinical presentation of the infant with left outflow obstruction will depend on the severity of obstruction, whether the defect is dependent on postnatal patency of the DA and the size of the PFO.

1.5.2.1 Aortic Stenosis and Aortic Coarctation

After birth, obstruction from a stenotic aortic valve will increase (Fig. 1.4c). If flow across the aortic arch has been antegrade, left ventricular cardiac output should be adequate to sustain postnatal circulation, with the caveat that cardiac dysfunction decreased compliance from endocardial fibroelastosis, or a hypoplastic/stenotic mitral valve can increase LV end-diastolic and left atrial pressures resulting in pulmonary venous congestion. If retrograde flow in the transverse arch was noted in utero (Fig.1.6c), the infant's systemic circulation will be dependent on the PDA until balloon valvuloplasty or surgery relieves the obstruction. When the PDA closes in the newborn with coarctation (Fig.1.4d), the afterload to the LV will increase, LV stroke volume will decrease, the LV end-diastolic left atrial pressure will increase, and the infant will develop pulmonary venous congestion. If the ductus is not reopened with prostaglandin to reduce LV afterload and improve systemic blood flow, the infant will develop severe and unrelenting shock and metabolic acidosis.

1.5.2.2 Hypoplastic Left Heart Syndrome (Fig. 1.5b)

The newborn with aortic atresia will also require continued patency of the DA until surgery or an alternative intervention can be done. In addition to ductal patency, systemic and pulmonary vascular resistances must be titrated in favor of a right-to-left (pulmonary-to-systemic) shunt. Increasing pulmonary vascular resistances by respiratory therapy with nitrogen or CO_2 can increase the percentage of right-to-left shunt through the DA and improve systemic output. Conversely, ventilation with oxygen will decrease pulmonary vascular resistance and promote a left-to-right shunt to the detriment of systemic tissue perfusion. Another concern in the newborn with aortic atresia and HLHS is the size of the PFO. If the newborn has mitral atresia, the entire cardiac output must pass through the PFO, so restriction to the left-to-right shunt across the latter results in pulmonary edema and cyanosis. If there is severe restriction or an intact atrial septum, an immediate balloon septostomy or laser creation of an atrial communication will be lifesaving [46].

1.5.2.3 The Infant with Obstructed Pulmonary Blood Flow

Defects in this category include tricuspid atresia and VSD with normally related great vessels, pulmonary atresia and intact ventricular septum, Ebstein's anomaly of the tricuspid valve with functional pulmonary atresia, and tetralogy of Fallot with severe pulmonary stenosis or atresia, or absent pulmonary valve.

1.5.2.4 Tricuspid Atresia and Pulmonary Atresia with Intact Ventricular Septum (Fig. 1.11b)

Postnatal blood flow patterns and oxygenation depend on the presence of a VSD, the degree of RV hypoplasia, and the size and patency of the tricuspid valve. The size of the pulmonary arteries depends on ductal flow.

When the ventricular septum is intact, postnatal blood flow patterns do not differ substantially from fetal blood flow patterns. RV size depends on tricuspid valve size and function. The RV will be small if the tricuspid valve is small; a larger tricuspid valve means a larger RV but often increased tricuspid insufficiency. As the ductus arteriosus constricts after birth, pulmonary blood flow decreases resulting in hypoxemia and acidemia. The PFO usually remains patent because it is larger than normal due to the increased RA-to-LA shunt in utero and because the flap of the foramen does not close the defect due to low left atrial pressures from decreased pulmonary blood flow.

An important determinant of LV function in infants with pulmonary/tricuspid atresia and intact ventricular septum are the sinusoids and abnormal coronary connections discussed previously. Although these coronary findings can be suggested by echocardiography, most infants receive a cardiac catheterization with RV and aortic root angiograms to more accurately define coronary artery anatomy. If the sinusoids are large, or the coronary arteries do not connect to the aorta

(RV-dependent coronary circulation), cardiac transplantation is recommended because of the high risk of myocardial ischemia and sudden death.

If a small VSD is present, the postnatal hemodynamics are like patients with pulmonary atresia with intact ventricular septum. In the presence of a larger VSD usually seen with tricuspid atresia (Fig.1.12), the size of the VSD and the degree of pulmonary outflow obstruction determine postnatal hemodynamics. If the VSD is large, the pulmonary arteries are usually not obstructed because of left-to-right shunting through the VSD in utero. After birth, the pathophysiology is like that of a large VSD: there would be pulmonary blood flow, left atrial pressure and ventricular end-diastolic pressures all increase, and there will be pulmonary venous congestion.

1.5.3 Ebstein's Anomaly/Tricuspid Valve Dysplasia

The timing of delivery and management of the newborn with severe tricuspid valve disease is one of the most challenging areas of pediatric cardiology. Delaying delivery until fetal lung maturity is assured often results in hydrops and possibly intrauterine demise. While decreased pulmonary vascular resistance after birth may promote antegrade flow across the RVOT, the RV stroke volume remains low because of the large regurgitant flow and atrialization of the RV which is incapable of generating sufficient pressure to provide adequate pulmonary blood flow. The common association of pulmonary insufficiency with tricuspid insufficiency and RV dysfunction often results in a "circular shunt."

The newborn with severe tricuspid insufficiency is hypoxic for many reasons: high right atrial pressures promote a right-to-left atrial shunt through the PFO which is enlarged because of the regurgitant volume. Pulmonary blood flow is reduced because of reduced RV stroke volume, hypoplastic pulmonary arteries, and in the presence of a PDA increased pulmonary artery pressure and vascular resistance. Heralding a poor neonatal outcome are a cardiothoracic ratio of >90%, 66% in the fetus, functional pulmonary atresia with pulmonary insufficiency, and LV dysfunction. Other features associated with neonatal demise include pulmonary hypoplasia (due to severe and long-standing cardiomegaly), hydrops, and atrial arrhythmias, including atrial flutter [60].

1.5.3.1 Transposition of the Great Arteries (Fig. 1.14b)

A successful transition to postnatal life in the fetus with D-TGA and intact ventricular septum is possible only with persistence of the PFO and the PDA. Without these fetal shunts, oxygenated and deoxygenated blood cannot mix, and the newborn will develop several cyanosis and acidemia. It is difficult to determine if the PFO will be large enough for adequate oxygenation of the newborn, but prenatal findings of a hypermobile intra-atrial septum that "jump-ropes" from the LA to the RA may be predictive of the restriction. Other clues seen on fetal echocardiography are if the PDA diameter is <3 mm, if there is continuous flow in the PDA (suggesting ductal constriction), or if the aneurysm of the fossa ovalis bulges >50% into the left atrium [61]. Urgent balloon atrial septostomy (BAS) is necessary in 10–50% of newborns with D-TGA and intact ventricular septum; in the author's institution, 50% of newborns with a prenatal diagnosis of D-TGV have required BAS.

Other changes that occur following delivery of an infant with D-TGV are increased vascular resistance and afterload on the systemic RV and decreased afterload and resistance on the LV. Increases in pulmonary blood flow and LA pressure have one of two effects: if the PFO is small, these changes promote restriction or even closure of the PFO. If the PFO is large, increased LA pressure promotes a left-to-right shunt and improve mixing and oxygenation of the infant. If the PFO is large, ductal patency may not be necessary and prostaglandin can be discontinued.

1.6 Summary

Understanding the natural history of the fetus with congenital cardiac anomalies and preparing for the transition to extrauterine life has been advanced by fetal echocardiography. Despite the spectrum of complexity seen in fetal congenital heart disease, the transition to postnatal life can be predicted, based on blood flow and oxygenation patterns in the fetus. Anticipating the changes in cardiovascular hemodynamics that occur after birth allows fetal cardiologists to risk-stratify the postnatal management of the fetus with congenital heart disease. Infants with simple defects such as mild pulmonary stenosis can be safely delivered in the community hospital. On the other hand, infants with HLHS and intact atrial septum require a multidisciplinary team at a cardiac center of excellence to have any chance of survival.

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Chapter 2
Triage and Transport of Infants and Children with Cardiac Disease

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2.1 Principles and Practice

Advances in cardiology, intensive care, and surgical techniques have led to the survival of children with previously lethal congenital cardiac defects [1–6]. A large number of these children present to local community hospitals, nurseries, and emergency rooms for their initial stabilization before being transferred to regional tertiary care centers for more invasive diagnostic, surgical, and/or critical care intervention. As a result, pediatric transport systems have become a significant component of the pediatric cardiac care continuum.

The primary goal of any transport system is to provide a safe and timely transfer to a center specializing in the required care needed without an increase in morbidity or mortality. Accomplishing this goal requires a team capable of providing an extension of the pediatric cardiac critical care unit (i.e., skills and equipment) to the referring hospital [7, 8]. A multicentered study reported that nearly 10% of children requiring interfacility transport have a diagnosis of cardiac disease [9]. The leading reason for transport in this group was cyanotic heart disease with others, including congestive heart failure (CHF), respiratory distress, and sepsis syndrome [9]. Initial stabilization and transport of these children is often complicated by an increased need for stabilizing interventions [9], a lack of confirmed diagnosis, and their underlying severity of illness. For these reasons, infants and children with either congenital and/or acquired heart disease must be transported by a team with pediatric experience and, more importantly, specialized training in the area of pediatric cardiac disease [7–9].

2.2 Initial Call Triage

A successful transport begins at the time of initial referral request, at which point the call is triaged by a command physician who collects pertinent patient information and gives recommendation for further stabilization efforts. In calls involving children with suspected or confirmed cardiac disease, either the cardiology or cardiac intensive care unit (CICU) physician should be consulted. During the initial call, several pieces of information must be collected, which can be accomplished with a brief but concise report including:

- *Past medical history*
- *Present condition*
- *Vital signs (ABC's = airway, breathing, circulation, and sugar)*
  - A. Airway patency
  - B. Respiratory rate
  - C. Heart rate
  - D. Blood pressure
  - E. Perfusion
- *Neurologic assessment*
  - A. Level of consciousness (LOC)
  - B. Glasgow coma scale (GCS)
  - C. Presence of seizure activity

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- *Lab data*
  A. Blood glucose level
  B. Complete blood count (CBC)
  C. Electrolytes
  D. Cultures (blood, urine, sputum)
- *Radiological interpretations*
- *Interventions received*

2.3 Physical Assessment

Airway Assessment of the pediatric airway is broken down to two functional areas: airway patency and airway protection. Rapid assessment of these areas will lead the clinician to the next step in gaining control of the child's airway. It may be as simple as repositioning the child's head or as invasive as endotracheal intubation.

Breathing The initial assessment of breathing starts with a visual inspection of the child when entering the room, prior to interaction [10, 11]. Identifying the patient's position, respiratory rate and pattern, level of distress, and behavior will provide an immediate indication of the severity of the situation.

Circulation Assessment of circulation and peripheral perfusion can be done simultaneously during the initial patient survey. Assessment should include heart rate, central versus peripheral pulses, capillary refill time, level of consciousness, and urine output [10, 11]. Early identification and resuscitation of children with poor perfusion is paramount in limiting the adverse outcomes associated with uncompensated shock and multi-organ dysfunction syndrome [10, 11].

Sugar A serum blood sugar level is easily obtained with a bedside glucometer and should be documented at the time of the initial transfer request and at the team's earliest convenience during transport [12]. Evaluating a blood glucose level is critical as it has been reported that 18% of children requiring major intervention in the emergency room were found to be hypoglycemic (blood sugar <40 mg/dl) with an associated mortality rate of 55% [13].

2.4 Presentation and Stabilization

Stabilization is the shared responsibility of the referring facility, receiving institution, and the transport team. Stabilization always begins at the time of initial transport request and is focused around procurement of a patent airway, establishing effective respiration, ensuring adequate circulation, and identifying hypoglycemia or hypocalcemia.

For the purpose of this chapter, we classified children with heart disease into four groups which are defects with increased pulmonary blood flow, decreased pulmonary blood flow, special considerations, and arrhythmias. Each specific diagnosis will be discussed in terms of age of presentation and stabilization following the ABC's algorithm.

2.4.1 Defects with Increased Pulmonary Blood Flow

Congenital cardiac defects with increased pulmonary blood flow frequently present with signs of pulmonary overcirculation. These children present with symptoms of CHF around 3 months of age. Younger infants (<8 weeks of age) with CHF should be evaluated for left heart outflow tract obstruction as the symptoms may proceed the closure of a patent ductus arteriosus (PDA) and the onset of shock. Other causes of CHF include cardiomyopathy, infectious myocarditis, and tachyarrhythmias.

2.4.1.1 Clinical Presentation

As previously mentioned, patient assessment must begin with the ABC's as recommended by the PALS and APLS curricula [10, 11]. Infants and children with lesions resulting in CHF present mainly with respiratory symptoms as a result of pulmonary edema or complicating infectious pneumonitis. A history from the parent(s) or care taker(s) will reveal a progressive increased work of breathing, poor feeding tolerance, and lack of weight gain. These children often appear thin and pale but with normal length and head circumference.

A physical assessment reveals tachycardia, tachypnea with respiratory distress of varying degrees, and hepatomegaly. Auscultation of the lungs does not usually reveal rales; more commonly found are wheezes; however, some patients may present with clear breath sounds. These children rarely present with low cardiac output (CO) and shock but more often are hypoxic and with impending respiratory failure. Chest radiograph will demonstrate an enlarged heart and liver with or without increased pulmonary vascular markings [14–16]. The lungs may be either atelectatic or hyperinflated secondary to airway obstruction from bronchial wall edema.

2.4.1.2 Stabilizing Intervention

The initial management of these patients should focus around alleviating hypoxemia, lessening respiratory distress, and preventing the need for endotracheal intubation. Oxygen should be administered immediately to improve hypoxemia. Lowest con-

centrations required to increase the arterial saturation level (SpO_2) to an acceptable level should be used, as oxygen is a potent pulmonary vasodilator and may worsen the left-to-right shunt. Infants with an increased work of breathing but maintaining adequate gas exchange should be administered intravenous diuretics such as furosemide [17]. If supplemental oxygen and diuretic therapy do not alleviate the respiratory distress or the child's condition worsen, noninvasive positive pressure ventilation (NIPPV) or endotracheal intubation should be considered.

In situations with poor cardiac function, an inotropic agent with peripheral vasodilatory properties should be initiated. Dobutamine is useful at doses ranging between 5 and 20 mcg/kg/minute; however, phosphodiesterase III inhibitors such as amrinone and milrinone may be used as well [18]. If an infant requires high levels of inotropic support, other diagnosis such as sepsis should be considered.

- *Atrial septal defects* (ASD) and *ventricular septal defect* (VSD) cause pure volume overload of the right heart and lungs. If an infant or child presents with CHF, oxygen, inotropes, and diuresis are indicated. Moderate fluid restriction and maintenance fluid rates of 60–80 cc/kg/hour/day may be helpful in the absence of shock.
- *Patent ductus arteriosus* (PDA) refractory to indomethacin therapy requires transfer to pediatric tertiary care centers for surgical intervention. Oxygen should be used with caution in preterm infants with large PDA as it will further increase pulmonary overcirculation by decreasing PVR. If left untreated, the pulmonary overcirculation may result in pulmonary hypertension reversing the shunt, thus resulting in hypoxia. A past medical history of a PDA is often associated with endocarditis in children.
- *Truncus arteriosus* (TA) results in pulmonary overcirculation as the common "trunk" is exposed to systemic pressure causing a large left-to-right shunt. Severe hypoxia is rare. Older children post TA repair may present with CHF secondary to truncal insufficiency or conduit stenosis.
- *Anomalous pulmonary venous return* (APRV) clinical presentation depends on the number, location, and presence of obstruction within the anomalous connection(s). In infants with total APRV, cyanosis may present in the neonatal period due to the elevated PVR limiting pulmonary blood flow. As the PVR drops, pulmonary blood flow increases, and the SpO_2 will rise to the upper 80s low 90s%. These infants usually present around 6 months of age with right heart failure. Total APRV with venous obstruction usually presents in the first few days of life and requires urgent surgical intervention. Fluid overload must be avoided, and initiation of PGE_1 may not improve hypoxia in these infants as mixing occurs at the atrial and ventricular levels. However, PGE_1 should still be started as some infants may have restricted mixing at the atrial level requiring a PDA for systemic blood flow. This lesion is difficult to differentiate from primary pulmonary hypertension (PPHN) in the transport environment.

2.4.2 Left Heart Outflow Tract Obstruction

Obstruction to systemic output is the most common cause of cardiogenic shock in infants <1 month of age. These infants may present with symptoms of CHF prior to ductal closing. Once ductal patency is lost, the infant appears septic due to low CO and profound metabolic acidosis. For this reason, septic shock is the principal differential diagnosis, and the infant should be treated for both conditions. Infants with left heart outflow tract obstruction often become symptomatic over hours; however, they may present as late as 8 weeks of age.

2.4.2.1 Clinical Presentation

Physical examination reveals tachypnea with increasing respiratory distress or apnea, tachycardia, lethargy, irritability, hepatomegaly, and severe shock. Pulses may be weak or absent. Arterial blood gas analysis will reveal a severe metabolic acidosis (pH < 7.20) with a low $PaCO_2$ and mild hypoxia with a PaO_2 between 50 and 70 torr. Hypoxemia is a result of pulmonary edema and/or right-to-left shunting across the PDA; however, the addition of oxygen may constrict the PDA limiting systemic blood flow and should be used with caution in these patients. Chest radiograph will reveal cardiomegaly with pulmonary edema.

2.4.2.2 Stabilizing Intervention

The emergency stabilization of left heart outflow tract obstruction focuses around reestablishing ductal patency and increasing systemic blood flow. Prostaglandin E_1 (PGE_1) infusions are critical for reopening the ductus arteriosus providing a pathway for this to occur. Once systemic blood flow is improved, peripheral pulses will return, urine output will increase, and metabolic acidosis will slowly clear. Severe acidosis will decrease myocardial function and should be buffered with sodium bicarbonate ($Na\,HCO_3$). In cases where poor cardiac function is present, intravenous inotropic support with dopamine and/or dobutamine should be initiated [18]. Amrinone or milrinone may be useful for increasing CO, peripheral vasodilatation, and lusitropic properties [18].

Endotracheal intubation is indicated in infants who have apnea, refractory shock, and altered mental status (GCS < 8 or 3 less than baseline) or in those whose respiratory status poses a risk of decompensation while en route. Advanced airway management should also be considered in infants receiving high-dose PGE_1 infusions as clinically significant apnea may

occur [19, 20]. Ventilator management should be aimed at preventing pulmonary overcirculation by maintaining a pulmonary to systemic perfusion (Q_p:Q_s) ratio of 1:1 [16, 19, 20]. Maintaining oxygen saturations between 80% and 85% and a PaO_2 in the 35–40 mm Hg range has been recommended [17].

- *Aortic stenosis* (AS) may present either during the immediate newborn period or childhood. Critical AS presents in the neonatal period when ductal patency is lost limiting systemic blood flow through a stenotic aortic value. Blood pressure in all four extremities will be low as the obstruction is below the root of the subclavian arteries.

Undiagnosed AS in the older child presents with a history of fatigue, dyspnea on exertion, and less commonly syncope. These children rarely require interfacility transport. However, children in this age group may suffer from restenosis following repair leading to severe aortic insufficiency and ultimately left heart failure.

- *Coarctation of the aorta* (COA) may present as late as 8 weeks of age and should be considered in any infant within this age group who has signs of cardiogenic shock. Assessment of pulses will reveal significant difference in the carotids and upper extremities compared with the femoral and lower limbs. Blood pressure measurements should be performed and recorded in all four extremities. The BP will be greater above the obstruction (arms) and lower below the obstruction (legs). A difference greater than 20 mm Hg is considered significant.
- *Hypoplastic left-sided heart syndrome* (HLHS) commonly presents within the first 7 days of life. Rapid deterioration occurs as the only source of systemic blood flow (PDA) closes resulting in profound cyanosis, hypotension, and metabolic acidosis. Endotracheal intubation and immediate initiation of PGE_1 are indicated. These infants often require inotropes and multiple boluses of Na $HCO_3$for pH buffering. Maintaining Q_p:Q_s ratio at 1:1 is essential for survival. Arterial blood gases should be in the ranges of pH 7.40, PaO_2 40 mm Hg, $PaCO_2$40 mm Hg, and HCO_3 24 mmol/L, and FiO_2 should be set to achieve a SpO_2 in the 70s [17]. Sedation and paralysis may be useful in controlling the aforementioned parameters. If SpO_2 rises and the metabolic acidosis worsens, there is excessive pulmonary blood flow (Q_p), and if the SpO_2 drops and the HCO_3 increases, there is too little pulmonary blood flow. Blood glucose and calcium level should be followed throughout transport.

2.4.3 Defect with Decreased Pulmonary Blood Flow

Cyanosis in the newborn presenting to a local community hospital without pediatric cardiology poses a significant diagnostic problem as the cause may be pulmonary, cardiac, or a combination of both. In a resource-limited environment, such as transport, distinctions must be made by obtaining an accurate familial and prenatal history, conducting a thorough physical exam, and utilizing specific lab data.

2.4.3.1 Clinical Presentation

Familial and Prenatal History Upon arrival, the transport team should quickly evaluate the family history for congenital heart defects, birth defects, syndromes, and early deaths [17]. A prenatal history should be reviewed for a maternal history of diabetes, or for any exposure to rubella, coxsackievirus, or radiation. The onset of cyanosis and/or respiratory distress should also be noted as it may give important clues to whether the symptoms are related to the closure of the ductus arteriosus or the development of sepsis.

Physical Examination The physical assessment should begin with the appearance and level of respiratory distress. Agitation, irritability, tachypnea, nasal flaring, grunting, and retractions suggest pulmonary pathology. Infants with cyanotic heart disease usually have central cyanosis and appear comfortable with little to no increased work of breathing which is generally referred to as "quit tachypnea." Pre- and post-ductal pulse oximetry is extremely useful in identifying the presence of ductal shunting [21, 22]. Evaluating for the presence of differential cyanosis is also useful as blue upper extremities and pink lower extremities are highly suggestive of congenital heart disease.

Lab Data A chest X-ray with any of the following is suggestive of cyanotic heart disease: cyanosis in the presence of clear lung fields, cardiomegaly (cardiothoracic ratio >0.50), and decreased pulmonary vascular markings. If any of the following is present, a hyperoxia test may be useful in identifying the etiology of the cyanosis. A right-to-left shunt is likely when the PaO_2 is <200 mm Hg on 100% oxygen [17]. Immediate intervention is indicated in any cyanotic infant whose arterial blood gas reveals a pH <7.28 or $PaCO_2$ >50 mm Hg or PaO_2 <50 mm Hg on a FiO_2 ≥0.5 [17, 23].

2.4.3.2 Stabilizing Intervention

Prostaglandin E_1 should be initiated in any situation where there is a high suspicion of cyanotic heart disease. Some have recommended intubation prior to transport in all infants who require PGE_1 infusions to avoid clinically significant apnea and to lessen the risk of severe hypoxia [17]. Further control of the infant's respiratory status may be facilitated with the use of sedation and paralytics.

- *Tetralogy of Fallot* (TOF) in the newborn period may have little right-to-left shunting, occasionally referred to as "pink tetralogy." A chest X-ray in this period reveals a "boot-shaped" heart. As the infant grows, the infundibular obstruction becomes more significant increasing right-to-left shunting resulting in hypoxia. Sudden onset of severe hypoxia or "tet spells" commonly occurs between 2 and 4 months of age for reasons including anxiety, pain, and manipulation of an artificial airway, for example, suctioning. Tet spells are treated with supplement oxygen, administration of morphine sulfate, initiation of vasoactive agents to increase the systemic vascular resistance, or simply placing the child in the knee-chest position [17]. Intubation may be indicated and depends on the degree of cyanosis and acidosis and frequency of these hypercyanotic spells. Endocarditis should be considered in febrile children with a history of TOF.
- *Pulmonary stenosis* (PS) and *pulmonary atresia with intact ventricular* cause obstruction of forward flow across the pulmonary valve resulting in profound cyanosis. These infants require PGE_1infusions to ensure adequate pulmonary blood flow and in the presence of ventricular dysfunction may require inotropic support [18]. Older children with progressive PS rarely present with cyanosis; if present, its usual cause is an ASD with a right-to-left shunt [17]. Children who are symptomatic may require inotropic support and intravenous diuretics.
- *Transposition of great arteries* (TGA) is the most common cyanotic heart defect [17]. It should be suspected in any infant with differential cyanosis: blue upper extremities and pink lower extremities. Little response occurs from the administration of oxygen, and initiation of PGE_1 is then indicated; however, older infants may not respond to PGE_1 and may require an urgent atrial septostomy to facilitate adequate mixing. Time to a pediatric tertiary center where an emergent septostomy can be performed is an important factor in the survival of these infants. Infants with an associated VSD may present in CHF. Inotropic support and diuresis are often indicated. Calcium should be monitored keeping in mind the possibility of DiGeorge syndrome.

2.4.4 Special Considerations

- *Cardiomyopathy* is a common etiology of pediatric heart failure. Dilated and hypertrophic cardiomyopathies are two types which pose a significant challenge to the transport team. Delineation of the two is based on clinical, hemodynamic, and structural features, of which there is some degree of overlap [23].

2.4.4.1 Clinical Presentation

Infants and children with either type present with symptoms of CHF. However, in more gravely ill children, it presents as cardiovascular failure and shock. Children with poor cardiac function will appear anxious with tachycardia, tachypneic possibly with grunting, prolonged capillary refill, and hypotension. Low blood pressure results from low cardiac output, and in the most severe cases, fulminant pulmonary edema may be present. Stabilization is focused around decreasing myocardial workload on the failing heart while increasing its function.

2.4.4.2 Stabilizing Intervention

The level of cardiopulmonary compromise dictates the extent of stabilization. Noncritical patients may only require supplemental oxygen and diuretics to improve fluid homeostasis. In the most severe cases, airway control and work of breathing must be removed from the patient and controlled by the team. Removing the work associated with breathing will decrease the metabolic demands of both the respiratory muscles and heart, thus decreasing stress on the already failing cardiopulmonary system. In addition, a higher mean airway pressure will decrease intrapulmonary shunting created by the fluid-filled alveolus. High levels of positive end-expiratory pressure (PEEP) should be used with caution as it may limit venous return to the heart. Following stabilization of the airway and breathing continuous infusions of inotropic agents should be initiated. Sympathomimetic agents such as dopamine, dobutamine, and epinephrine have been advocated [24]. High doses of dopamine will amplify cardiac action but will also increase peripheral vasoconstriction and may be proarrhythmic [24]. Amrinone or milrinone may also be useful in improving CO, promoting peripheral vasodilatation, and increasing diastolic function [10]. Peripheral vasodilators such as nitroprusside and hydralazine may be useful in decreasing afterload [24]. In the presence of a metabolic acidosis, buffering with Na HCO_3 is indicated as severe acidosis will further compromise myocardial function.

- *Dilated cardiomyopathy* (DCM) is the most common form of cardiomyopathy and a major reason for cardiac transplantation, with 31% either succumbing to the disease or receiving transplantation within 1 year post diagnosis [25, 26]. This type of cardiomyopathy is characterized by ventricular dilation and systolic dysfunction. A chest radiograph will show cardiomegaly often with pulmonary venous congestion [23].
- *Hypertrophic cardiomyopathy* is primarily a disease of the myocardium which is distinguished by left ventricular hypertrophy without ventricular dilation [23]. Typically, a

chest radiograph is normal [23, 27]. This type of cardiomyopathy is the leading cause of sudden death in children and adults.

2.4.5 Arrhythmias

The transport team's management of arrhythmias should be focused around those which may potentially or are at the time compromising hemodynamic stability. It is essential to assess and support the ABC's as often the underlying cause of the arrhythmia is related to compromise of the airway, breathing, circulation, or hypoglycemia [10, 11, 28].

Most transport monitors used today have the capacity to record and print rhythm strips which are potentially useful in diagnosing the exact arrhythmia which occurred. All strips should be saved in the presence of a suspected arrhythmia for later evaluation by a pediatric cardiologist. A continuous EKG strip should also be obtained during any attempt at converting the arrhythmia by noninvasive methods such as vagal maneuvers or infusions of anti-arrhythmic agents. Recording the onset and/or termination of an arrhythmia will offer vital clues in identifying the most successful method of management.

2.4.6 Tachyarrhythmias

- *Supraventricular tachycardia* (SVT) most commonly occurs in infants under the age of 4 months and often presents as poor feeding, inconsolability, tachypnea, prolonged capillary refill time, and mottling [28–32]. It should be considered in any infant with a narrow complex (≤0.08 second) tachycardia with a heart rate 220 or greater or in any child with a heart rate 180 or greater. SVT is associated with Ebstein's anomaly.

2.4.6.1 Stabilizing Intervention

Treatment of SVT depends on the degree of hemodynamic instability. In stable infants and children, ice may be applied to the face without occluding the airway [28–32]. In older children, carotid sinus massage or *Valsalva* maneuvers may be useful. If IV access is available, adenosine should be given rapidly via the two-syringe technique. The technique is easily accomplished by using a stopcock or double-lumen t-connector. One port is used to push the adenosine and the second port used to flush with ≥5 mL of normal saline [28]. If the patient is unstable or IV access is unavailable, synchronized cardioversion at 0.5–1 J/kg should be administered [10, 11, 28–32]. If unsuccessful, a repeat shock can be delivered at 2 J/kg. Consider amiodarone or procainamide prior to the third shock [10, 11, 28–32].

- *Ventricular tachycardia* (VT) is differentiated from SVT by a wide complex (≥0.08 second) and poor perfusion. Most children who present with VT have a history of congenital or acquired heart disease.

2.4.6.2 Stabilizing Intervention

If the child is unstable and VT is suspected, immediate synchronized cardioversion should be performed at 0.5–1 J/kg once the airway and breathing is stabilized. A dose of adenosine may be useful in determining if the rhythm is SVT with aberrant conduction; however, cardioversion should not be delayed [28]. If a second shock is required, it should be delivered at 2 J/kg [10, 11, 28]. If a second shock is unsuccessful or the VT recurs quickly, amiodarone or procainamide should be considered prior to a third shock. Close monitoring of the ECG and blood pressure should be performed during the administration of any anti-arrhythmic agent. In the presence of VF with hemodynamic stability, an expert should be consulted as all arrhythmia therapies have a significant potential for causing serious adverse effects [28].

Bradycardic Arrhythmia The most common cause of bradycardia in children is hypoxemia with or without hypoventilation. Other etiologies include hypothermia, hypoglycemia, hypothyroidism, increased intracranial pressure, seizures, and vagal stimulation from the placement/adjustment of nasogastric tubes or endotracheal tubes. Children who have had cardiac transplantation have denervated hearts and often develop bradycardia.

Atrioventricular blocks (A/V blocks) are rarely symptomatic in children; however, these will be discussed considering their varying etiologies. They include structural heart disease, infection, inflammatory disorders, neurodegenerative disease, muscular dystrophies, infiltrative disorders, trauma, and drug intoxications.

- *First-degree AV block* is defined as a prolonged PR interval (PR > 0.20 in any age group) [10, 11, 17, 28]. Neonatal PR interval is usually between 0.09 and 0.12. Rarely does this type of heart block present symptomatically; thus, it is of little concern.
- *Mobitz type 1* or *Wenckebach block* is defined as increasing prolongation of the PR interval eventually producing a nonconducted P wave. It is caused by the same etiologies stated above with the addition of *digoxin* toxicity [33].
- *Mobitz type II second-degree block* and *third-degree heart block* indicate more serious cardiac pathologies

and should be considered when the P waves are found to be "marching through" the EKG tracing with little to no association with the QRS complex. Both can present as a late postoperative complication when scarring begins to infiltrate the conduction system. Inflammatory disorder, such as myocarditis, is another cause of these types of advanced heart blocks. Congenital complete heart block occurs in approximately 1 in 15,000–20,000 live births and should be considered in any infant who presents with complete heart block in the newborn period from a mother with history of connective tissue disease (commonly systemic lupus erythematosus) [26].

2.4.6.3 Stabilizing Intervention

The initial management of bradycardia and AV blocks is focused on the establishment of a patent airway, reversal of hypoxemia, and treatment of any underlying metabolic derangement. The upper airway should be rapidly assessed for obstruction, easily identified by the presence of little or no airflow, upper airway stridor, or asynchronous chest and abdominal motion. Endotracheal intubation may be indicated. In severe symptomatic bradycardia, cardiopulmonary resuscitation must begin without delay. Intravenous administration of agents which modify the autonomic nervous system is indicated in persistent symptomatic bradycardia. They include atropine, which can be given as a single bolus (0.02 mg/kg) up to four doses or as a continuous in fusion (10–40 μg/kg/min), epinephrine (0.1–1.0 μg/kg/min), or isoproterenol (0.05–0.50 μg/kg/min) [17]. Temporary transcutaneous pacing should be considered in any child with severe bradycardia unresponsive to pharmacological therapy [10, 11, 17, 28–32].

2.4.7 ECMO Transport

An emerging area of the pediatric cardiac critical care continuum is that of extracorporeal membrane oxygenation (ECMO) transport or mobile ECMO. Technological advances such as maglev centrifugal pumps, poly-methylpentane oxygenators, and bio-coated circuits have led to the feasibility of ECMO transport [34]. Use of ECMO technology in the transport environment allows for increased stability during transport while gaining access to centers with increased resources including cardiac transplant programs. Survival rates for patients transported on ECMO have been found to be similar to those patients that did not require interfacility transport [35]. It has also been demonstrated that interfacility mobile ECMO can be achieved safely during both long- and short-distance transfers [36].

Safe and successful ECMO transport of any patient requires a highly competent team well trained in neonatal pediatric critical care, ECMO physiology, cannulation techniques, transport medicine, and air medical physiology. All team members should have training and competencies prior to the initiation of the program. All programs should meet the ELSO guidelines for training [38].

2.5 ECMO Transport Equipment

Commercially available ECMO transport system is becoming more accessible; however, currently there are patient size limitations resulting in customized systems being developed by the receiving center. These systems must have primary and backup pumps, monitoring (pressures, flow, and RPM) capabilities, medical-grade gas tanks, IV pumps, and the ability to be safely secured and operate in all modes of transport [38]. Each mode of transport must have high-capacity inverters and medical gas systems that can support the additional oxygen/air requirements. The following equipment should be carried on all interfacility ECMO transfers:

- *ECMO pumps*: centrifugal pumps allow for miniaturization of the transport systems with backup pump capabilities. For these reasons and a greater safety profile, these pumps are advocated for the transport environment.
- *Backup ECMO circuit/supplies*: size-specific spare cannulas, sterile tubing connectors, tubing, and appropriately sized oxygenator should be carried on transport. They are needed in the event that there is a failure of any of the aforementioned components. If available, all components should be bio-coated, as surface coating has been found to decrease inflammatory response to foreign surfaces that occur with circuit changes [37].
- *Laboratory devices*: activated clotting time (ACT) and blood gas monitoring capabilities are essential during transport. These devices help ensure hemostatic and acid base hemostasis during the transfer.

2.6 Responsibility of the Referring Institution

Most commonly, mobile ECMO is used for children on long-term ECLS referred to centers with transplant or ventricular assist device capabilities. At the time of formal transfer request, the following information should be collected:

- Detailed medical history including diagnosis, reason for cannulation, duration of ECLS support, occurrence of CPR, neurologic status, and any diagnostic procedures performed.

- ECMO information must include pump type and size, cannula location and size(s), and oxygenator type. The most recent oxygenator blood gas information will help identify the functional status of device, allowing the team to prepare for the transfer.
- Hemostatic indices should be obtained by the transport physician and should include the most recent ACT, PTT, PT, platelet count, hemoglobin, and hematocrit, Xa, and fibrinogen levels. These data will provide input regarding the need for additional stabilizing interventions. It will also provide information regarding the status of the ECMO circuit and blood product consumption.
- Current medication administration information should include dose, concentration, time, and site of administration. The information will help the team prepare for the trip by obtaining indicated medication prior to departing on transport.
- Ventilatory support information should be gathered at the time of call ensuring the transport team has the indicated device for transport. Most transport ventilators used today are capable of supporting the needs of most patients on ECMO.

2.7 Transport Team Responsibility at the Referring Institution

At first patient contact, the team should conduct a thorough assessment that includes review of laboratory and radiographic studies, evaluation of physiologic changes, and trends in ECMO-specific parameters [38]. All stabilization efforts should be under the direction of the transport physician, following the receiving institution's transport and ECMO guidelines.

2.8 Transport Phase Considerations

Once the patient is stabilized, patient transfer to and from the transport vehicle, the effect of attitude on the oxygenator, and recognition and/or management of in-transport unplanned events are critical for the success of transport [38]. Best practice supports a "time-out" prior to each patient move. "Time-out" should be managed by the team leader using good situational awareness, which ensures all crew members are prepared in advance.

- Altitude and temperature effect on the oxygenator: gas exchange and functionality will decrease with decreasing barometric pressure that occurs with increasing altitude [38]. This must be considered during air transport of ECMO patients, as PaO_2 will correlate directly with the gas capacity of the oxygenator. In addition, temperature changes found in the transport environment must be considered. Extreme low temperatures will make plastic components fragile increasing the risk of breakage, which can be catastrophic. Small cracks may lead to air entrainment or blood loss. Measures should be taken to protect all circuit components.

Interfacility ECMO transport is complex, requiring expertise in all aspects of extracorporeal life support, critical care, and transport medicine. Additional information is available in the *Extracorporeal Life Support Organization's ECMO Extracorporeal Cardiopulmonary Support in Critical Care 4th edition* [38]. High-level planning that includes administrative support and resources are required to ensure the success of these low-volume high-risk transfers.

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Chapter 3
Airway Control, Mechanical Ventilation, and Respiratory Care

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Abstract Mechanical ventilation is often required for infants and children with cardiovascular disorders. This chapter briefly reviews the physiology of lung inflation and deflation with tidal breathing, the principles involved with the practice of conventional ventilation, the design and functional characteristics of conventional ventilators, the theory and practice of respiratory care, and special forms of artificial respiration.

3.1 Introduction

Mechanical ventilation is often required for infants and children with cardiovascular disorders. This chapter briefly reviews the physiology of lung inflation and deflation with tidal breathing, the principles involved with the practice of conventional ventilation, the design and functional characteristics of conventional ventilators, the theory and practice of respiratory care, and special forms of artificial respiration.

3.2 Physiology

The primary determinants of lung inflation are the pressure difference between the airway opening and the alveoli, the resistance of the conducting airways, and the compliance of the regional alveolar segments. *Time constant* is the product of compliance and resistance and is defined as the time taken to cause a given change in lung volume with a constant distending pressure. One time constant is the time taken to cause a 63% change in volume, and three time constants is the time taken to cause a 95% change in volume [1]. Expiration is for the most part passive, because of the elastic recoil of the lung, which is attributable to alveolar surface tension and tissue elasticity. Since inspiratory and expiratory resistances are different, their time constants may be different. Increased airway resistance and decreased chest and lung compliances would require a greater Ptp (transpulmonary pressure) to inflate the lung to the same lung volume. This imposes a greater workload on the respiratory muscles and increases the oxygen cost of breathing (OCB). When the oxygen supply–demand balance to the respiratory muscles is perturbed, respiratory failure may ensue due to muscle fatigue.

Systemic arterial oxygenation depends upon the inspired oxygen concentration and tension, lung volume, cardiac output, ventilation–perfusion matching, and magnitude of venous admixture or intrapulmonary shunting. A critical opening pressure is required to maintain both the patency of the terminal airways and alveolar volume. Alveolar collapse, which readily occurs below the critical opening pressure, leads to inadequate oxygenation due to increased intrapulmonary shunting resulting from ventilation–perfusion (V/Q) mismatch. Inadequate ventilation, reflected by an increase in arterial carbon dioxide ($PaCO_2$), results from a minute alveolar ventilation that is insufficient to meet the metabolic production of carbon dioxide.

3.2.1 Indications for Mechanical Ventilation

The primary indication for institution of assisted ventilation is respiratory failure. Apnea or respiratory arrest is an extreme form of respiratory failure and an absolute indication for mechanical ventilation.

Respiratory failure is generally defined as the presence of the following:

1. Inadequate oxygenation
2. Inadequate ventilation
3. Both

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Inadequate oxygenation, objectively, is defined as an arterial oxygen tension (PaO_2) less than 60 torr in room air, a PaO_2/FiO_2 ratio of <300, and a calculated or measured intrapulmonary shunt fraction >15%.

Inadequate ventilation is defined as an arterial carbon dioxide tension ($PaCO_2$) >50 torr in the absence of chronic hypercapnia. Impending respiratory failure characterized by rapidly rising $PaCO_2$, progressive respiratory distress, $PaCO_2$ out of proportion to the respiratory effort, or fatigue of respiratory muscles is a relative indication for mechanical ventilation.

Intubation and institution of mechanical ventilation under these circumstances are likely to be more controlled than when full-blown respiratory failure develops. Therefore, in critically ill children, it is preferable to institute mechanical ventilation before respiratory failure develops.

Cardiovascular dysfunction can result in decreased respiratory reserve, can increase respiratory work, and may ultimately result in respiratory failure. Positive pressure ventilation decreases lactate production by respiratory muscles during circulatory shock, and withdrawal of ventilatory support results in a marked increase in cardiac work [2, 3]. Therefore, mechanical ventilation may not only decrease the work of breathing under these circumstances but also decrease the oxygen demand of the heart.

Acute neurologic disorders may require mechanical ventilation for the following reasons:

1. Decreased ventilatory drive and acute hypercapnia
2. Loss of airway protective reflexes
3. To deliberately hyperventilate in disorders associated with intracranial hypertension to produce hypocapnia and respiratory alkalosis
4. Decreased ventilatory effort.

3.2.2 Modes of Ventilation

A detailed review of the physical characteristics and functional design of ventilators is beyond the scope of this chapter, and the reader is referred to several excellent reviews on this subject [4–8]. When the termination of a breath is under the control of the mechanical ventilator, it is referred to as a *mandatory breath*. A mandatory breath may be initiated by the ventilator or it can be initiated by the patient. A mandatory breath is always cycled by a preset time, pressure, or volume and is not under the control of the patient. Whether the mandatory breath is initiated by the ventilator or by the patient, the characteristics of the breath (changes in flow, pressure, and volume) and the inspiratory time of the breath are the same. *Assist control* refers to a mode of ventilation when a patient receives a combination of ventilator-initiated and patient-initiated mandatory breaths. When the initiation and termination of a breath is under the control of the patient's breathing efforts, it is referred to as *spontaneous breaths*. A spontaneous breath with an inspiratory pressure that is greater than the expiratory pressure is referred to as a *supported* or an *assisted* mechanical breath for which the trigger can be either pressure or flow. When all minute ventilation is provided by the ventilator, it is referred to *as total ventilatory support*. When all breaths are mandatory breaths, it is referred to as continuous mandatory ventilation (CMV). Total ventilatory support is provided entirely by CMV. When spontaneous breathing is responsible for some of the minute ventilation and the rest by the ventilator, it is referred to as *partial ventilatory support*. Minute ventilation provided by ventilator-initiated mandatory breaths is referred to as controlled mechanical ventilation, and those provided by assisted mechanical breaths (patient-initiated) are referred to as assisted mechanical ventilation (AMV). When spontaneous breathing is responsible for the entire minute ventilation without any assistance from the ventilator, then it is referred to as complete spontaneous breathing. Partial ventilatory support can be provided by CMV, AMV, or a combination of both. The two most common forms of controlled mechanical ventilation are *pressure-regulated* and *volume-regulated ventilation*.

3.2.3 Volume-Regulated Mandatory Breaths

Volume-regulated ventilation can be delivered either by volume-cycled breath, where inspiration is terminated after a preset volume is delivered, and inspiratory time is allowed to vary, or by volume-regulated time-cycled breaths, where the cycling mechanism is preset time, and the tidal volume delivered is regulated by adjusting the inspiratory flow rate. In volume-regulated ventilation, the tidal volume is delivered throughout inspiration. The peak inspiratory pressure (PIP) is variable and is dependent on the flow rate, the total resistance, and the total compliance of the ventilator circuit and the patient's lungs. Changes in resistance or compliance will be reflected by an increase in PIP, and the ventilator can be set to alarm at a pressure limit that is generally set 5–10 cm above the PIP.

Most modern ventilators deliver the preset tidal volumes quite reliably, but the tidal volumes delivered to the patient on a breath-to-breath basis may not always be constant. The tidal volume delivered by the ventilator is distributed between the ventilator circuit, the airways, and the patient's lungs.

The effective tidal volume (VT_{eff}) delivered to the patient can be approximated by the following formula: $VT_{eff} = VT_{del} - Cvent (PIP - PEEP)$, where VT_{del} is tidal volume delivered by the ventilator and C_{vent} is the compliance of the ventilator circuit. VT_{del} is equal to the inspired tidal volume, when there is no leak in the total respiratory system. But, when there is a leak in the system, such as with the use of uncuffed endotracheal tubes, then VT_{del} is less than the inspired tidal volume. During exhalation, expiratory flow curves depend on the type of expiratory resistance or PEEP valve in the system.

3.2.4 Pressure-Regulated Mandatory Breaths

Pressure-regulated ventilation can be either pressure-cycled or pressure-limited and time-cycled ventilation. In pressure-cycled ventilators, inspiration is terminated when a preset pressure limit is reached. In this mode of ventilation, the inspiratory time may vary depending on the changes in resistance and compliance of the total respiratory system. This mode of ventilation is not widely used these days except for intermittent positive pressure breathing treatments. Pressure-limited time-cycled ventilation is most commonly used in the neonate with respiratory distress syndrome and in children with ARDS. In this mode, inspiratory and expiratory times are constant, and the PIP reaches a preset limit quickly early in inspiration and is then maintained at that level during the rest of the inspiratory phase. Usually a high flow rate is used (4–10 L/kg/min). The tidal volume delivered depends on the compliance and resistance of the ventilator circuit and the patient's lungs. Pressure-controlled ventilation results in higher mean airway pressure for the same amount of minute ventilation.

3.2.5 Intermittent Mandatory Ventilation

Intermittent mandatory ventilation (IMV) refers to a pattern of controlled ventilation where spontaneous breathing is permitted. Between mandatory machine breaths, the patient can breathe spontaneously, and the required gas flow is delivered either through a continuous flow or a demand system [9]. The spontaneous breaths are not assisted by a ventilator breath. Therefore, the tidal volumes generated by the spontaneous breaths are dependent on the patient's effort alone and not on the ventilator support. When IMV is synchronized to the patient's inspiratory efforts, it is referred to as synchronized IMV (SIMV). Each time a synchronized breath is delivered, the machine recomputes the time required to deliver the next mandatory breath. In SIMV, the total number of mandatory breaths will only be equal to the preset frequency of mandatory breaths. SIMV breaths can be volume-regulated, or pressure-limited.

3.3 CPAP/PEEP

CPAP refers to the maintenance of positive airway pressure throughout the respiratory cycle with no positive pressure breaths being delivered to the patient. Positive end-expiratory pressure (PEEP) refers to the maintenance of positive airway pressure above atmospheric pressure at the airway opening at end expiration [10]. CPAP/PEEP can be applied by:

1. An underwater column
2. A water-weighted diaphragm
3. A venturi valve
4. A spring-loaded valve
5. A pressurized exhalation valve
6. A magnetic valve
7. A fixed or adjustable orifice

CPAP may be provided through the endotracheal tube, through specially designed nasal prongs or nasal cannula, or through a face mask.

3.3.1 Selection of Parameters for Mandatory Breaths

The first parameter is the VT_{eff}. A desirable VT_{eff} for most patients is 8–10 ml/kg. The end-inspiratory alveolar pressure should not exceed 40 cm of H_2O. During mechanical ventilation, end-inspiratory alveolar pressure can be estimated by measuring the end-inspiratory airway pressure using an end-inspiratory hold maneuver.

Ventilator rate is the next parameter to be selected and depends upon the age of the patient and the ventilatory requirements of the patient. The initial ventilator rate for a newborn infant usually ranges from 25 to 30/min; for a 1-year-old, between 20 and 25/min; and, for an adolescent, from 15 to 20/min.

The *inspiratory time* is selected to provide an inspiratory-to-expiratory time (I:E) ratio of at least 1:2 in most patients. Inspiratory time must be selected to allow sufficient time for all lung segments to be inflated.

Similarly, sufficient *expiratory time* must be provided for all lung segments to empty. If inspiration starts before the lung has completely emptied, this will result in air trapping and inadvertent PEEP.

PEEP is the next parameter to be selected. The level of PEEP will depend on the clinical circumstance. The goals of PEEP are listed below:

1. Increasing FRC above closing volume to prevent alveolar collapse
2. Maintaining stability of alveolar segments
3. Improvement in oxygenation
4. Reduction in work of breathing

The optimum PEEP is the level at which there is an acceptable balance between the desired goals and the undesired adverse effects.

Fraction of the inspired oxygen (F_iO_2) is the next parameter to be selected. F_iO_2 is adjusted to maintain an adequate PaO_2. In certain cyanotic heart diseases, it may be desirable to use the lowest possible FiO_2 to maintain an adequate balance between the pulmonary and systemic circulations.

3.3.2 Pressure Support Ventilation

In pressure support ventilation (PSV), the ventilator assists patient's own spontaneous effort with a mechanical breath with a preset pressure limit. The patient's spontaneous breath creates a negative pressure (pressure-triggering) or a change in flow through the circuit (flow-triggering), which triggers the ventilator to deliver a breath. With initiation, the machine delivers high inspiratory flow to achieve a peak airway pressure level that is selected by the operator [11–13]. The pressure limit stays constant as long as the patient's inspiratory effort is maintained with a variable gas flow rate from the ventilator [12, 13]. As inspiration continues, the inspiratory flow rate decreases. A threshold reduction in the flow rate is a signal for the termination of the inspiratory assist, with the opening of an expiratory valve, following which passive exhalation occurs [11–13]. PSV is entirely dependent on the patient's effort; if the patient becomes apneic, the ventilator will not provide any mechanical breath.

3.3.3 Dual Control Modes

Dual control modes are newer modes that allow the ventilator to control pressure or volume based on a feedback loop. They cannot control both at the same time, but rather one or the other. There are currently two techniques for performing dual control. In both these techniques of dual-control modes, there is an attempt made to assure a certain target tidal volume. These can be classified as dual control within a breath or dual control breath to breath.

Two examples of dual control modes within a breath are volume-assured pressure support (VAPS) (Bird 8400ST and Tbird, Bird Corp., Palm Springs, CA) and pressure augmentation (PA) (Bear 1000, Bear Medical, Riverside, CA). Both these techniques can operate during mandatory breaths (pressure-limited time-cycled) or pressure-supported breaths.

Dual-control breath-to-breath mode with mandatory pressure-limited time-cycled breaths is referred to as pressure-regulated volume control (PRVC with Siemens 300), adaptive pressure ventilation (APV with Hamilton Galileo), autoflow (Evita 4), or variable pressure control (Venturi), depending on the manufacturer. In this form of pressure-limited, time-cycled ventilation, delivered tidal volume is used as a feedback control for continuously adjusting the pressure limit. All breaths in these modes are time- or patient-triggered, pressure-limited, and time-cycled. One difference between devices is that the Siemens 300 only allows PRVC in the CMV mode. The newer $Servo_i$ ventilator and the other ventilators allow dual control breath to breath using CMV or SIMV. In this mode, the ventilator attempts to target the "desired" tidal volume and makes adjustments to the PIP to achieve the goals.

Dual control breath to breath in the pressure support mode quite simply is closed-loop pressure support ventilation, with tidal volume as the input variable. It is referred to as *volume support* (Siemens 300, Siemens Medical Systems, Inc., Danvers, MA) and *variable pressure support* (Venturi, Cardiopulmonary Corporation, New Haven, CT). All breaths are patient-triggered, pressure-limited, and flow-cycled. Volume support is selected with the mode selector switch, and the desired tidal volume is set. Similar to the PRVC mode described above, the pressure support level is adjusted to maintain the set tidal volume with changes in compliance and resistance. In addition to the volume support settings, a mandatory ventilator frequency must be set. This frequency is set based on the age of the patient.

3.4 Principles of Mechanical Ventilation

3.4.1 Alveolar Recruitment and Derecruitment

Alveolar recruitment with maintenance of lung volume by preventing derecruitment during mechanical ventilation is a goal during mechanical ventilation. The benefits of optimal lung recruitment and prevention of derecruitment are:

1. A reduction in the intrapulmonary shunt fraction and venous admixture resulting in an improvement in arterial oxygenation
2. Improvement in lung compliance
3. Prevention of repeated alveolar collapse and reopening which may ameliorate or prevent ventilator-induced lung injury

The primary determinants of alveolar recruitment and derecruitment are transpulmonary pressure and PEEP, respectively. Mean airway pressure has been shown to be an excellent marker of mean alveolar pressure [14]. Increasing mean airway pressure will improve oxygenation if there is alveolar recruitment. Recruitment of the lungs can be achieved by manual inflation to high airway pressures, increasing PEEP in a stepwise manner, application of a sign maneuver, using pressure-limited time-cycled ventilation with a high PIP, or combining titrated levels of PEEP with increased inflation pressures. Ventilatory sighs are effective in recruiting alveoli in ARDS [15].

3.4.2 Heart Failure

The goals in respiratory management in congestive heart failure are relief of work of breathing and reversing alveolar collapse. This can be provided by a judicious combination of controlled ventilation, PEEP, and sedation. The greater the inotropic support a heart needs, the greater should be the respiratory support provided. In adults with congestive heart failure, positive pressure ventilation improves cardiac output by unloading the left ventricle [16, 17]. Cardiopulmonary interactions ought to be taken into account in specific scenarios (see Chap. 4 on Heart-Lung Interactions in this book).

3.4.3 Postoperative Management After Repair of Congenital Heart Disease

Many infants and children require mechanical ventilation during the postoperative period. The duration of requirement of mechanical ventilation depends on several factors such as age of the patient, complexity of the cardiac lesion, complexity of the operative procedure, duration of bypass, duration of circulatory arrest, postoperative bleeding, and postoperative cardiopulmonary status. Prolonged intubation and mechanical ventilation are more likely in children under a year of age, with more complex heart lesions, prolonged bypass and prolonged circulatory arrest times, and postoperative respiratory failure and hemodynamic instability.

In the immediate postoperative period, patients should be on controlled mechanical ventilation until hemodynamic functions improve. Adequate PEEP should be applied to prevent and relieve atelectasis. The choice of ventilatory parameters depends on the goals for each individual patient. In patients with *pulmonary hypertension*, hyperventilation to provide respiratory alkalosis will decrease pulmonary vascular resistance and right ventricular afterload. In patients who have undergone a *Fontan procedure*, early extubation is desirable, and if that is not possible, then spontaneous ventilation should be encouraged. Since these patients are totally dependent upon venous return for their cardiac output, airway pressures must be kept at a minimum. High intrathoracic pressure may not only impede venous return but also decrease pulmonary blood flow from increased pulmonary vascular resistance.

3.4.4 Diseases with Abdominal Distention

Positive intra-abdominal pressure tends to elevate the diaphragm, decrease Ptp in the lung bases, and decrease alveolar lung volumes in the lung bases. In order to maintain normal lung volumes, a greater Ptp has to be generated. This increases the airway pressures during positive pressure ventilation and increases work of breathing during spontaneous breathing. During positive pressure ventilation, a higher Ptp may cause hyperinflation of the apical regions while restoring normal volumes in the bases. Therapy should be directed primarily toward reducing the intra-abdominal pressure.

3.4.5 Altering Inspired Oxygen and Carbon Dioxide Concentration

A low alveolar oxygen tension increases pulmonary vascular resistance (hypoxic pulmonary vasoconstriction) [18]. With certain types of congenital heart diseases, such as hypoplastic left heart syndrome, it is critical to control pulmonary blood flow and prevent pulmonary overflooding. One approach is to decrease the F_iO_2 to <0.21 by blending room air with nitrogen. The exact F_iO_2 delivered must be monitored to avoid administering excessively low inspired oxygen. The other approach especially in mechanically ventilated patients, both preoperatively and postoperatively, is to increase the inspired carbon dioxide concentration (F_iCO_2) [19], which increases pulmonary vascular resistance. The advantage of increased F_iCO_2 is the ability to ventilate without producing hypocarbia. The disadvantage is an increased spontaneous ventilatory drive due to an increased $PaCO_2$. This increases the work of breathing and with marginal cardiac reserve may impose undue strain on the heart. Therefore, neuromuscular blockade and total ventilatory support may be necessary with increased F_iCO_2 to avoid an increased workload on the heart.

3.4.6 Inhaled Nitric Oxide

Inhaled nitric oxide produces selective pulmonary vasodilation. Indications for inhaled nitric oxide include diaphragmatic hernia, pulmonary hypertension after repair of congenital heart disease, primary pulmonary hypertension,

and isolated right heart failure. In severely hypoxemic babies with pulmonary hypertension, inhaled NO rapidly increases arterial oxygen tension without causing systemic hypotension [20–23]. Nitric oxide binds to hemoglobin to produce methemoglobin. Therefore, methemoglobin levels should be monitored during administration of nitric oxide. In addition, nitric oxide combines with oxygen to form nitrogen dioxide. Nitrogen dioxide is known to cause lung injury. Therefore, the concentration of nitrogen dioxide should be monitored in the inspired gas to keep it below 1–2 ppm.

3.4.7 Negative Pressure Ventilation in Cardiovascular Disorders

Several studies have shown beneficial effects of *negative pressure ventilation*, specifically in certain children after cardiac surgery [24–28]. In patients with Fontan-type operations, negative pressure ventilation increased pulmonary blood flow and cardiac output and also decreased the pulmonary valvular incompetence in patients with restrictive right heart physiology after repair of Tetralogy of Fallot [25]. In children after repair of total cavopulmonary connection and Tetralogy of Fallot and after Fontan-type procedures, negative pressure ventilation provided using a Hayek external high-frequency oscillator improved cardiac output by 42–46% almost entirely by an increase in stroke volume with improvement in mixed venous oxygen saturation [26]. A similar finding was observed in children after transcatheter occlusion of an asymptomatic patent ductus arteriosus and after open heart surgery [27]. Raine et al. in 1992 reported that negative pressure ventilation is a viable alternative to positive pressure ventilation in patients with phrenic nerve palsy after pediatric cardiac surgery by reducing the need for diaphragmatic plication and facilitating weaning from positive pressure ventilation [28]. These studies show that negative pressure ventilation is a useful technique in selected patients after cardiac surgery where positive pressure ventilation is not desirable or results in unwanted hemodynamic effects.

3.4.8 High-Frequency Ventilation

High-frequency ventilation (HFV) refers to diverse modes of ventilation characterized in general by supraphysiologic ventilatory frequencies (>60 cycles/min) and low tidal volumes (less than or equal to physiologic dead space during conventional ventilation). Four distinct methods of HFV are recognized: high-frequency positive pressure ventilation (HFPPV), high-frequency jet ventilation (HFJV), high-frequency oscillatory ventilation (HFOV), and high-frequency chest wall oscillation (HFCWO). Only HFPPV, HFJV, and HFOV have been extensively used clinically. The principal theoretical advantage for the use of HFV lies in the ability to ventilate effectively at low airway pressures.

Recent studies have suggested a role for HFV in children after cardiac surgery and with ARDS [29–34]. HFJV has been shown to improve cardiac function after a Fontan procedure [29]. HFJV and HFOV have been shown to improve oxygenation and ventilation compared with conventional ventilation in children with respiratory failure [31–34]. There are many reported strategies while using HFV:

1. "High lung volume strategy," which requires HFV to be provided at a mean airway pressure that is at least 3–5 cm higher than with conventional ventilation.
2. Combined HFV and conventional ventilation (usually used with HFJV), where conventional tidal breaths are interposed during HFV usually at a rate of 5–8 breaths/min.
3. Application of HFV at the same mean airway pressure as conventional ventilation. The high lung volume strategy seems to be the most promising one at least for HFOV.

3.5 Respiratory Care During Mechanical Ventilation

3.5.1 Pulmonary Hygiene

The goals of pulmonary hygiene are clearance of secretions for the prevention and relief of atelectasis. The most effective method of clearing secretions is a combination of changing body position and vigorous coughing by the patient [35]. When the patient is unable to cough effectively, it is common practice to resort to chest physiotherapy and active suctioning of the trachea. Chest physiotherapy refers to a variety of respiratory maneuvers performed to aid in the clearance of airway secretions and promoting lung expansion. These are:

1. Postural drainage
2. Chest percussion and chest vibration
3. Deep breathing exercises

The efficacy of chest physiotherapy in intubated patients is unclear. For details on the specific types of secretion clearance techniques, the reader is referred to several other reviews [36, 37].

3.5.2 Weaning from Mechanical Ventilation

Weaning is defined as liberation from mechanical ventilation while allowing spontaneous breathing to assume the responsibility for effective gas exchange. It can be considered a success when a patient can maintain effective gas exchange with complete spontaneous breathing. It can be considered a failure when spontaneous efforts are incapable of sustaining effective gas exchange without mechanical ventilator support. Extubation is defined as the removal of an endotracheal tube. The timing of extubation should coincide with an assessment that the patient is capable of maintaining effective gas exchange without any mechanical ventilator support. It is important to avoid both premature extubation and unnecessary prolongation of mechanical ventilation. Weaning should start:

1. When the underlying disease process is improving
2. When gas exchange is adequate
3. When no conditions exist that impose an undue burden on the respiratory muscles, such as cardiac insufficiency, severe hyperinflation, severe malnutrition, and multiple organ system failure
4. When the patient is capable of sustaining spontaneous ventilation as ventilator support is decreased without expending an excessive amount of energy

Patients cannot be arbitrarily forced to wean. The pathophysiologic determinants of weaning outcome include the following:

1. Adequacy of pulmonary gas exchange
2. Respiratory drive
3. Respiratory muscle performance and capacity
4. Respiratory muscle load
5. Amount of dead space ventilation
6. Work of breathing and ventilatory requirements

3.5.3 Weaning Problems

Trial failure is defined as a failure to sustain effective gas exchange and breathing during a trial of spontaneous breathing while still intubated [38]. *Extubation failure* is defined as the requirement for re-intubation within 48 h after extubation. Some patients take longer than others to wean. Factors that prolong the weaning process are:

1. Slow resolution of the underlying disease process
2. Ventilatory pump failure
3. Psychological factors

In many instances, weaning is delayed due to the slow resolution of the underlying disease process. Phrenic nerve injury usually results as a complication of birth trauma or operative procedures involving the heart and other thoracic structures [39–42]. This may result in either pareisis or paralysis of one or both hemidiaphragms.

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Chapter 4
Heart–Lung Interactions

Shekhar T. Venkataraman

Abstract One of the key functions of the respiratory and circulatory systems is to transfer oxygen from the atmosphere to the tissues and carbon dioxide from the tissues to the atmosphere. To accomplish this, the two systems need to act in concert and consequently interact with each other in many different ways. Broadly, these interactions can be classified into *neural*, *humoral*, *functional*, and *mechanical*.

4.1 Introduction

One of the key functions of the respiratory and circulatory systems is to transfer oxygen from the atmosphere to the tissues and carbon dioxide from the tissues to the atmosphere. To accomplish this, the two systems need to act in concert and consequently interact with each other in many different ways. Broadly, these interactions can be classified into *neural*, *humoral*, *functional*, and *mechanical*.

The central nervous system exerts control over both the respiratory and circulatory systems through afferent feedback and efferent effectors. Neural interactions refer to the changes in one system that is mediated by these neural connections when the other system is perturbed. For example, hypoxemia stimulates peripheral chemoreceptors that trigger a ventilatory response of hyperventilation and hyperpnea [1]. Similarly, lung inflation can induce reflex changes in heart rate. These are examples of neural heart–lung interactions.

Many humoral substances are released, processed, filtered, or metabolized by the lungs. These include cytokines, prostaglandins, and vasoregulatory peptides [2]. Cardiovascular function may be affected by many of these substances. These are referred to as humoral heart–lung interactions.

When the heart fails, breathing and gas exchange can be compromised. Heart failure may result in pulmonary edema, which increases the work of breathing and increases intrapulmonary shunting resulting in hypoxemia. Similarly, chronic lung disease may increase pulmonary vascular resistance (PVR) and cause pulmonary hypertension, which may result in right ventricular failure. These are referred to as functional heart–lung interactions.

Mechanical heart–lung interactions refer to those interactions that are due to lung inflation and deflation. This chapter deals exclusively with the mechanical heart–lung interactions.

4.2 Primary Determinants of Hemodynamic Effects of Ventilation

Both spontaneous and positive pressure ventilation (PPV) increase lung volume during inspiration. During spontaneous breathing, intrathoracic pressure (ITP) is negative, whereas during positive pressure breathing, it is positive. Both lung inflation and ITP can independently affect the function of the heart. Heart–lung interactions can, therefore, be grouped into interactions involving changes in lung volume or ITP. Since lung volume changes are similar, the interactions can be grouped into three phenomena:

1. Inspiratory increase in lung volume
2. Decrease in ITP with spontaneous inspiration (SV)
3. An increase in ITP with PPV

Heart–lung interactions can also be understood by the effect of lung inflation and changes in ITP on the factors that affect global cardiac performance, i.e., heart rate, preload, contractility, and afterload.

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4.3 Changes in Heart Rate

Heart rate may be affected by lung inflation and changes in ITP by many mechanisms. Lung inflation at normal tidal volumes increases heart rate by inhibiting the vagus nerve [3]. Heart rate may also be affected by changes in cardiac output induced by heart–lung interactions as discussed subsequently.

4.3.1 Right Ventricular Preload

Right ventricular (RV) preload is determined by systemic venous return. Venous return is determined by the gradient between mean systemic pressure (Pms) and the right atrial (RA) pressure [4]. Mean systemic pressure, which is the upstream pressure for venous return, is determined by blood volume, vascular tone, and blood flow distribution within the vascular reservoirs. RA pressure (Pra) is directly affected by changes in ITP. Venous return is maximized at a Pra that is just below atmospheric pressure. SV decreases Pra and increases the gradient to venous return and results in an increased right ventricular preload. On the other hand, PPV increases Pra and decreases the gradient to venous return and, therefore, decreases right ventricular preload. Under normal conditions, SV results in an increase in RV preload and an increase in cardiac output. Venous return becomes maximal due to flow limitation with more negative pressure swings such as that may occur during severe airflow obstruction with status asthmaticus. Under normal conditions, PPV results in a decrease in RV preload and therefore a decrease in cardiac output. The decrease in RV preload due to PPV can be mitigated by fluid administration, which increases the circulating blood volume and the mean systemic pressure. Ventilation can also alter venous return by affecting Pms. During inspiration, diaphragmatic descent can increase intra-abdominal pressure, which increases Pms. Recent studies by Fessler et al. [5] showed that PEEP applied during mechanical ventilation decreased venous return by compression of the intrathoracic inferior vena cava by the hyperinflated lung.

4.3.2 Right Ventricular Afterload

PVR is lowest at functional residual capacity (FRC). A change in lung volume on either side of FRC increases total PVR. The increase in PVR below FRC is primarily due to two mechanisms:

1. Alveolar hypoxia and hypoxic pulmonary vasoconstriction
2. Kinking of vessels with atelectasis

The increase in PVR above FRC is primarily due to alveolar vessel compression. The lung blood vessels can be partitioned into alveolar and extra-alveolar vessels based on their behavior during lung inflation [6]. Alveolar vessels are compressed while extra-alveolar vessels dilate during lung inflation. The increase in PVR with PPV can be explained by the West's zones of the lung [7]. The blood flow through a lung segment is determined by the pressures in the pulmonary artery (Ppa), alveolus (Palv), and pulmonary vein (Ppv). Under Zone 3 conditions, the pulmonary blood flow (PBF) is determined by the difference between Ppa and Ppv and not affected by Palv. Under Zone 2 conditions, the PBF is determined by the difference between Ppa and Palv and is not affected by Ppv. PBF is then directly proportional to the Palv. Under Zone 1 conditions, there is, theoretically, no flow possible through the alveolus. In neonatal animals, studies have shown that mechanical ventilation with PEEP increases PVR and the increase in PVR is directly proportional to the increase in mean airway pressure or level of PEEP applied [8, 9]. In neonatal animals, the increase in PVR with PEEP has two components: one due to compression of alveolar vessels and the other due to active vasoconstriction. This PEEP-induced pulmonary vasoconstriction is Ca^{2+} channel dependent and is dose dependent with PEEP. PEEP-induced pulmonary vasoconstriction may have clinical implications for those children with a very reactive pulmonary vasculature [9].

4.3.3 Left Ventricular Preload

Left ventricular (LV) preload is affected by many mechanisms. Changes in RV preload will directly affect LV preload. During spontaneous inspiration, RV preload increases followed by a few beats later with an increase in LV preload. Instantaneous effects are, on the other hand, mediated through ventricular interdependence. For example, when RV end-diastolic volume increases, LV end-diastolic volume and compliance decrease, leading to reduced LV filling. This is thought to be the mechanism for pulsus paradoxus. An increase in PVR may increase RV volume causing the interventricular septum to shift into the LV. This will also decrease LV compliance and filling. When the lung is inflated, it can cause deformation and compression of the cardiac fossa [10].

4.3.4 Left Ventricular Afterload

Left ventricular afterload can be defined as the maximal systolic wall tension. It can be calculated as the transmural pressure of the ventricle during systole, which is the intracavitary

pressure minus the pericardial pressure. When ITP increases, pericardial pressure increases as well. With SV, transmural pressure increases, and with PPV, transmural pressure decreases. Since transmural pressure is reflective of ventricular afterload, PPV decreases LV afterload, and spontaneous breathing increases LV afterload. The practical application of this concept is given below.

4.4 Practical Applications of Heart–Lung Interactions

4.4.1 Functional Heart–Lung Interactions

Normally, oxygen cost of breathing under resting conditions is about 5% of the total oxygen consumption [11]. When the oxygen demand of the respiratory muscles outstrips the cardiovascular system's ability to supply it, respiratory pump failure ensues [12].

4.4.2 Use of Respiratory Variation in Hemodynamics to Predict Preload Responsiveness

During spontaneous breathing, the pleural pressure decreases. If the right atrial pressure drops in response to a spontaneous inspiration, it indicates that the venous return curve is intersecting the ascending part of the cardiac function curve. If the heart is on the ascending part of the cardiac function curve, it should respond to an increased preload with an increased output. If, on the other hand, the venous return curve intersects the plateau of the cardiac function curve, then spontaneous inspiration does not result in a decrease in right atrial pressure, and such a heart will not be preload responsive. This has been demonstrated to be true in patients [13].

Variations in systolic arterial pressure can also be used to determine preload responsiveness. In a preload responsive heart, there is an increase in systolic blood pressure followed by a fall in blood pressure during the inspiratory phase of mechanical ventilation. The normal difference between the peak increase and peak decrease is about 5–10 mmHg. In adults, the magnitude of this systolic pressure variation predicts responsiveness to increased preload [14–16]. Thus, if the pulse pressure variation was greater than 15%, then cardiac output always increased, and if it was less than 15%, then cardiac output did not increase in response to fluid loading [17]. On the other hand, in a preload-independent heart, such as with congestive heart failure, positive pressure inspiration will result in an increase in systolic blood pressure during inspiration due to a decrease in left ventricular afterload with no decrease below the baseline.

4.4.3 Effects of Initiating Mechanical Ventilation in Patients with Heart Failure

Mechanical ventilation may improve cardiovascular performance in patients with heart failure by many mechanisms. By reducing the work of breathing, the demand on the heart is reduced. PEEP applied during PPV decreases alveolar edema formation and improved gas exchange. PEEP also helps recruit atelectatic lungs, thereby improving lung mechanics. Moreover, PPV decreases LV afterload and improves LV emptying [18]. PPV decreases lactic acid production by respiratory muscles during circulatory shock, and withdrawal of ventilatory support results in a marked increase in cardiac work [19, 20].

4.4.4 Mechanical Ventilation and Postoperative Issues After Glenn or Fontan Procedures and Surgery for Univentricular Hearts

Following a simple Fontan procedure for tricuspid atresia where the PBF is passive, any increase in ITP will not only decrease venous return but also increase PVR. Therefore, PPV may be detrimental to cardiac output in these patients. Early extubation and spontaneous breathing are to be encouraged. Some patients may develop atelectasis and may need lung inflation or a distending pressure to maintain adequate lung volumes. Negative pressure ventilation offers an attractive alternative to these patients. In patients with Fontan-type operations, PBF and cardiac output increase with spontaneous inspiration, and PPV decreases antegrade PBF [21–23]. These studies show that negative pressure ventilation is a useful technique in selected patients after cardiac surgery, whereas PPV is not desirable, or it results in unwanted hemodynamic effects.

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Chapter 5
Cardiac Catheterization

Sara M. Trucco and Jacqueline Kreutzer

Abstract Over the last 80 years, the field of diagnostic and interventional cardiac catheterization has grown tremendously. In the current era, cardiac catheterization remains a key tool in the management and treatment of patients with congenital heart disease, in particular for those who are critically ill. For many simple cardiac lesions, interventional cardiac procedures have replaced open surgical repairs. For those with more complex cardiac disease, cardiac catheterization works hand in hand with surgical interventions to optimize the patient's care.

This chapter reviews the indications for cardiac catheterization and basic concepts in hemodynamics and angiography and discusses the expanding role of catheter-based interventions for individual cardiac lesions. Post-catheterization intensive care considerations, including procedural complications, are also reviewed in detail.

Although the use of diagnostic cardiac catheterization has decreased with the advances in noninvasive imaging, it continues to be a significant tool in the management of many complex congenital heart defects. This chapter summarizes basic aspects of diagnostic cardiac catheterization including hemodynamic evaluation and angiography and clinical indications and reviews the role of cardiac catheterization in the critically ill and the role therapeutic cardiac catheterization plays in pediatric cardiology. Possible reasons for admission to the intensive care unit (ICU) after cardiac catheterization and subsequent management are discussed in each section.

Nowadays, transcatheter intervention has replaced surgery for many simple cardiac defects. In complex heart disease, the role of catheter interventions works hand in hand with surgery, increasing treatment strategies and allowing an improved outcome.

5.1 Introduction

Invasive pediatric cardiology developed as a subspecialty over the past five decades after the first pediatric angiogram was performed by Agustin Castellanos in 1937 [1]. With the introduction of the balloon atrial septostomy by William Rashkind to alleviate cyanosis in transposition of the great arteries [2], the field of interventional pediatric cardiology was initiated and subsequently expanded explosively. Cardiac catheterization plays a role in almost every heart defect.

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5.2 Diagnostic Cardiac Catheterization

5.2.1 Indications

Although the use of preoperative diagnostic cardiac catheterization has decreased, and continues to decrease significantly for most lesions with the advances of noninvasive testing, there are specific conditions for which it is thought to be necessary:

1. Pulmonary atresia with intact ventricular septum, to rule out coronary anomalies which would preclude a biventricular repair.
2. Tetralogy of Fallot with pulmonary atresia, multiple aortopulmonary collaterals, and other conditions when collaterals are suspected, or when central pulmonary arteries are very small or cannot be identified.
3. Single ventricle variants, prior to Stages II and III of palliation.
4. Primary or secondary pulmonary artery hypertension, particularly outside of infancy.

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5. Pulmonary vein anomalies with or without stenosis (if anatomy cannot be well identified by noninvasive methods).
6. Coronary artery anomalies (although noninvasive technologies continue to advance in resolution, for most children, particularly in infants, angiography continues to be the gold standard to diagnose coronary artery abnormalities).
7. Postoperative evaluation: To evaluate postoperative conditions, diagnostic cardiac catheterization continues to be used routinely, often as a first step prior to transcatheter interventions (see below). Examples include evaluation of homograft or conduit stenosis, residual shunts, and palliated single ventricle patients or evaluation of most postoperative lesions unexplained fully by noninvasive testing.
8. Pretransplant evaluation.
9. Prior to transcatheter intervention: Diagnostic cardiac catheterization is performed in all patients with indication for transcatheter intervention, to determine the need for intervention, which is performed during the same procedure. Immediately after intervention, repeat diagnostic cardiac catheterization is performed to assess the results of the intervention.
10. Others: Diagnostic cardiac catheterization may also be necessary in patients with common conditions and unusual clinical presentation and whenever symptoms cannot be fully explained by noninvasive testing.

It is likely that over time the use of diagnostic cardiac catheterizations will continue to evolve, with a significant decrease in its use for common lesions and increased demand of studies on patients with complex postoperative conditions, which, in the past, survivors would not have existed. In the current era, simple diagnostic cardiac catheterizations are indeed a rarity. Almost 50% of planned diagnostic cardiac catheterizations in patients with single ventricle physiology result in interventions. These include, for example, coil occlusion of venous or arterial collaterals, balloon dilation and/or stent placement for venous or arterial stenoses, or device closure of baffle leaks or fenestration.

5.2.2 Access

Most common sites of vascular access are the femoral artery and vein at any age and the umbilical vessels in the newborn [3]. Other access sites (subclavian, jugular, hepatic) may be necessary when standard sites are not available, or in patients with complex anatomy (i.e., post bidirectional Glenn), or when certain interventions are planned (i.e., transhepatic access in a patient with occluded femoral vessels and need for transeptal puncture or internal jugular access for transcatheter closure of an apical ventricular septal defect). The preferred and most commonly used technique for access is the percutaneous Seldinger technique [3], which has become highly successful in children, making surgical cutdowns almost historical.

The smallest French size of catheter and/or sheath which would allow adequate hemodynamic and angiographic evaluation should be chosen.

Heparin is administered intravenously (100 units/kg) at the start of the procedure, and ACTs are monitored to be kept above 200 s [4].

Most recently, vascular ultrasound-guided access has become a common approach. It is thought that visualization of the vascular anatomy with directed puncture under imaging would result in a reduction of vascular access-related adverse events, avoid failed attempts at occluded vessels, and help identify optimal sites [5].

5.2.2.1 Hemodynamic Evaluation

Pressure and Saturations Accurate pressure measurements are essential for hemodynamic diagnosis. Two simultaneous transducers are used and should be accurately calibrated. Normal tracings have been published widely (Table 5.1) [6–8]. The most common sequence of measurements includes:

- Superior vena cava (SVC) saturation: occasionally pressure is recorded as well (patients with surgical caval anastomoses, transvenous pacing wires, or history of indwelling lines, in whom a pullback from superior vena cava to right atrium should be recorded)
- Right atrium (RA) (pressure and saturation)
- Right ventricle (RV) (pressure and saturation)
- Pulmonary arteries (PA) (pressure and saturation) and bilateral wedge pressures simultaneous with systemic ventricular end-diastolic pressure
- Measurement of oxygen consumption (this can be selectively measured or assumed according to tables normalized by heart rate and age)

Table 5.1 Hemodynamic values considered normal in children

Site of pressure measurement	Average normal	Range
Right atrial mean	3 mmHg	0–8 mmHg
Right ventricular	24/4 mmHg	15–35 mmHg
Pulmonary artery (mean)	21/9 (12) mmHg	11–26/2–14 (8–19)
Pulmonary capillary wedge or left atrial mean	8 mmHg	2–12 mmHg
Left ventricular	96/8[a]	60–130/–12[a]
Systemic arterial	110/65[a]	Largely variable with age

Values derived from combination of published normal hemodynamic data
[a]Pressure variable with age normal values for systemic blood pressure

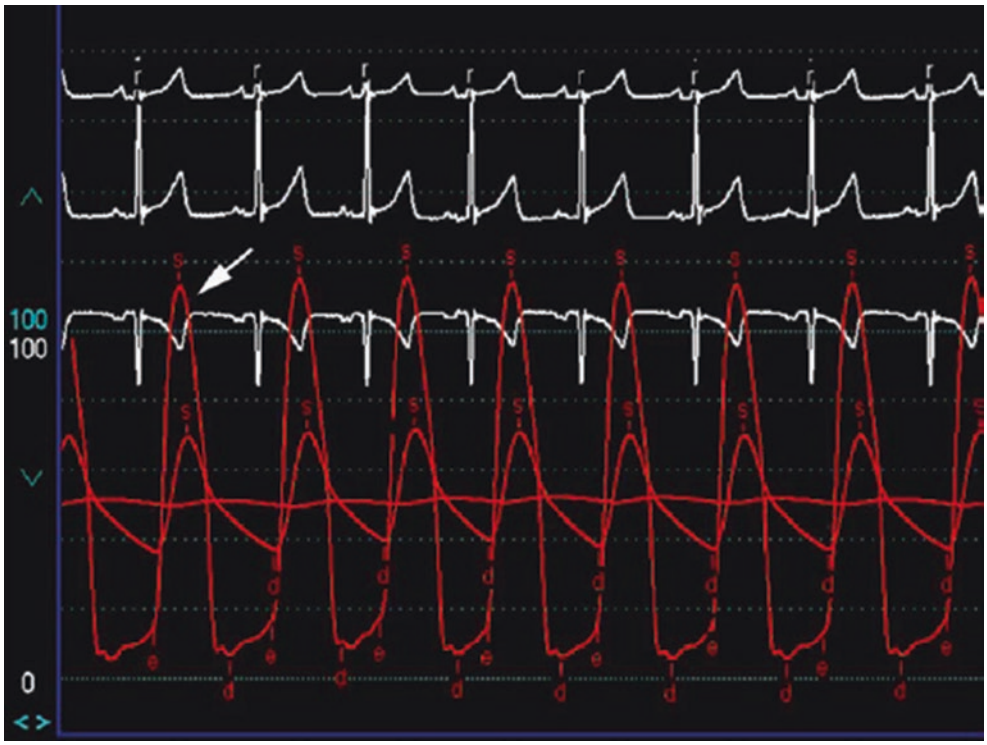

Fig. 5.1 Pressure tracings are demonstrated from the left ventricle (arrow) and the ascending aorta simultaneously. There is a peak gradient of 44 mmHg, indicating moderate aortic stenosis

- Second set of saturations in the pulmonary artery, aorta, and superior vena cava, which should be consistent with the initial values obtained, assuming an unchanged condition
- Pullback tracings from pulmonary artery to the right atrium and systemic ventricle to the descending aorta

The sequence of measurements may vary according to the underlying diagnosis. In all patients with cyanosis, pulmonary venous saturation should be measured whenever possible. Pulmonary venous wedge pressures are measured to determine PA pressures in patients with difficult access to the pulmonary arteries. An abnormal value above 20 mmHg should be confirmed with direct pulmonary artery pressure measurement. Gradients across lesions can be determined with two catheters (one positioned proximal and one distal to the stenosis) (Fig. 5.1) or via pullback recordings.

Cardiac Output and Shunts Based on the Fick's principle, by measuring oxygen consumption (VO_2) and oxygen content in systemic arterial, systemic venous, pulmonary arterial, and pulmonary venous blood, it is possible to determine the cardiac output (CO) or Qs and the pulmonary blood flow or Qp and calculate shunts. The cardiac index is estimated by relating the CO to the body surface area [7]. The saturation of the superior vena cava is considered the best representative of the mixed venous saturation [6, 7].

$$\text{CO or Qs}\left(\text{l}/\text{min}\right)=\frac{\text{VO}_2\left(\text{ml O}_2/\text{min}\right)}{\text{SA O}_2\text{ content}-\text{SV O}_2\text{ content}\left(\text{ml O}_2/\text{l}\right)}$$

SA= Systemic Artery
SV= Systemic Vein
O_2 Content = saturation × Hb (g/dl) × 1.36 mlO_2/g × 10 + (pO_2 × 0.03 mlO_2/l)

In patients receiving inhaled O_2 and an arterial pO_2 over 100, dissolved O_2 should be accounted for. This is particularly important for the determination of lability of pulmonary vascular resistance to selective pulmonary vasodilators in patients with pulmonary hypertension and intracardiac shunts.

$$\text{Qp}\left(\text{l}/\text{min}\right)=\frac{\text{VO}_2\left(\text{ml O}_2/\text{min}\right)}{\text{PV O}_2\text{ content}-\text{PA O}_2\text{ content}\left(\text{ml O}_2/\text{l}\right)}$$

PV = Pulmonary Vein
PA = Pulmonary Artery

Qp/Qs can be determined to estimate clinical significance of left-to-right shunt and is more useful than shunt calculations per se. The effective pulmonary blood flow (Qe) is the amount of deoxygenated blood which gets oxygenated.

$$\text{Qe}\left(\text{l}/\text{min}\right)=\frac{\text{VO}_2\left(\text{ml O}_2/\text{min}\right)}{\text{PV O}_2\text{ content}-\text{SA O}_2\text{ content}\left(\text{ml O}_2/\text{l}\right)}$$

The absolute left-to-right shunt is the difference between the Qp and the Qe. Similarly, the absolute right-to-left shunt is the difference between the Qs and the Qe.

In patients with no source of right-to-left or left-to-right shunting, cardiac output can be accurately determined by thermodilution [9]. This is particularly useful in patients with left-sided obstructive lesions (i.e., congenital aortic stenosis) or cardiomyopathies. Thermodilution would be inaccurate in patients with pulmonary regurgitation (i.e., postoperative tetralogy of Fallot), severe peripheral pulmonary artery stenosis, or tricuspid regurgitation and cannot be used in the presence of any intracardiac shunting. A normal CI is 3–3.5 l/min/m^2.

Resistances Vascular resistances are determined by dividing the pressure difference through the circulation being considered by the flow (l/min) across it and are expressed in mmHg per l/min (Wood units or hybrid resistance units), or converted into metric resistance units (dyne sec cm-5) or absolute resistance units, by multiplying by 80. These units are more commonly used in adults, and not in children, for whom resistances are expressed by body surface area, giving a resistance index. A normal pulmonary vascular resistance (PVR) is less than 3 indexed units (mmHg l/min/m^2) [6]. The systemic vascular resistance (SVR) is typically 10–15 indexed units.

$$\text{PVR} = \frac{\text{Mean pulmonary artery pressure} - \text{Mean left atrial pressure or pulmonary vein pressure}}{\text{Qp indexed}}$$

$$\text{SVR} = \frac{\text{Mean arterial blood pressure} - \text{Mean right atrial pressure}}{\text{Qs indexed}\left(\text{or CI}\right)}$$

$$\text{PVR} = \frac{\text{Mean PA pressure} - \text{Mean LA pressure}}{\text{QP index}}$$

$$\text{SVR} = \frac{\text{Mean AO pressure} - \text{Mean RA pressure}}{\text{QS index}\left(\text{or CI}\right)}$$

Calculations should be performed in room air or the patient's baseline condition. Different specific conditions may need to be studied according to the patient's diagnosis, such as drug testing (i.e., response of pulmonary vascular resistance to nitric oxide) or transcatheter balloon testing (i.e., test occlusion of atrial septal defect in a patient with mitral stenosis or small left-sided structures or test occlusion of a source of right-to-left shunt through an atrial septal defect or Fontan fenestration). To accurately estimate the pulmonary vascular resistance in patients with branch pulmonary artery stenoses, it is necessary to determine the distribution of pulmonary blood flow to each lung by lung scintigraphy or MRI. Since the resistances are in parallel, the total resistance can then be calculated using the formula:

$$\frac{1}{\text{Total resistance}} = \frac{1}{\text{Right lung resistance}} + \frac{1}{\text{Left lung resistance}}$$

This would be important to take into consideration when evaluating hemodynamics in a patient with single branch pulmonary artery proximal stenosis. The pressure may be elevated in the contralateral lung, but the overall resistance may be normal if calculated accurately.

Valve Areas Valve areas in pediatrics are calculated similarly as in adults, using the Gorlin and Gorlin formulae. A valve area is directly proportional to the flow across the valve and inversely related to the square root of the mean pressure drop across it [7].

$$\text{Aortic or pulmonary valve area} = \frac{\text{Systolic flow}\left(\text{ml/s}\right)}{\left(44.5\right)\times\left(\begin{array}{l}\text{square root}\\ \text{of mean systolic}\\ \text{gradient}\end{array}\right)}$$

$$\text{Systolic flow}\left(\text{ml/s}\right) = \frac{\left(\text{C.O.}\right)\times\left(\text{R to R interval}\right)}{\left(60\right)\times\left(\text{systolic ejection time}\right)}$$

$$\text{Mitral or tricuspid valve area} = \frac{\text{Diastolic flow}\left(\text{ml/s}\right)}{\left(31.5\right)\times\left(\begin{array}{l}\text{square root}\\ \text{of mean diastolic}\\ \text{gradient}\end{array}\right)}$$

$$\text{Diastolic flow}\left(\text{ml/s}\right) = \frac{\left(\text{C.O.}\right)\times\left(\text{R to R interval}\right)}{\left(60\right)\times\left(\text{diastolic ejection time}\right)}$$

The mean gradient can be accurately obtained by planimetry. Otherwise, it can be approximated from the average of the gradients measured from vertical lines placed 1 mm apart throughout the area in between the pressure tracings (either ventricular and arterial, or auricular and ventricular).

5.2.3 "Test" Conditions

The hemodynamic response to specific conditions can be tested in the catheterization laboratory to plan further surgical, transcatheter, or medical intervention. Hemodyamics and calculations are determined before and after 10 min in the new condition. Examples of these include:

1. Balloon test occlusion of an atrial septal defect or a fenestration prior to the closure in patients with right-to-left shunting and abnormal right heart structures

2. Test occlusion of a Blalock-Taussig shunt before coil embolization
3. Test occlusion of a patent ductus arteriosus to determine the presence of aortic coarctation or ductal-dependent hypoplastic arch
4. Drug studies (testing of response of the pulmonary vascular bed to selective vasodilators in pulmonary hypertension, or the effect of intravenous verapamil in patients with hypertrophic cardiomyopathy)
5. Rhythm modification (i.e., patients with Fontan circulation and junctional rhythm can be tested in the catheterization laboratory with atrial pacing to determine the hemodynamic benefit of pacemaker implantation; some with cardiomyopathy can be studied to test effects of biventricular pacing or different pacing modalities)
6. Fluid challenge (administration of a fluid bolus to evaluate for underlying diastolic dysfunction or restrictive/constrictive physiology).

5.2.3.1 Angiographic Evaluation

Angiography is most commonly performed using angiographic catheters (i.e., pigtail or Berman) connected to a power injector [10]. For small structures, selective injection can be performed by hand using any end-hole catheter. Occasionally, balloon occlusion angiography is preferred, where the injection occurs proximal (Berman catheter) or distal (wedge end-hole catheter) to the balloon. Biplane angiography is preferred in congenital heart disease and, particularly, necessary in infants and in patients of any age when interventional procedures are being considered. Common angiographic views for diagnosis of congenital heart defects are [10, 11]:

- Straight AP 0°/lateral 90°: (a) right ventriculogram in normal related to great arteries, transposition of the arteries, double outlet right ventricle, pulmonary atresia with intact ventricular septum and postoperative tetralogy of Fallot, and single ventricle ventriculograms. (b) Venous pathways, systemic and pulmonary arteries, and pulmonary veins
- Cranial frontal (+20°–30°) and straight lateral: particularly used to visualize the right ventricular outflow tract and main pulmonary artery with bifurcation in tetralogy of Fallot or in patients with pulmonary stenosis
- Caudal frontal, extreme (−30° to 45°): (a) a "laid-back" aortogram technique, particularly useful in transposition of the great arteries to visualize coronary artery anomalies (Fig. 5.2) [11] or after Norwood to visualize distal arch. (b) Branch pulmonary artery stenosis, to visualize bifurcation
- Long axial oblique (70° left anterior oblique and 20–30° cranial on the lateral camera): particularly useful for left ventriculogram to visualize ventricular septal defects and left ventricular outflow tract (Fig. 5.3)

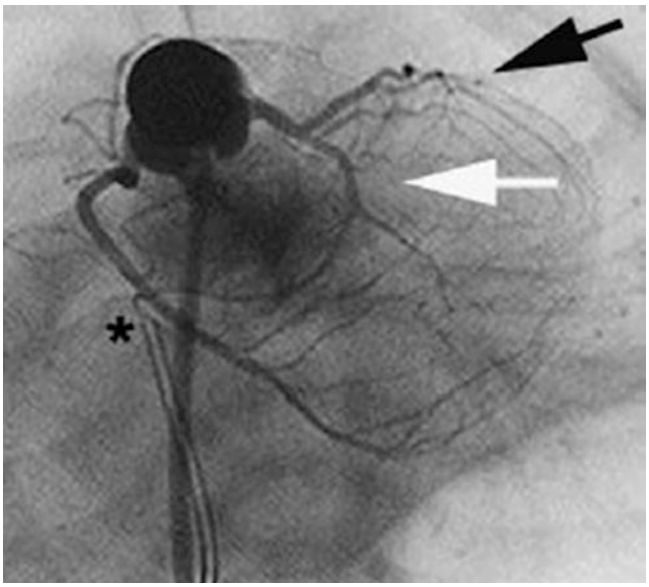

Fig. 5.2 Laid-back aortogram in a patient with {S, D, D} transposition of the great arteries and normal coronary artery anatomy for d-transposition. Note the right coronary artery (∗) comes off the rightward facing sinus of Valsalva. The left coronary artery comes of the leftward and anterior sinus, giving off the circumflex (*white arrow*) and the left anterior descending coronary artery (*black arrow*)

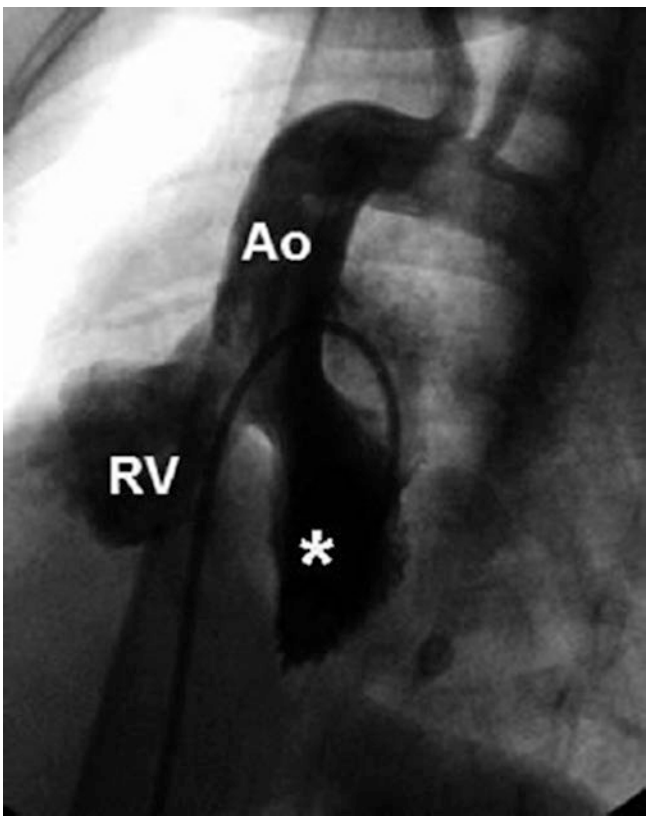

Fig. 5.3 Transvenous left ventriculogram performed in long axial oblique projection demonstrates a large cono-ventricular septal defect (often called perimembranous). ∗Left ventricle; Ao, ascending aorta; RV, right ventricle

– Hepatoclavicular view (40° right anterior oblique in the AP camera, 40° left anterior oblique, and 40° cranial on the lateral camera): useful for left ventriculogram to visualize inlet ventricular septum and septal defect in tricuspid atresia and endocardial cushion defects

Modified views can be adapted in specific conditions, such as complex branch pulmonary artery stenosis, or postoperative arch obstruction.

5.2.4 Complications

Even though diagnostic cardiac catheterizations are performed in patients of increasing risk, and in spite of a substantial increase in the number and complexity of interventional procedures, the incidence of complications has consistently decreased over the years. Currently, mortality from a cardiac catheterization is exceedingly rare, in the order of 0.1%, and almost exclusively occurring in infants, low-weight patients, or high-risk patients undergoing interventional procedures [12–15]. The reported incidence of all adverse events is approximately 8%, including the complications related to interventions. Within this group, the incidence of major complications (e.g., death, cardiac arrest, cardiac perforation, complete heart block, ventricular tachycardia or fibrillation, decreased pulse requiring surgery, or cardiac tamponade) is 1–2%. Common minor complications include fever in the 12 hours following the procedure and hematoma at the vascular access site.

Complications of cardiac catheterization and transcatheter intervention may be a reason for admission to the ICU. Some of the complications are specifically related to the intervention performed, for instance, the presence of segmental high-perfusion pulmonary edema following pulmonary artery angioplasty procedures or an arterial pulse loss associated with retrograde aortic balloon valvotomy. These problems will be discussed in more detail in the specific sections to follow.

5.3 Interventional Cardiac Catheterization

Table 5.2 A summary of transcatheter interventions in congenital heart disease

Table 5.2 Summary of transcatheter interventions

Therapeutic goal	Intervention	Indicated in patients with:
Create or enlarge an ASD	Balloon atrial septostomy	TGA/IVS with restrictive ASD (electively or with severe cyanosis)
		TGA/VSD or DORV with poor mixing and severe cyanosis
		Tricuspid atresia or PA/IVS with restrictive ASD (rarely)
	Blade or balloon atrial septoplasty	HLHS with restrictive or absent ASD
		Other complex CHD with left atrioventricular valve stenosis or atresia and restrictive or absent ASD
Balloon valvuloplasty	Pulmonary balloon valvotomy	Critical PS (newborn), moderate-to-severe PS
		Severe PS in TOF with hypoplastic pulmonary arteries and high surgical risks
		Other complex CHD with severe PS, hypoplastic pulmonary arteries, and high surgical risks
	Aortic balloon valvotomy	Critical AS (newborn), moderate-to-severe AS
Angioplasty and/or stent implantation	Pulmonary artery	Branch pulmonary artery stenosis (isolated or in association with other CHD)
		Hypoplastic pulmonary arteries (isolated or in association with other CHD)
	Coarctation	Native coarctation of the aorta
		Postoperative recurrent coarctation
	Systemic vein	SVC syndrome and SVC obstruction (postoperatively, secondary to indwelling lines or cannulation sites)
	Pulmonary vein	Severe pulmonary vein stenosis often
	PDA	ductal-dependent lesions, or other with decreased pulmonary blood flow
Closure	Device or coil	Patent ductus arteriosus
		Atrial septal defect
		Ventricular septal defect
		Aortopulmonary collaterals (patients with dual source of pulmonary blood flow: central pulmonary artery and collateral)
		Arteriovenous malformation (i.e., pulmonary)
		Pulmonary sequestration (i.e., in Scimitar syndrome)
Miscellaneous	Balloon dilation/stenting local thrombolysis	PDA stenting (patients with ductal-dependent lesions awaiting transplantation; HLHS as part of hybrid approach)
		Blalock-Taussig shunt reopening
		APC dilation/stenting or reopening post failed unifocalization
	Endomyocardial biopsy	Myocarditis and cardiomyopathies
	Foreign body retrieval	Retained intracardiac lines (i.e., post-cardiac surgery)

ASD atrial septal defect, *AS* aortic stenosis, *APC* aortopulmonary collateral, *CHD* congenital heart disease, *DORV* double outlet right ventricle, *HLHS* hypoplastic left heart syndrome, *IVS* intact ventricular septum, *PDA* patent ductus arteriosus, *PS* pulmonary stenosis, *TGA* transposition of the great arteries, *TOF* tetralogy of Fallot, *VSD* ventricular septal defect

Interventions can be classified according to the purpose to treat:

1. Valvular obstruction
2. Vascular stenosis
3. Creation or enlargement of defects
4. Closure of defects
5. Others

5.3.1 Valvular Obstruction

5.3.1.1 Pulmonary Valve Stenosis/Atresia

Intervention for pulmonary valve stenosis is indicated if a peak-to-peak gradient is above 40 mmHg as measured by cardiac catheterization. Balloon dilation has become the standard first-line therapy, with very high success rate [16–18]. However, patients with so-called dysplastic pulmonary valves as seen in Noonan syndrome, with markedly thick leaflets and often associated stenosis at the sinotubular junction (supravalvar), have traditionally had lower success. Nowadays, the use of high-pressure balloon valvotomy for these resistant valves can achieve success in most patients, so that surgical intervention is limited only to a very few. Patients are recovered overnight and discharged the following morning. Rarely, significant dynamic subpulmonary stenosis can develop post dilation. In some cases, this can be severe, especially in the absence of a right-to-left shunt at the atrial level, and can lead to a low output state ("suicidal right ventricle"), requiring admission to the ICU and intravenous beta-blockers. In the newborn and infant with an open atrial communication, variable degree of right-to-left shunting at atrial level causing cyanosis is common. This is expected to improve over time, as the right ventricle remodels and becomes more compliant and less hypertrophied.

Though balloon dilation may result in valvar regurgitation, given that the pulmonary artery pressure is normally quite low, the physiologic consequences of the insufficiency are rarely significant. Pulmonary valve regurgitation does worsen with time; however, the degree of regurgitation remains lower with balloon valvuloplasty when compared to surgical valvotomy [19]. Long-term, rare cases of restenosis and need for surgical valve replacement are noted.

A special group of patients are the newborns with critical pulmonary valve stenosis and ductal-dependent circulation. It is common to see the associated variable degrees of right ventricular hypoplasia, although over time the right ventricle is almost always adequate to allow a biventricular circulation [20, 21]. However, it may take several weeks or months for the right-to-left shunting at the patent foramen ovale to be eliminated or significantly reduced. Typically, prostaglandins are discontinued immediately following balloon dilation, although many patients require ongoing prostaglandins for a few more days or weeks, especially if the severity of the right ventricular hypoplasia is marked. Patent ductus arteriosus (PDA) stenting or surgical intervention (placement of a Blalock-Taussig shunt +/− a right ventricular outflow tract patch) may be necessary for those patients who cannot wean off prostaglandins after 14 days of dilation.

Radiofrequency-assisted valve perforation followed by balloon valvotomy [22] can be performed in patients with membranous pulmonary atresia (Fig. 5.4). Although successful perforation has been reported in up 75–90% of selected patients, the procedure is definitive for only 35%, as they commonly require additional intervention either transcatheter or surgical.

Patients with pulmonary valve atresia may have right ventricular-dependent coronary circulation which would contraindicate right ventricular decompression. Typically, patients with this condition have small right ventricles and small tricuspid valve annulus. For these patients, cardiac catheterization is typically purely diagnostic, unless stenting of the patent ductus arteriosus is performed as a temporizing measure to more definitive surgical intervention (single ventricle pathway versus cardiac transplantation).

5.3.1.2 Aortic Valve Stenosis

Balloon valvotomy is considered as the procedure of choice for the management of severe or critical aortic valve stenosis in most centers. In the newborn, severe aortic stenosis can present as critical, ductal-dependent lesion [23–25]. Transcatheter balloon dilation can be performed antegrade (femoral vein or umbilical vein to left ventricle and aorta across foramen ovale) or retrograde (umbilical artery or femoral artery). For premature babies, the carotid artery approach via surgical carotid cutdown is a good alternative to avoid femoral arterial damage. Other approaches for access have also been reported (axillary, subscapular, transventricular). Currently, the procedure can be performed using low-profile balloons advanced via femoral approach through a 3F sheath in the newborn, with which the incidence of iliofemoral artery thrombosis in the retrograde approach has significantly lowered. A gradient of over 50 mmHg is considered the cutoff for intervention, although smaller gradients may

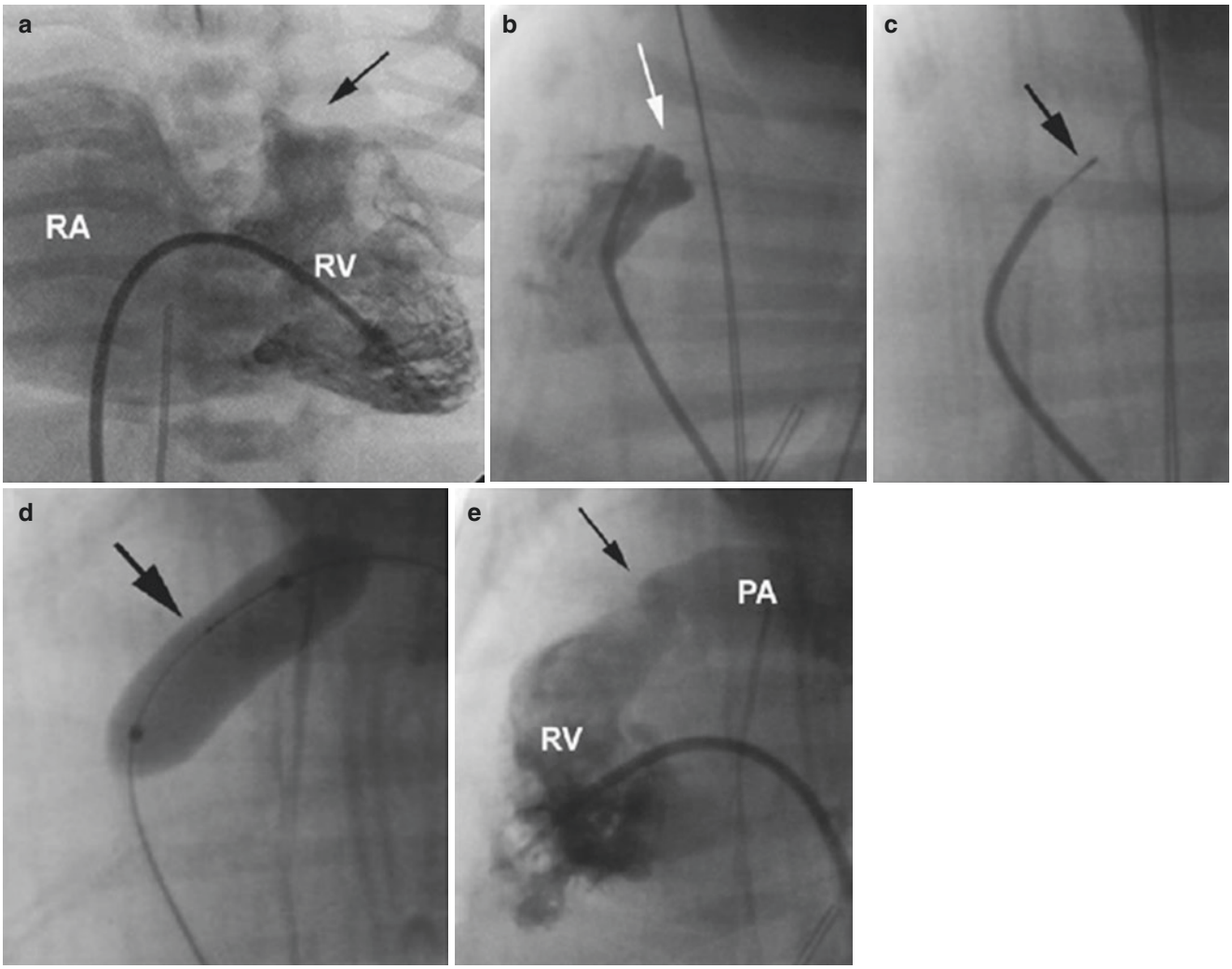

Fig. 5.4 (**a**) The right ventricle demonstrates membranous pulmonary valve atresia (arrow), with severe tricuspid valve regurgitation, with contrast filling the right atrium (RA). The right ventricle (RV) is well developed. (**b**) In the lateral projection, the right ventriculogram demonstrates membranous atresia (arrow). A right coronary catheter is used to position its tip under the atretic valve, in preparation for radiofrequency perforation. (**c**) The radiofrequency wire has been advanced across the atretic valve. (**d**) After a wire is advanced across the coaxial catheter, a balloon is inflated across the valve. (**e**) A right ventriculogram post radiofrequency perforation and balloon valvotomy demonstrates a widely open pulmonary valve (arrow). RV, right ventricle; PA, pulmonary artery

not correlate with severity in patients with severe LV dysfunction or cardiomyopathy.

Some degree of aortic insufficiency is commonly present after the procedure, although more than moderate regurgitation is rare. Attempts to completely alleviate obstruction by using large balloons result in an unacceptable amount of regurgitation [24]. Thus, after successful balloon dilation, it is common for patients to have residual obstruction in the mild-to-moderate range and/or insufficiency. In most cases, the residual physiologic abnormality is mild with average residual gradients of 22–35 mmHg. Moderate or severe aortic insufficiency occurs in 4–10% of patients, and this incidence tends to increase during follow-up [24, 25]. When subsequent intervention is needed, it may be due to recurrent obstruction, insufficiency, or both. In the first case, repeat valve dilation is an option. When aortic insufficiency becomes severe, surgery is required.

5.3.1.3 Mitral Stenosis

Isolated congenital mitral valve stenosis is very rare, occurring more commonly in association with other left-sided obstructive lesions in patients with Shone's syndrome or other complex congenital heart diseases. Congenital mitral valve stenosis has proven to be somewhat an intractable condition, except in those patients with isolated supravalvar mitral ring, in whom surgical resection is the procedure of choice [26]. Infants with severe congenital mitral stenosis have been reported to have a poor outcome regardless of

treatment modality. Given the palliative nature of any intervention, newborns who present with this condition are typically managed as patients with hypoplastic left heart syndrome (Norwood stage I procedure, followed by subsequent surgeries for a single ventricle palliation). The therapeutic options for symptomatic infants and children outside the newborn period presenting with severe mitral stenosis and pulmonary hypertension are few. In the presence of a supravalvar mitral ring, surgical resection should be performed. Depending on the underlying anatomy, mitral balloon valvotomy has been reported to immediately reduce the gradient in the majority, although sustained symptomatic improvement is only seen in less than half of the patients and up to 28% developed significant mitral valve regurgitation [26]. Given the lack of better options, mitral valve balloon valvotomy can be considered as a palliative procedure to delay the need for mitral valve replacement in these patients.

5.3.2 Vascular Stenosis

5.3.2.1 Pulmonary Artery Stenosis

Peripheral pulmonary artery stenosis can be congenital or acquired post-cardiac surgery and constitutes 2–3% of congenital heart disease. Congenital pulmonary artery stenosis occurs in isolation or association with other congenital heart defects (most commonly, tetralogy of Fallot +/− pulmonary atresia). As a primary lesion, it may be idiopathic or occur in the presence of syndromes, such as congenital rubella, Williams syndrome, and Alagille syndrome. Results of surgery for such branch pulmonary artery stenoses have been quite unsatisfactory, commonly leading to more severe stenoses than preoperatively. In addition, surgery cannot treat peripheral stenosis. Therefore, balloon angioplasty remains the first line and only therapy for many of these patients [27–29].

Indications for balloon dilation include elevated right-to-left ventricular pressure ratio of over 50%, right ventricular failure, angiographic narrowing, contralateral pulmonary arterial hypertension, and abnormal perfusion by lung scintigraphy. Although there are no contraindications to this procedure by age or size, newborns with severe branch pulmonary artery stenosis would undergo balloon angioplasty only if symptomatic and associated with systemic or higher right ventricular pressure, or ventricular dysfunction. Either discrete stenoses or long diffuse hypoplastic pulmonary arteries can be successfully dilated to variable degree [29]. Reported results indicate a rate of success of 50–75% [29], the latter with the use of high-pressure balloons. Most recently, the introduction of the cutting balloon and novel balloon technology (over 25 ATM of burst pressure) has increased the success rate of balloon pulmonary angioplasty to the order of over 92% [29–31]. The cutting balloon has microsurgical blades longitudinally and creates a predictable intimal tear. Stent implantation allows a further significant improvement in success (over 90%) [32, 33] (Fig. 5.5); however, not all lesions are stentable, and there are limitations in the available technology, as the cutting balloon is manufactured only up to 8 mm in diameter. Most stents implanted in children can be re-dilated at a later time to adult size diameters [33, 34] or intentionally fractured [35, 36]. Although limited data is currently available, the use of drug-eluting balloons may further reduce restenosis of these vessels.

Stents in infants offer some theoretical disadvantages: need for a larger introducer (more difficult vascular access) and for subsequent dilations to keep up with somatic growth. Still, some lesions that do not respond to dilation alone or to previous surgery can be successfully managed with stent implantation, regardless of the age.

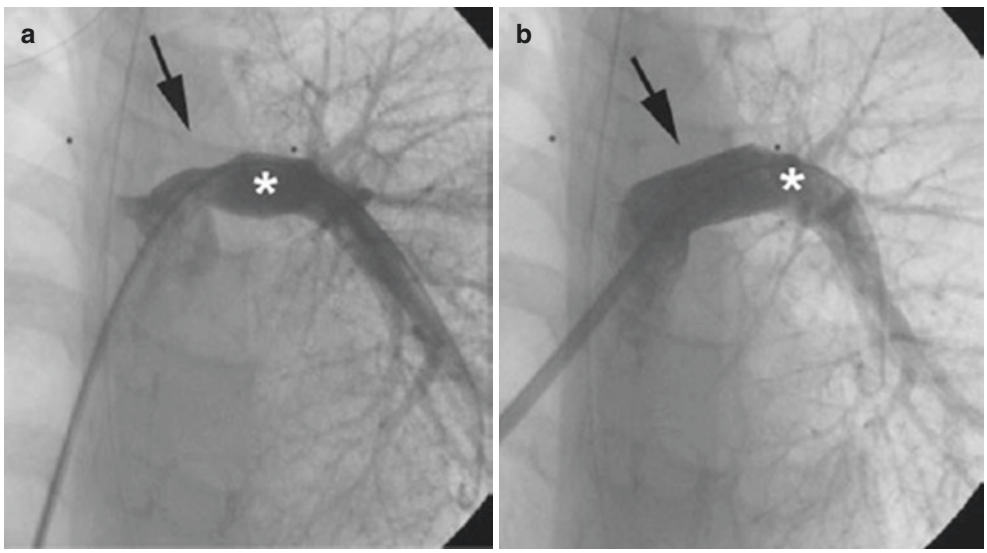

Fig. 5.5 (**a**) The left pulmonary angiogram demonstrates proximal left pulmonary artery stenosis (arrow). (**b**) Following stent implantation, there is significant improvement in vessel diameter without any residual stenosis (arrow). ∗Left pulmonary artery

Balloon dilation of peripheral pulmonary artery stenosis carries a procedural-related mortality of 0–3% [37], related to vessel rupture (tears) or cardiac arrest in high-risk patients – those with suprasystemic right ventricular pressure and poor right ventricular function. Immediate transcatheter management of significant pulmonary artery trauma using coil closure of unconfined tears or implantation of covered stents can be lifesaving [34] and likely will almost eliminate mortality in the future. In addition, high-risk patients with suprasystemic right ventricular pressures and dysfunction may benefit from creation of an atrial-level communication prior to balloon dilation to allow a pop-off. The incidence of morbidity related to the procedure is in the order of 10%, including nonfatal pulmonary artery tears, segmental pulmonary edema, distal vessel aneurysm formation, and deep vein thrombosis [37, 38]. Patients with hyperperfusion pulmonary edema may need to remain mechanically ventilated for 24 h in the ICU on PEEP and be managed with diuretics for a few days.

5.3.2.2 Aortic Coarctation

Balloon dilation of native coarctation of the aorta [39–41] remains a controversial subject in pediatric cardiology. Generally, indications for intervention in infants and children, whether surgical or transcatheter, include the presence of anatomic coarctation associated with a systolic pressure gradient between upper and lower extremities of over 20 mmHg, or a systolic blood pressure greater than 95% for age, or the presence of left ventricular dysfunction. In the newborn, surgery is indicated only in symptomatic patients, with congestive heart failure, failure to thrive, or upper extremity hypertension associated with left ventricular dysfunction, given that during the first month of life there is a higher postoperative restenosis rate. Surgery is considered as the management approach of choice for neonates and young infants with severe coarctation, given the unacceptably high incidence of restenosis following balloon angioplasty (at least 50%). However, there are specific clinical conditions where balloon dilation of the native coarctation in infants can be considered: patients with high surgical risks (i.e., severe left ventricular dysfunction and unstable hemodynamic condition, severe pulmonary hypertension, or other pulmonary diseases that would significantly increase the risk of thoracotomy, recent intracranial hemorrhage, or other major systemic conditions), or if coarctation is identified at the time of cardiac catheterization for balloon valvotomy of congenital aortic valve stenosis.

Recurrence of stenosis post balloon dilation decreases as the age of the patient increases, reaching about 10% for children over 2 years of age. The procedure is generally safe, with a mortality of less than 1% and aneurysm formation rates of variable incidence reaching up to 14% in some reports. Recent long-term data supports balloon dilation of native coarctation as an acceptable therapeutic option for discrete coarctation of the aorta in patients older than 1 year of age with discrete stenosis, though some centers around the world perform this procedure in younger patients. However, the long-term significance of an aortic aneurysm in the adult is unknown.

In patients who are diagnosed during late childhood, adolescence, or adulthood, stenting of the coarctation at catheterization is widely gaining acceptance as a first-line treatment [42] (Fig. 5.6), particularly in the absence of any significant collaterals, given that the surgical repair is at risk

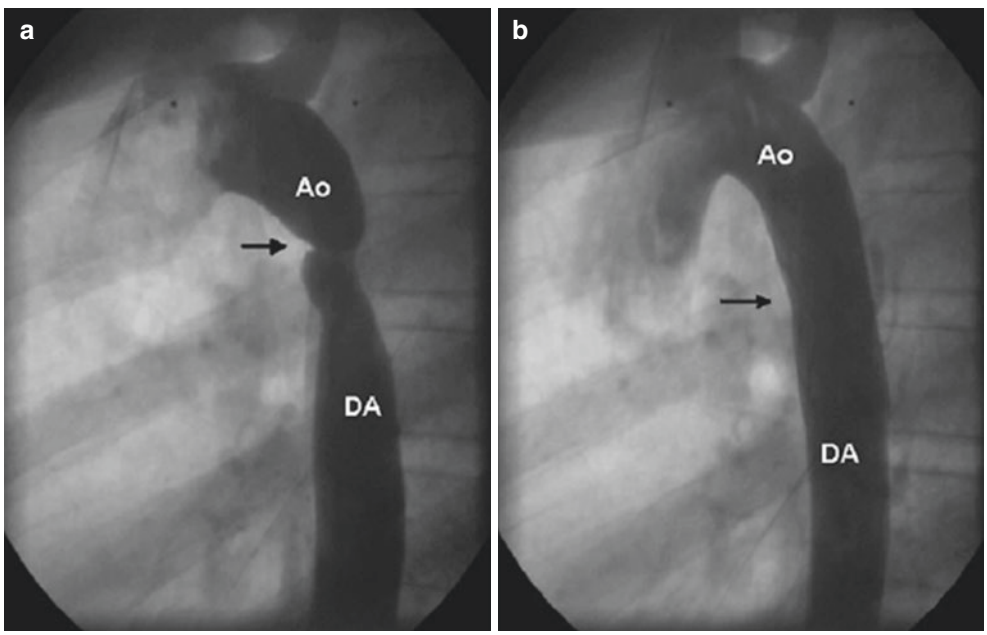

Fig. 5.6 (**a**) Aortogram demonstrates coarctation of the aorta with a narrow and tortuous course (arrow). (**b**) Following stent implantation, there is no residual coarctation (arrow). Ao, aorta, DA, descending aorta

of spinal cord ischemia. In 2016, the Food and Drug Administration (FDA) granted approval for the Cheatham platinum (CP)-covered stent, which is now widely used in coarctation stenting procedures, particularly in patients with acute or chronic aortic wall injury, those with near atresia of the descending aorta, and those with known genetic syndromes associated with aortic wall weakness [43]. The availability of covered stents has greatly improved the safety of this procedure, providing lifesaving therapy for acute aortic wall injury.

Long-term results of coarctation stenting are still relatively scarce. Stents result in effective relief of the obstruction in between 92% and 100% of cases. At follow-up, recurrent coarctation can be managed with repeat balloon dilation and/or re-stenting.

For infants with postoperative recurrent or residual coarctation, balloon angioplasty is considered as the procedure of choice, regardless of the type of previous surgical repair [44, 45] (Fig. 5.7). Mortality is 0.7%, with a low incidence of aneurysm formation (less than 2%). Success occurs in over 90% with a restenosis rate of less than 20% and can be managed with repeat balloon dilation.

5.3.2.3 Systemic or Pulmonary Vein Stenosis

Symptomatic systemic venous obstruction can occur in infants and children following cardiac surgery or after placement of chronic indwelling lines. Indications for intervention include symptoms of systemic venous hypertension, SVC syndrome, and chronic effusions. Balloon dilation of venous stenoses has been performed since the mid-1980s. The immediate success rate is over 90% for balloon dilation alone, but the restenosis rate is over 50%, for which primary stent implantation is preferred (Fig. 5.8) [46].

Recanalization of completely thrombosed systemic veins can be performed using the AngioJet technique (transcatheter mechanical thrombolysis) or using catheter

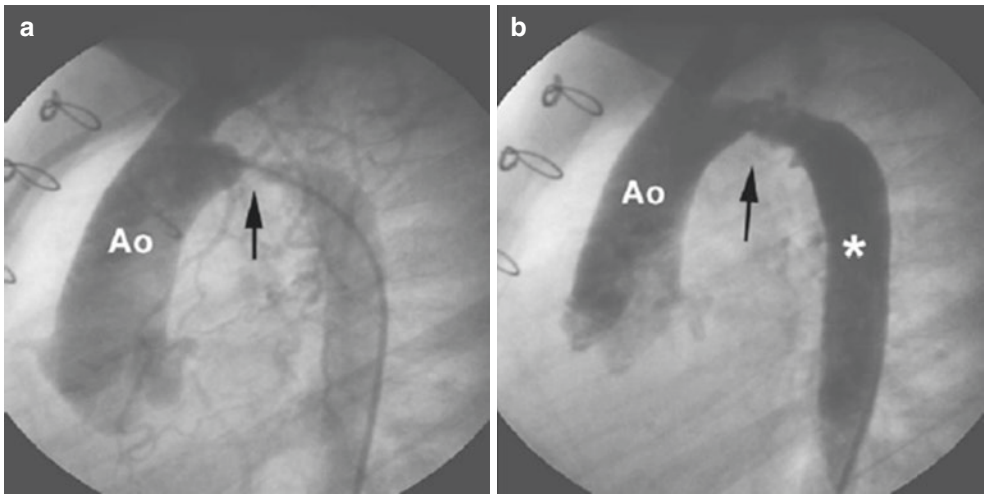

Fig. 5.7 (**a**) The aortogram demonstrates severe coarctation of the aorta (arrow) after surgical arch repair. (**b**) Following balloon angioplasty, there is significant improvement in vessel diameter. Ao, ascending aorta; ∗descending aorta

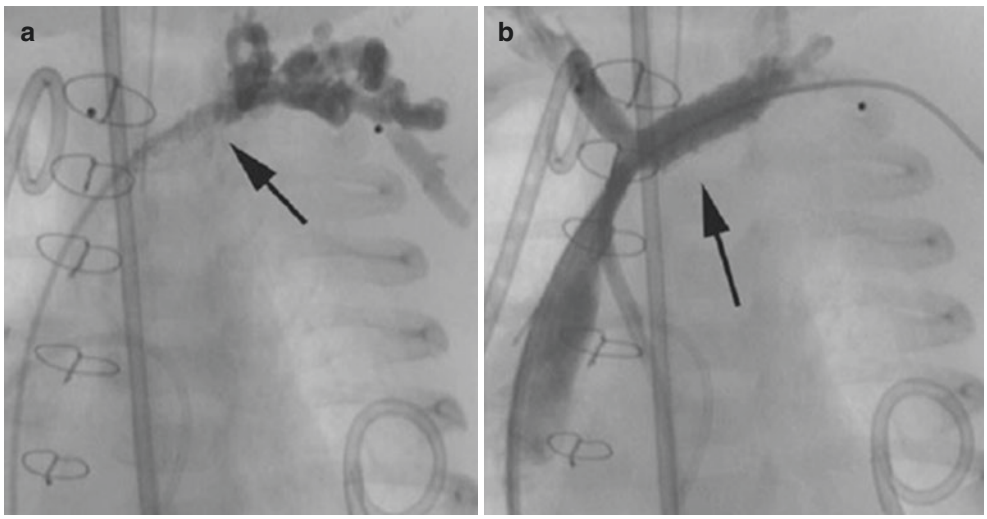

Fig. 5.8 (**a**) Venogram performed in the left subclavian vein demonstrates near extensive occlusive thrombus in the innominate vein (arrow). (**b**) After use of AngioJet balloon dilation and stenting, patency has been re-established (arrow)

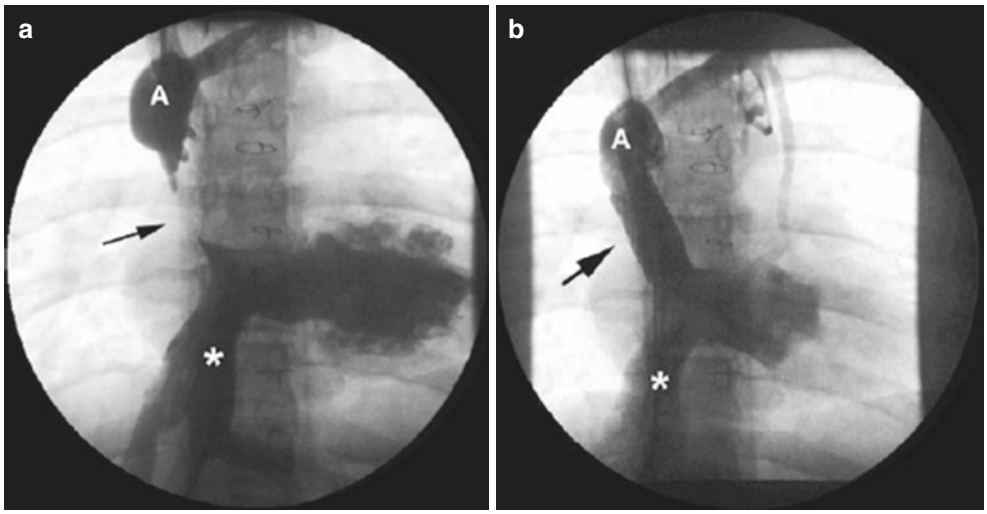

Fig. 5.9 (**a**) The angiogram demonstrates complete occlusion (arrow) of the superior limb of the Mustard baffle in a patient with transposition of the great arteries. (**b**) Following transcatheter recanalization and stenting, patency is re-established (arrow). (**a**) Superior vena cava; ∗inferior vena cava baffle

or RF perforation, followed by balloon dilation/stenting (Fig. 5.9).

Pulmonary vein stenosis is generally an intractable disease, occurring either congenitally or postoperatively. Balloon dilation and stent implantation [46] can only serve as a short-term palliation for symptomatic patients as a bridge to heart-lung transplantation. The use of drug-eluting balloons and stents, or the cutting balloon, may provide alternative options of more durability, although the experience with these techniques is only limited. The use of adjunct antiproliferative agents may improve the success of such interventions, though the prognosis for severe pulmonary vein stenosis remains poor [47].

5.3.3 Creation or Enlargement of Defects

5.3.3.1 Balloon Atrial Septostomy (BAS)

Following its initial introduction by Rashkind and Miller in 1966 [2], BAS has become an essential intervention in the management of most patients with transposition of the great arteries and other forms of congenital heart disease with transposition-like physiology (i.e., double outlet right ventricle). At most centers, BAS is performed routinely on patients with d-transposition of the great arteries and intact ventricular septum, often in the ICU under echocardiographic guidance. In patients with left-sided obstructive lesions, thick atrial septum, small left atrium, and restrictive atrial septal defect, BAS is rarely successful [48]. For these patients, other techniques of atrial septal defect (ASD) creation and septoplasty are preferred (see below). The success rate of balloon atrial septostomy in newborns is over 98%, with a procedural mortality of less than 1%, and an incidence of major complications is reported in the order of 0–3% [48].

5.3.3.2 Atrial Septoplasty/Blade Septostomy

Blade septostomy [49] is almost not used nowadays, having been replaced by the use of a combination of Brockenbrough transseptal puncture [48], followed by serial balloon dilations using angioplasty balloons, including the use of the cutting balloon, and occasionally stent implantation. Various radiofrequency-based techniques have also been described as a safe and effective alternative method for crossing the atrial septum when traditional transseptal puncture fails [50–52].

5.3.4 Closure of Defects

5.3.4.1 Atrial Septal Defects (ASDs)

In the current era, most ASD secundums are closed via transcatheter devices. Some are still not candidates for device implantation, given the lack of adequate rims of tissue around the defect to anchor the device. ASDs of the sinus venosus or ASD primums cannot be closed with devices. Although devices are available to close very large holes (up to 40 mm in diameter), the larger devices will fit only in the heart of a large adult. Currently, there are two devices approved for use in the USA for closure of ASD: the Amplatzer Septal Occluder [53] and the Gore Cardioform Septal Occluder (GSO) occlude [54]. The CardioSEAL device was in the past used for this purpose while under investigation and is now approved for closure of ventricular septal defects. The Gore Helex Septal Occluder [55] was discontinued when the newer Gore GSO was introduced. Currently under investigation is the newest of the Gore devices, the Gore Cardioform ASD Occluder (GCO), which is designed to close larger defects [56]. The procedure is performed under transesophageal or intracardiac echocardiographic guidance. Patients

receive low-dose aspirin for 6 months and adhere to bacterial endocarditis prophylaxis precautions for 6–12 months. Several studies have documented efficacy of device closure comparing the method to surgery: in general, they show no or little difference in efficacy rates between the two strategies (complete closure rates of 95–98%) [57, 58], with longer hospital stay and higher rate of complications after surgical closure. The actual numbers reported for complications as well as length of stay vary substantially, but severe complications are very rare. The main difference in complication rate between surgical closure and device closure can be attributed to post-procedure pericardial effusion, which is relatively common after surgery and rare after device closure. The timing and underlying cause for effusions differ for both methods. While postoperative effusions are thought to relate to postpericardiotomy syndrome, post-device effusions are typically thought to be related to erosion or perforation of the atrial wall caused by the device or the catheters used during the procedure. These have been reported to occur early or late, even several years after device implantation, and are thought to be in the order of 1:1000–5000.

5.3.4.2 Ventricular Septal Defects

Most ventricular septal defects (VSD) cannot be closed with devices, due to their significant size in relatively small hearts as well as the proximity to intracardiac valves. An option to overcome the limitations of the technique in an infant is a hybrid or combined surgical-catheter approach [59, 60]. In this method, the heart is exposed via a thoracotomy and the device delivery catheter advanced through the free wall of the right ventricle and across the VSD, under echocardiographic guidance. This technique has the advantage of avoiding cardiopulmonary bypass and eliminating the risk of vascular damage in small children.

The CardioSEAL device was the first device approved by the FDA for closure of muscular VSDs in the USA. This device requires a large introducer sheath for delivery (10–11 French) and cannot be retrieved once opened up. The Amplatzer muscular VSD occluder [61] has subsequently received FDA approval. This device has been used widely and offers attractive properties and high success rate for closure of muscular ventricular septal defects. The Amplatzer membranous VSD occluder designed for perimembranous VSDs did not receive FDA approval primarily due to the incidence of complete heart block, even late after implantation.

5.3.4.3 Patent Ductus Arteriosus (PDA)

Small and moderate PDAs are typically closed in the catheterization laboratory with either embolization coils [62] or devices (Amplatzer duct occluder) [63] (Fig. 5.10), while many large symptomatic PDAs in the newborn are treated surgically. Transcatheter closure of PDA has been extensively studied. A European registry series reported an overall efficacy of 95% in over 1200 procedures performed between 1994 and 2001 [62]. In this series, successful occlusion was less likely in larger PDAs. Since that report, the closure device described above (Amplatzer PDA occluder) has been approved in the USA, achieving high closure rate of close to 100% [63]. Thus, nowadays, the use of coils for small PDAs and devices for moderate and large ones allows a high efficacy of greater than 97% with a very low complication rate. More recently, the FDA-approved Medtronic Micro Vascular Plug has been used for PDA device closure in small preterm infants, as its low-profile

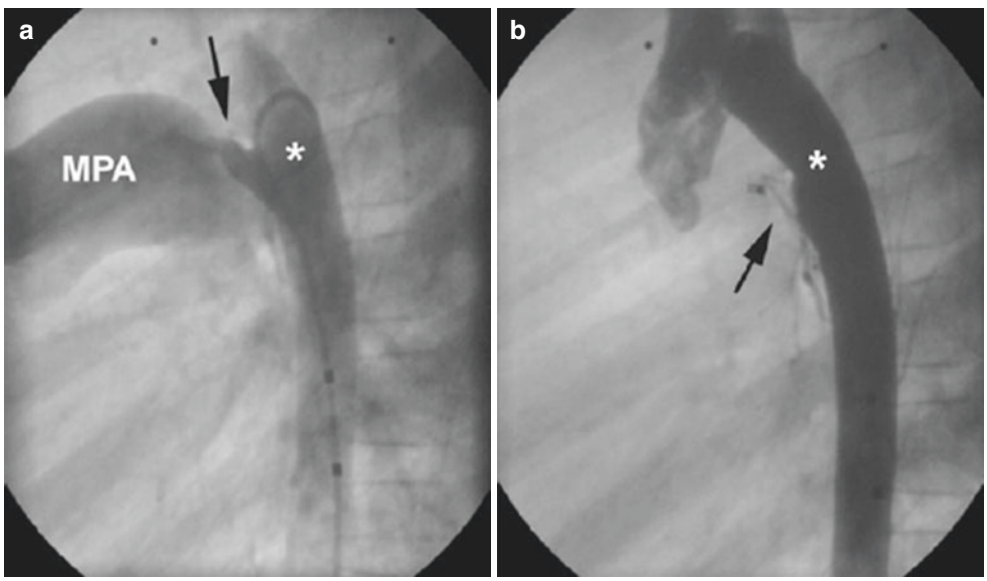

Fig. 5.10 (**a**) The aortogram demonstrates a moderate size patent ductus arteriosus (arrow). (**b**) Following implantation of an Amplatzer PDA occluder, there is no residual PDA flow (arrow). ∗Descending aorta; MPA, main pulmonary artery

design permits delivery through a 4 French catheter [64]. The Amplatzer Duct Occluder II Additional Sizes is still under investigation in the USA, but has been reported to have a high success rate for PDA closure in preterm infants in European and Middle Eastern studies [65].

5.3.4.4 Others

Other interventions include closure of collaterals, reopening occluded vessels, retrieval of foreign bodies, preservation of ductal patency using stents, coil embolization of coronary artery fistula, and some novel catheter interventions, such as prenatal interventions (for opening of stenotic valves, or restrictive atrial septum) and transcatheter pulmonary valve implantation. These relatively novel procedures have become much more common during the last decade and will continue to do so as catheter technology continues to advance.

Closure of Collaterals

Lesions amenable to closure by embolization therapy include systemic venous anomalies [66] (i.e., left superior vena cava to left atrium) or collaterals (abnormal vessels which are seen in patients with single ventricle palliation), aortopulmonary collaterals, pulmonary sequestration, or congenital arteriovenous malformations [67, 68]. Coil embolization of collaterals is one of the most common procedures in children with congenital heart disease, particularly in patients with functional single ventricle. It is safe and highly successful, with over 95% complete closure rate. The use of platinum coils rather than that of stainless steel allows for future cardiac MRI imaging. In tetralogy of Fallot variants and diminutive or absent central pulmonary arteries, coil embolization is indicated for those collaterals to lung segments with dual sources of pulmonary blood flow.

Transcatheter Thrombolysis

Reopening of thrombosed vessels or surgical anastomoses [69] can be performed nowadays with good results, although the experience in pediatrics is relatively limited. Often thrombolysis is associated with balloon angioplasty and stenting to achieve success.

Preservation of Ductal Patency

Stenting of the patent duct can be performed instead of surgical Blalock-Taussig shunt in some newborns. The procedure can be performed using self-expanding stents or balloon-expandable stents [70]. Conditions for which this can be considered include:

- Hypoplastic left heart syndrome: stenting of the PDA in patients awaiting heart transplantation or as part of the interventions performed with the hybrid management approach for hypoplastic left heart syndrome [71, 72]
- Pulmonary atresia and intact ventricular septum, following transcatheter perforation and valvotomy, in patients who cannot wean from PGE_1
- Some complex single ventricle with diminished pulmonary blood

There are limiting factors to the consideration of PDA stenting in a newborn. The ideal approach is transvenous, via the femoral vein, into the pulmonary artery and down the PDA. In this way, it is likely that a 5 French or 6 French sheath could be used without much risk for vessel damage and allowing the use of a self-expanding stent if desired. If, on the other hand, the stent has to be performed transarterially, depending on the size of the newborn, the intervention may not be feasible without significant risk of vessel damage. The only stent which could be used for transarterial implantation would be a coronary stent, for what the PDA would have to be relatively small to begin with. Given the risk of vessel tear, if the PDA stent cannot be implanted transvenously, the risk/benefit ratio of transarterial stenting versus surgical shunting should be considered. The use of carotid cutdown and percutaneous carotid access has been increasingly used in this patient population as an alternative to the femoral artery, the main benefit being larger vessel size.

Prenatal Catheter Interventions

The pioneering work by the interventional group at Children's Hospital Boston introduced a new management option for fetuses with congenital aortic stenosis. Fetal echocardiography has demonstrated the natural history of fetal aortic stenosis [73]. Fetuses who present in mid-gestation with dilated and/or dysfunctional left ventricles and retrograde aortic flow are highly likely to develop hypoplastic left heart syndrome during fetal development. Fetal aortic balloon dilation is offered for these fetuses with the aim to alter the natural history and prevent left ventricular growth arrest and hypoplastic left heart syndrome (HLHS). The procedure is done percutaneously and transabdominally, providing both the mother and fetus anesthesia, requiring 50% of the time for laparotomy. The approach is via ultrasound guidance and needle puncture. The valve is dilated with a coronary balloon premounted on a coronary wire. The results demonstrate that

20% of fetuses only become candidates for biventricular circulation. It is not certain whether there is any benefit for the remaining fetuses, especially if some increase in antegrade aortic flow might be associated with improved brain development. Other fetal cardiac interventions include stenting of the atrial septum in patients with HLHS and pulmonary valve dilation in patients with hypoplastic right ventricle and pulmonary atresia [74]. The intermediate- and long-term results are still unknown.

Transcatheter Pulmonary Valve Implantation

Various forms of congenital heart disease develop right ventricular outflow tract (RVOT) dysfunction, either due to the native defect (e.g., tetralogy of Fallot) or as a result of their subsequent surgical repair (e.g., truncus arteriosus or patients undergoing a Ross operation with placement of an RV to PA conduit). Such lesions are subject to the development of pulmonary stenosis and insufficiency, ultimately leading to RV dilation and strain. Philipp Bonhoeffer was the first to percutaneously implant a stent-mounted bovine jugular venous valve as a means of delaying surgical conduit replacement in 2000 [75]. In 2006, this technology became commercially available via the Medtronic Melody valve, which gained Humanitarian Device Exemption (HDE) approval by the FDA in 2010, with full FDA approval for use in dysfunctional RV to PA conduits in 2015 and expanded approval for use in failing bioprosthetic valves in 2017 [76, 77] (Fig. 5.11). More recently, the Edwards Sapien valve, initially designed for use in the aortic position, was approved for use in dysfunctional conduits. The Edwards Sapien valve has the advantage of being available in larger diameters (up to 29 mm), though it is technically more challenging to implant [78]. Both valves are delivered through large 22 French sheaths through the femoral or jugular vein, report a high procedural success rate (98% and 93.5%, respectively), and marked improvement in hemodynamics.

Indications for percutaneous pulmonary valve implantation are the same as those for surgical pulmonary valve replacement and include:

- Pulmonary stenosis with gradient of 35 mmHg or greater
- Pulmonary valve insufficiency resulting in significant RV enlargement
- RV dysfunction
- Significant ventricular arrhythmias
- Symptomatology including abnormal stress testing

Severe complications associated with percutaneous pulmonary valve implantation occurred at a rate of 8–10% and included conduit rupture, coronary compression, distal PA perforation, and ventricular arrhythmias. Long-term follow-up is required for late complications that include endocarditis, stent fracture, and subsequent restenosis [76–78]. Off-label use of percutaneous pulmonary valves in the mitral and tricuspid positions has also been reported, though experience remains limited at this time.

5.4 Specific Problems

5.4.1 *Cardiac Catheterization in a Patient on Extracorporeal Membrane Oxygenation (ECMO)*

ECMO has been used increasingly for the management of the cardiac pediatric patients, often initiated semi-electively postoperatively [79, 80]. Cardiac catheterization is performed commonly in these patients to determine the underlying cause of the cardiovascular collapse or the failure to wean from the ECMO circuit. When a residual anatomic problem exists, interventional cardiac catheterization is often indicated and can be lifesaving. Indeed, it has been reported that over 80% of such studies end up requiring transcatheter

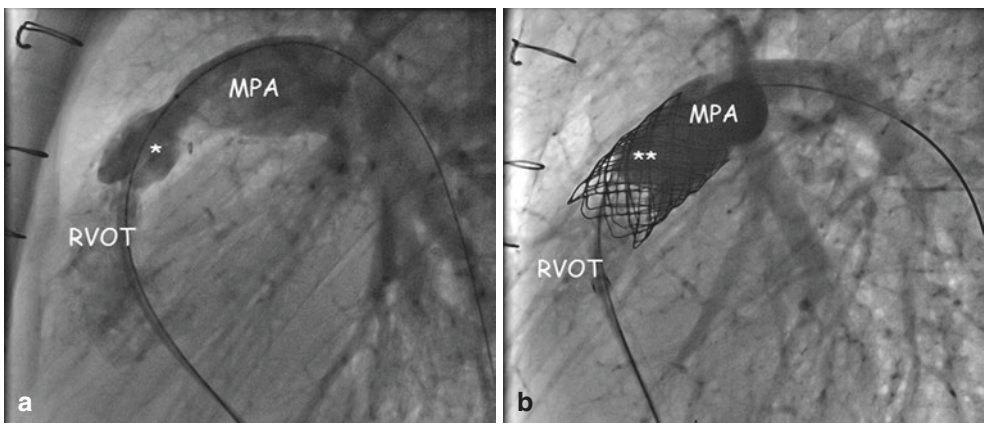

Fig. 5.11 (**a**) The pulmonary angiogram demonstrates severe conduit stenosis with mild-to-moderate pulmonary regurgitation. (**b**) Following Melody valve implantation, the conduit is unobstructed with trivial pulmonary insufficiency. ∗RV-PA conduit; ∗∗Melody valve stent; MPA, main pulmonary artery; RVOT, right ventricular outflow tract

intervention procedures, especially if ECMO was initiated immediately postoperatively.

From a technical standpoint, hemodynamic assessment has to be interpreted according to the flow condition of the time. Partial or total clamping of the ECMO cannulas is necessary to evaluate hemodynamics. If decreasing ECMO flows is not an option, hemodynamic assessment is impossible to perform. Still, angiographic assessment can be most helpful in diagnosing these patients. Angiography has to be performed with transient clamping of the ECMO cannulas, as otherwise visualization of the anatomy will be poor as the contrast will get diluted with the ECMO flow.

In some patients with decreased systemic ventricular function and no interatrial communication, the left atrial pressure may reach severely elevated levels, which induces pulmonary venous hypertension, and elevation in pulmonary artery pressures/pulmonary edema and potential lung damage. This could become a vicious circle that would prevent the patient to ever wean from ECMO. Left atrial decompression has to be performed emergently in this setting and is done with transseptal puncture and balloon dilation. Rarely, stenting of the atrial septal communication may be required [81].

Transport of the patient on ECMO to the cardiac catheterization laboratory is a team effort. Multiple experienced individuals are involved, including ECMO technicians, ICU nurses, anesthesiology team, cardiologist, and intensivist. Despite the severity of the condition of the patients, cardiac catheterization and transcatheter interventions are performed with a relatively low incidence of complications (3–15%) with the majority of complications being vascular in nature [82].

5.4.2 Specific Post-cardiac Catheterization Complications

Some specific complications post cardiac catheterization can lead to admission to the cardiac ICU. Among these are:

5.4.2.1 Arterial Pulse Loss

Following arterial puncture, lower extremity pulses are checked every 15 minutes for 1 hour, every 30 minutes for 2 hours, and every hour for the initial 6 hours. Pulse loss can be transient associated with arterial vasospasm. In those cases, the distal pulses return to normal within half an hour post line removal. The risk of pulse loss is related to the size of the sheath and the size of the vessel. The use of intravenous heparinization during the procedure lowers the chance of arterial loss. The treatment of pulse loss following cardiac catheterization [83, 84] includes heparinization for the first 12–24 hours (drip starts at 15–20 units/kg/hour plus heparin bolus depending on the ending of ACT measured in the catheterization laboratory and the time evolved since then). If no response by 24 hours (or sooner if extremity is cold), it is recommended to start thrombolytic therapy, with tPA infusion. The patient should be monitored in the ICU. A bolus of 0.1 mg/kg is initiated followed by 0.5 mg/kg/hour drip for 2 hours and then off. Heparinization is continued for 6 hours at 12–17 units/kg/hour. If the pulse has not returned, the bolus and drip of TPA are repeated, followed by heparin infusion for another 6 hours. The success rate with this protocol is quite high (95%). The use of vascular ultrasound as standard of care for access guidance over the past year is expected to reduce the incidence of vascular access complications and in particular arterial thrombosis.

5.4.2.2 Post-angioplasty Hyperperfusion Pulmonary Edema

This occurs when a severely stenotic pulmonary artery (with very low distal pressure) is successfully dilated and the distal mean pressure increases to over 25 mmHg due to a significant increase in flow. It can affect just one segment of the lung and may involve a lobe or the whole unilateral lung [38]. Pulmonary edema of the site takes place, often affecting oxygenation and requiring positive pressure ventilation for 24–48 hours. Sometimes significant bloody fluid can be suctioned from the endotracheal tube. Use of diuretics is needed. The edema typically resolves within 1–2 days. Short-term use of diuretics is prescribed, and patients are usually extubated within that time period, being able to discharge home at 2–4 days after the procedure.

5.4.2.3 Hemorrhage/Vessel Trauma

Vessel trauma associated with transcatheter intervention can be life-threatening. Angiographic evaluation following each angioplasty is essential, as early identification of problem would allow specific therapy. Tears can be confined [35] (extravasation of contrast is retained within the perivascular tissue) or unconfined. Unconfined tears need to be treated emergently in the catheterization laboratory with coil occlusion of the site of bleeding or use of covered stents and at times require emergent surgical intervention. If the vessel injury is significant, repeat angiography in the catheterization lab is recommended during the time of the procedure, in addition to post-catheterization MRI or CT scan to evaluate for further injury progression or ongoing bleed.

5.4.2.4 Arrhythmias

Complete heart block associated with cardiac catheterization can occur especially in patients with tetralogy of Fallot status post repair with a bifascicular block when the catheter is positioned retrograde into the left ventricle for angiography. Other predisposing conditions include patients with {S, L, L} segmental combination or patients with d-TGA during specific catheter manipulation (catheter crossing the right ventricular outflow tract into the ascending transvenously for angiography). Typically, it is transient and can be treated successfully in the cath lab with removal of the catheter, atropine, and if needed a temporary transvenous pacemaker. A short course of steroids can also help in treating heart block that is catheter induced.

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Chapter 6
Echocardiography

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Abstract Echocardiography in its current form has become an invaluable tool in the modern practice of pediatric cardiology. Coupled with clinical examination and monitoring techniques, echocardiography can provide real-time rapid and reliable diagnostic answers that are invaluable to patient care. This noninvasive test can be used to reliably evaluate cardiac anatomy of both normal hearts and those with congenital heart disease and has replaced cardiac angiography for the preoperative diagnosis of the majority of congenital heart lesions. In congenital or acquired cardiac disease, echocardiography may be further used to estimate intracardiac pressures and gradients across stenotic valves and vessels, determine the directionality of blood flow and pressure gradient across a defect, and examine the coronary arteries. Within the realm of critical care, echocardiography is useful to estimate cardiac systolic and diastolic function, to evaluate hemodynamics in critically ill patients and target specific intervention, to detect the presence of vegetation from endocarditis, to examine the cardiac structure, and to look for the presence of pericardial fluid and chamber thrombi. As with all tools, however, a thorough understanding of its uses and limitations are necessary before relying upon the information it provides.

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6.1 Introduction

Echocardiography in its current form, several generations removed from its origin in the 1950s [1], has become an invaluable tool in the modern practice of pediatric cardiology, particularly in the cardiac intensive care unit environment. Coupled with clinical examination and monitoring techniques, echocardiography can provide real-time rapid and reliable diagnostic answers that are invaluable to patient care. This noninvasive test can be used to reliably evaluate cardiac anatomy of both normal hearts and those with congenital heart disease and has replaced cardiac angiography for the preoperative diagnosis of the majority of congenital heart lesions [2–4]. In congenital or acquired cardiac disease, echocardiography may be further used to estimate intracardiac pressures and gradients across stenotic valves and vessels, determine the directionality of blood flow and pressure gradient across a defect, and examine the coronary arteries. Within the realm of critical care, echocardiography is useful to estimate cardiac systolic and diastolic function, to evaluate hemodynamics in critically ill patients and target specific intervention, to detect the presence of vegetations from endocarditis, to examine the cardiac structure, and to look for the presence of pericardial fluid and chamber thrombi. As with all tools, however, a thorough understanding of its uses and limitations are necessary before relying upon the information it provides [5].

6.2 Principles of Echocardiography

Echocardiography uses ultrasound technology to image the heart and associated vascular structures. Ultrasound is defined as sound frequencies above the audible range of 20,000 cycles per second. The primary components of an ultrasound machine include a transducer and a central processor. The transducer converts electrical to mechanical

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(sound) energy and vice versa. Electrical energy is applied to piezoelectric crystals within the transducer resulting in the generation of mechanical energy in the form of a series of sinusoidal cycles of alternating compression and rarefaction. The energy produced travels as a directable beam, which may be aimed at the heart. The sound beam travels in a straight line until it encounters a boundary between structures with different acoustical impedance, such as between blood and tissue. At such surfaces, a portion of the energy is reflected back to the same crystals within the transducer, and the remaining attenuated signal is transmitted distally. Within the ultrasound, machine is circuitry capable of measuring the transit time for the beam to travel from the transducer to a given structure and back again then calculate the distance traveled. A cardiac image is constructed from the reflected energy, or so-called ultrasound echoes.

Differing properties of tissues affect the portion of acoustic energy transmitted versus reflected. For example, air reflects the majority of the signal it receives and, therefore, prevents images from being obtained through windows where it is present. Anything hindering or augmenting the reflection of this acoustic signal, such as air, bone, dressings, an open chest, or lines, tubes, or other foreign bodies, will diminish the overall quality of the examination. Therefore, in the intensive care unit, an ultrasound study may be limited by difficulty in finding a good acoustic window to allow for accurate analysis [6].

6.2.1 Equipment and Settings

In order to perform an echocardiography, it is necessary to have an ultrasound machine with different modalities, including two-dimensional (2D) mode, M-mode, color flow Doppler mapping, pulse-wave (PW), and continuous-wave (CW) Doppler. To be able to evaluate systolic and diastolic phases, electrocardiogram gating is required, and this becomes even more important in functional assessment where precision in measurement is required. A permanent image archiving system is mandatory. The facility to perform offline assessment and to analyze studies is advantageous and allows minimizing the bedside time in the critical care unit and to compare the different studies.

Because of different patient sizes in pediatrics, ranging from the newborn to the adult size, several transducers with different frequencies are necessary, ideally from 12 MHz to 2.5 MHz. This allows acquisition of imaging at different depths and optimization of images. Higher-frequency transducers have higher resolution but less depth of penetration as compared to lower-frequency transducers. Therefore, high-frequency probes are used in the neonates and small children, whereas low-frequency probes are used in older children and adults. Mid-range frequency transducers are suitable for use in toddlers or small children.

Special care should be taken to adjust the ultrasound machine to optimize the echo image. The choice of transducer is the most important for enhancing image quality. It is important to choose appropriate presets, particularly for color Doppler. The image depth should be adjusted so that the heart fills the viewing screen. The 2D gain is used to adjust the strength of the returning echoes and may be controlled in two ways. Overall gain may be changed to enhance the brightness of the image. Additionally, time-gain compensation allows changes to the gain at various depth of interest and is controlled by a set of horizontal slide bars. The newer ultrasound machines provide enhanced facilities for auto-optimization to some extent, and they may not have horizontal slide bars. The image contrast can be optimized by adjusting the compression or dynamic range. With rapid advancement in technology, different ultrasound machines providing similar modalities may vary significantly in their appearance and functioning, and the operator should understand how to optimize imaging to get the best result.

6.3 The Anatomical Echocardiographic Examination

In order to obtain the best imaging windows, whenever possible, patients are placed in a left lateral decubitus position during a transthoracic echocardiogram. During two-dimensional (2D) echocardiography, all planes are described in reference to the heart and not the heart's position within the body. For a complete pediatric study, standard views (Figs. 6.1, 6.2, 6.3, 6.4, and 6.5) are obtained from the high left chest just lateral to the sternum (parasternal window), the left lateral chest just inferior and lateral to the nipple (apical window), sub-xyphoid area (subcostal window), and the suprasternal notch (suprasternal window). In patients with more complex anatomy, additional windows, such as the high right parasternal border, may be used to obtain additional information.

6.3.1 Parasternal Window

In the anatomically normal heart, the parasternal window allows visualization of the heart aligned along its long axis and short axis. In the long axis (Fig. 6.1a), the left ventricular

inflow and outflow tracts can be seen well. As a result, comments can be made from this view regarding the aorta, including its annulus, the sinuses of Valsalva, and the proximal portion of the ascending aorta, as well as its relationship to the mitral valve. Additionally, the ballet-slipper appearance of the left ventricle is featured as the inferoposterior wall and interventricular septum are visualized. The anterior and posterior leaflets of the mitral valve can be visualized. By angulating the transducer and performing a sweep, the right ventricle is brought into focus and an examination of both its inflow, including the right atrium and tricuspid valve, and its outflow tract, including the pulmonary valve, can be performed.

The transducer may be rotated clockwise 90° providing a series of short-axis views (Fig. 6.1b) that assist in the evaluation of the chambers of the heart, the semilunar and atrioventricular valves, and the coronary arteries. Sweeping from the apex of the heart toward the base will allow a close cross-sectional examination of the ventricular chambers. The normal left ventricle has circular geometry with symmetric contraction, whether it is visualized at the level of the mitral valve, papillary muscles, or apex during the short-axis sweep. In contrast, the normal right ventricle appears as a more trabeculated crescent-shaped structure when visualized at or below the level of the mitral valve. Sweeping farther toward the base of the heart, the mitral valve's papillary muscles and the valve itself are viewed. Progressing to the base of the normal heart, the tri-leaflet aortic valve takes the center stage with the right ventricular outflow tract and pulmonary wrapping in an inverted "U" anteriorly and leftward. Additionally, a portion of the atrial septum and the tricuspid valve may be profiled. Finally, continuing the sweep allows for the examination of the atrial appendages, ascending aorta in cross-section and branch pulmonary arteries.

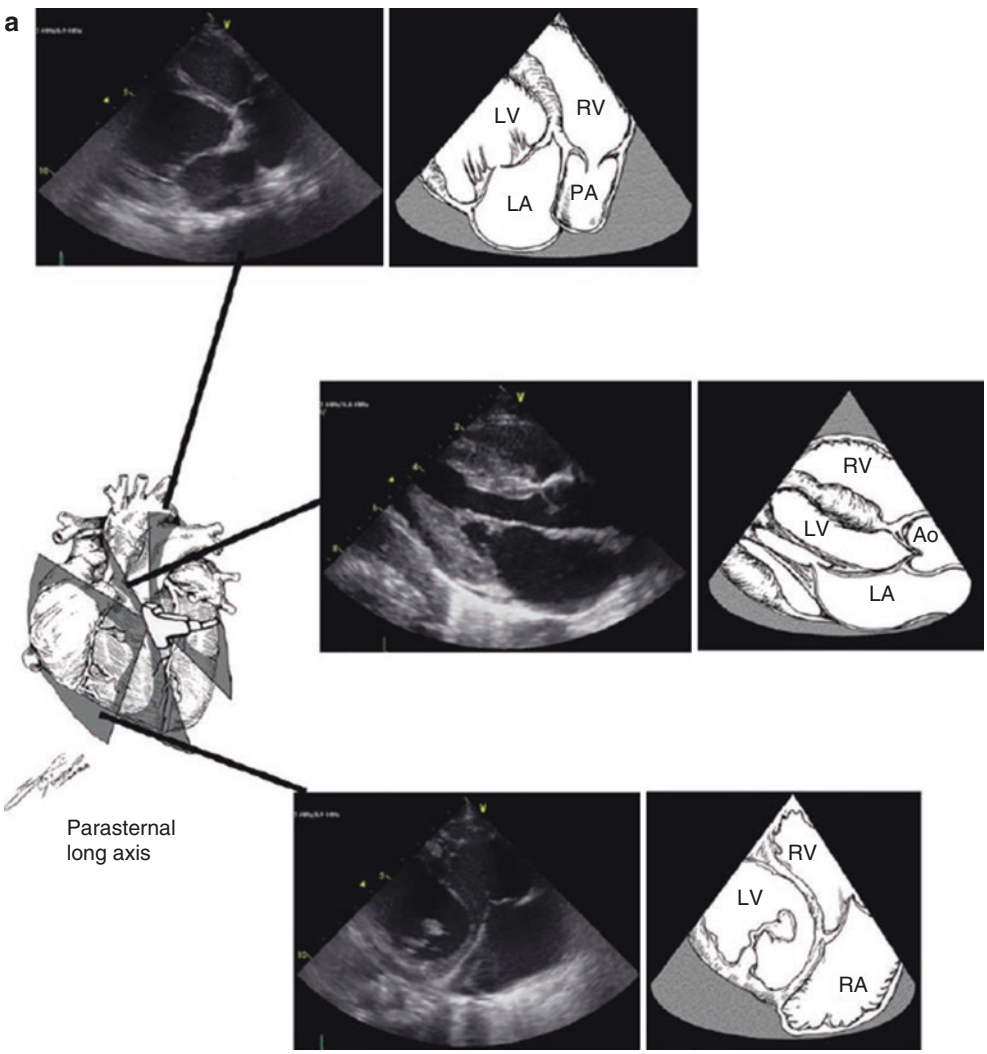
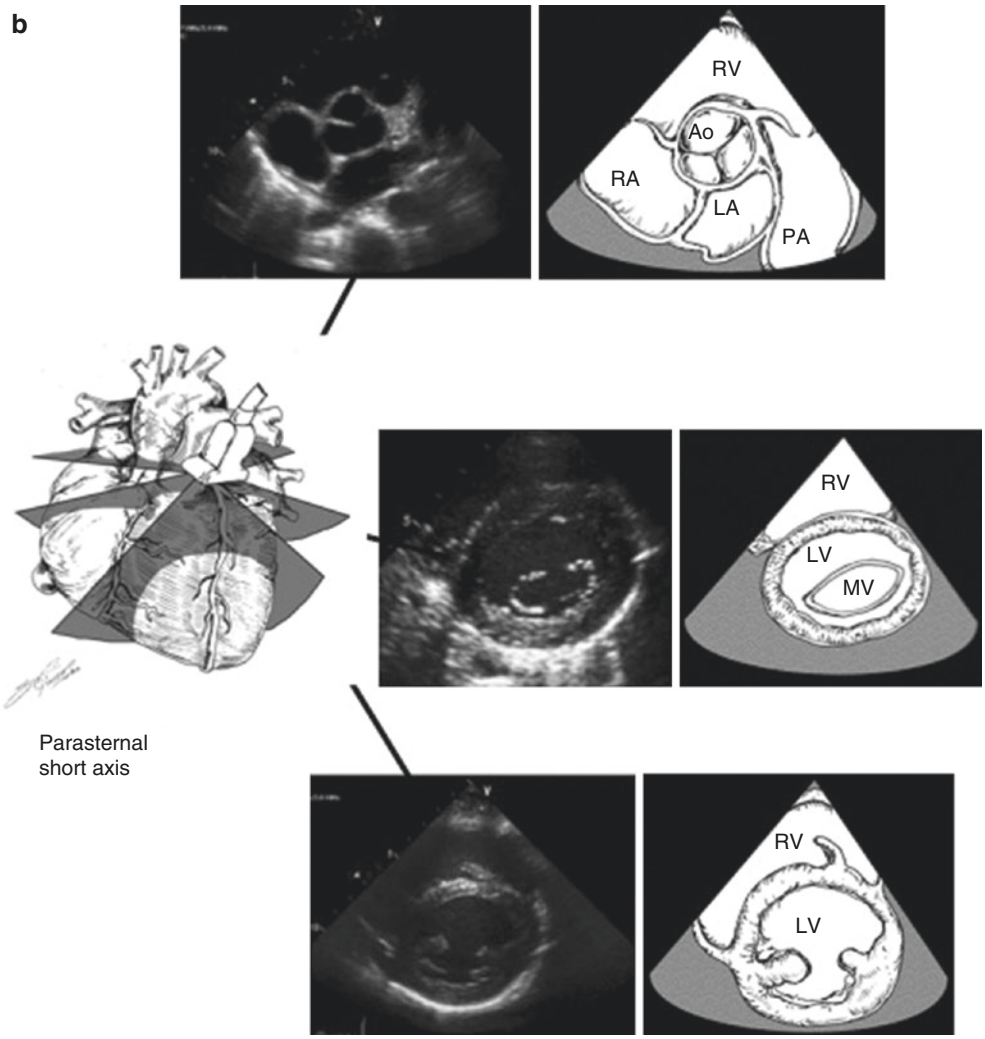


Fig. 6.1 Standard echocardiographic image planes from the high left chest just lateral to the sternum (parasternal window (**a**) and (**b**)), the left lateral chest just inferior to the nipple (apical window (**c**)), sub-xyphoid area (subcostal window (**d**)), and the suprasternal notch (suprasternal window (**e**) and (**f**)). RA right atrium, RV right ventricle, LA left atrium, LV left ventricle, LCA left coronary artery, LPA left pulmonary artery, Ao aortic valve, CS coronary sinus, PA pulmonary artery, RCA right coronary artery, RPA right pulmonary artery, RVOT right ventricular outflow tract, SVC superior vena cava (Drawings by Steven P. Goldberg, MD). (**g**) Suprasternal long axis view. Superior images: Innominate vein, SVC, Aorta. Inferior images: Aortic arch, left carotid artery and left subclavian in relation to Right pulmonary artery and left atrium, (**h**) Suprasternal short axis view. Superior images: Aorta, main pulmonary artery, RPA and LPA. Inferior images: Aorta, RPA, LA and pulmonary veins

Fig. 6.1 (continued)



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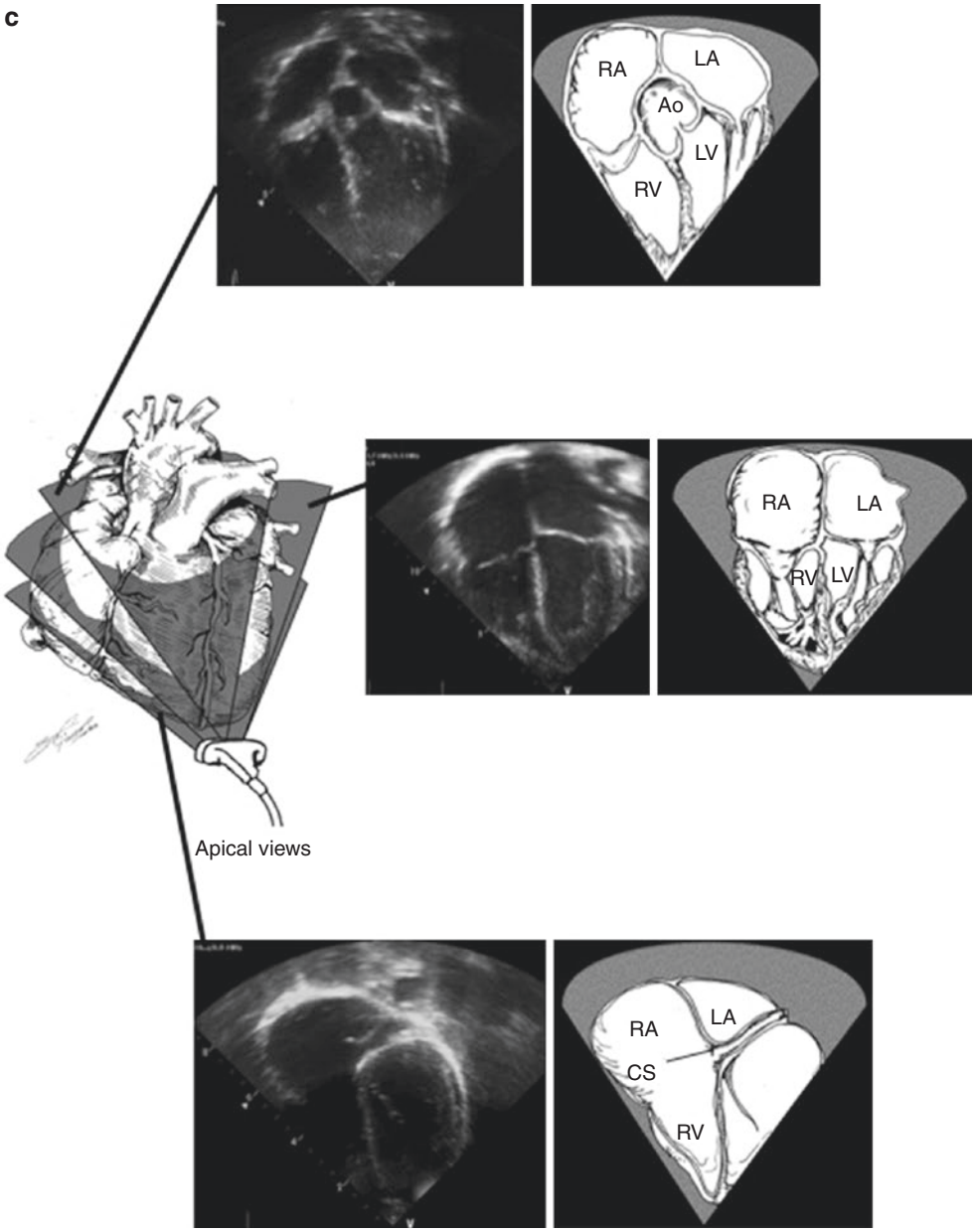

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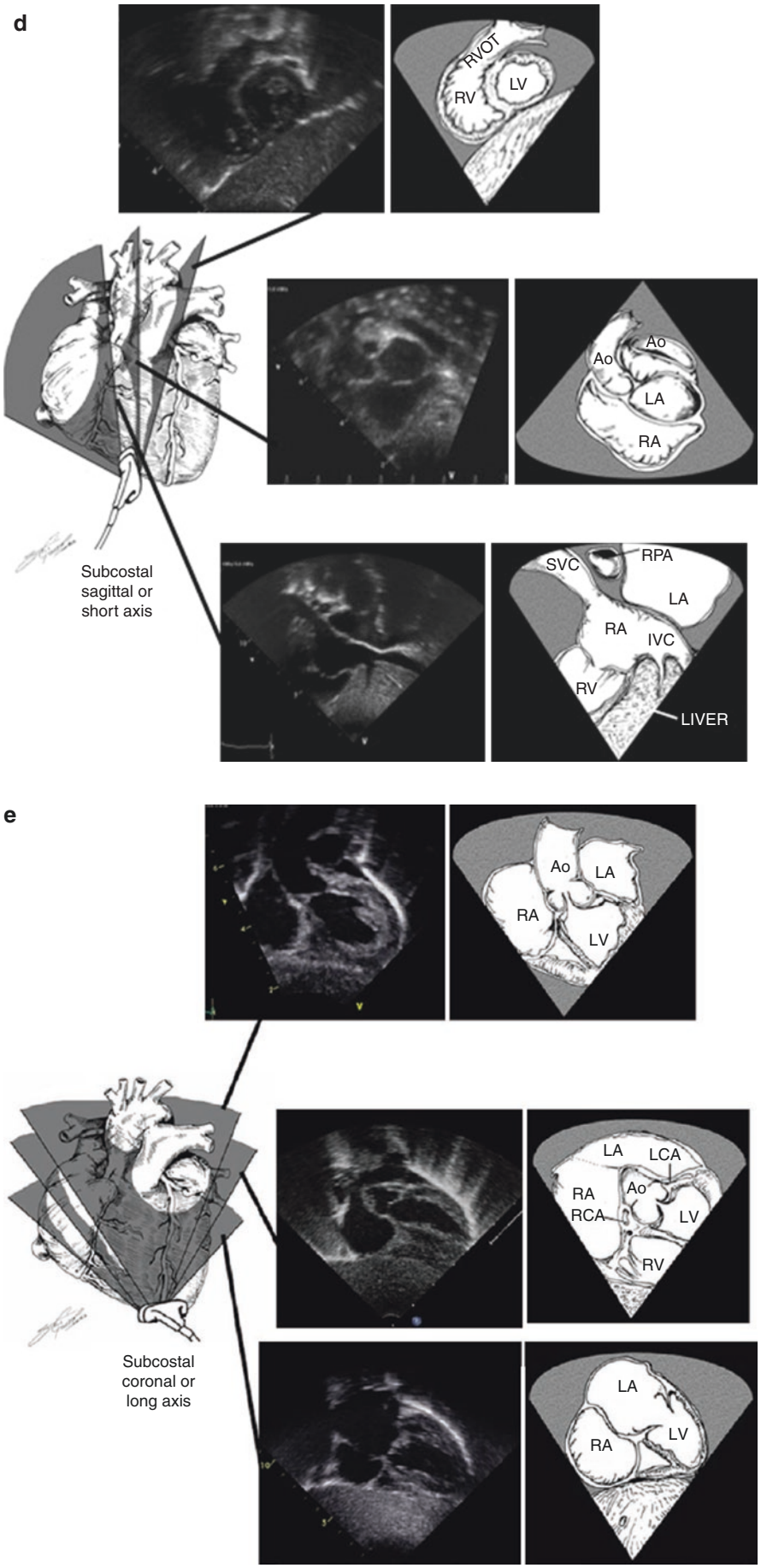

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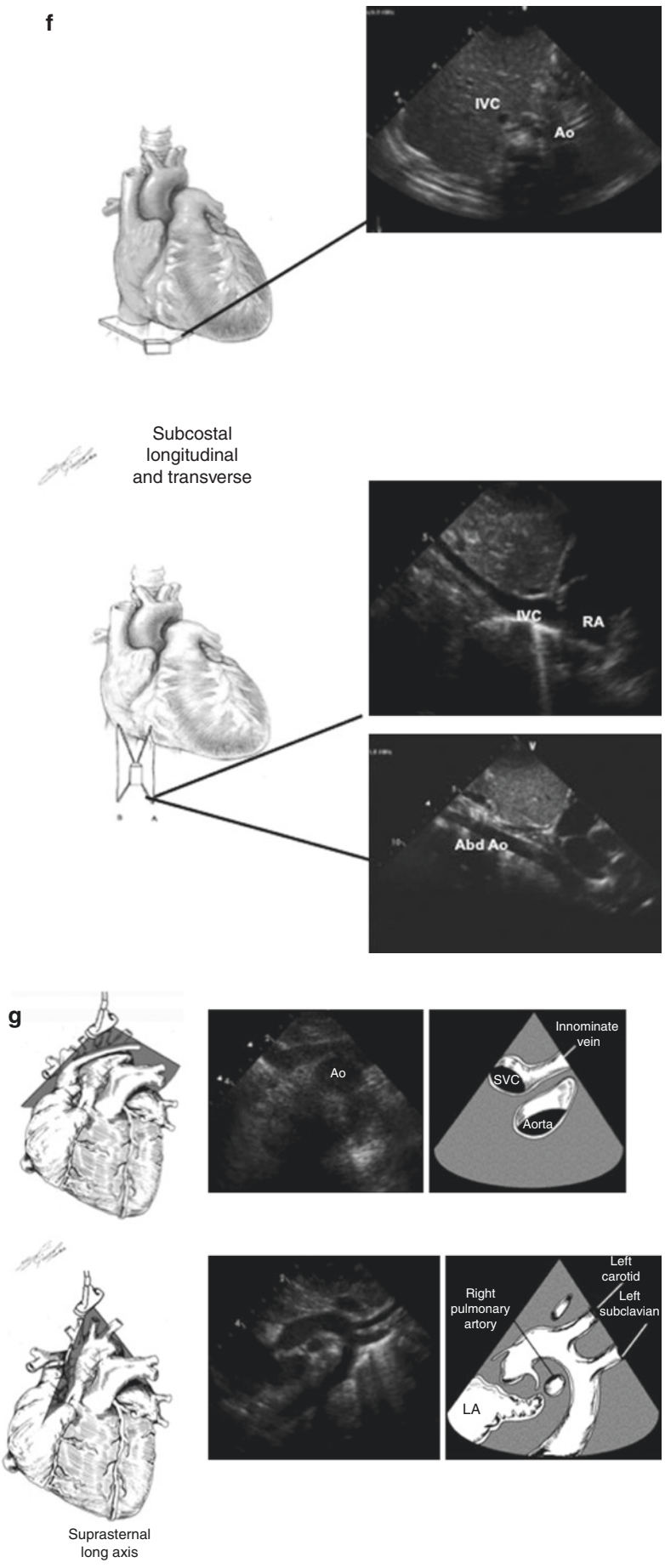

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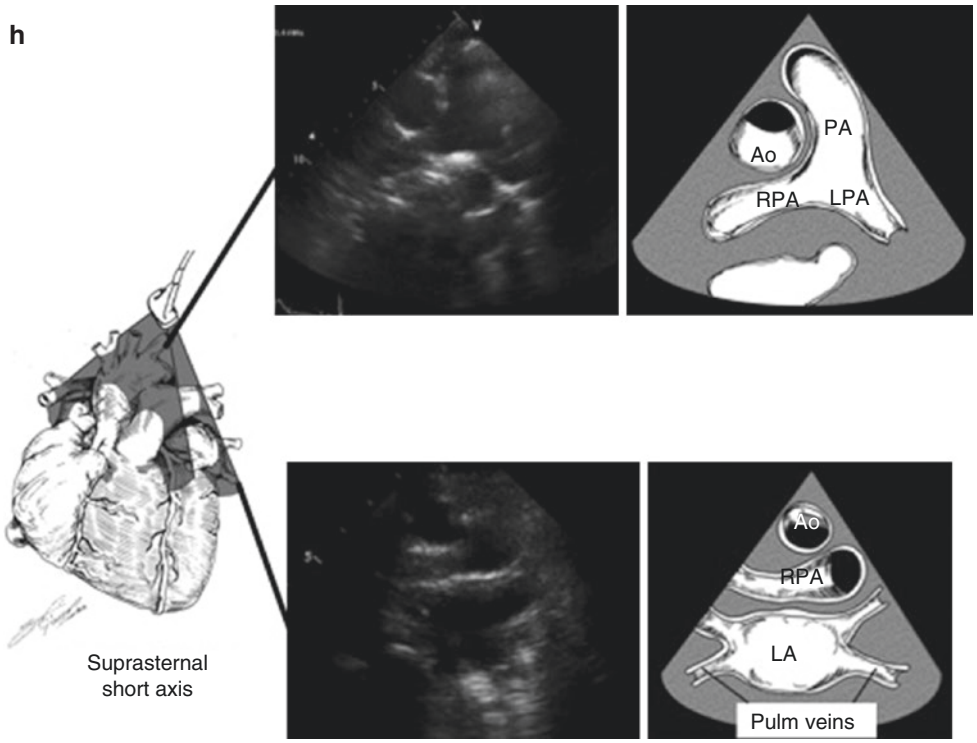
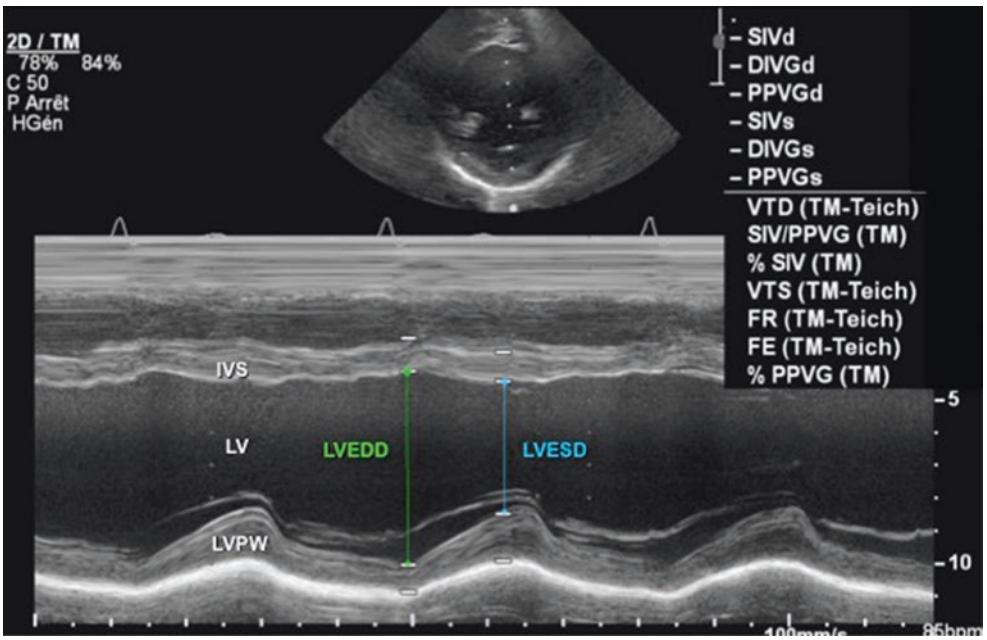


Fig. 6.2 M-mode echocardiography obtained in the parasternal short axis through the right and left ventricular chambers at the level of the papillary muscles (Courtesy of N. Sekarski, MD). *IVS* interventricular septum, LV left ventricle, LVEDD left ventricular end-diastolic dimension, LVESD left ventricular end-systolic dimension, LVPW left ventricle posterior wall



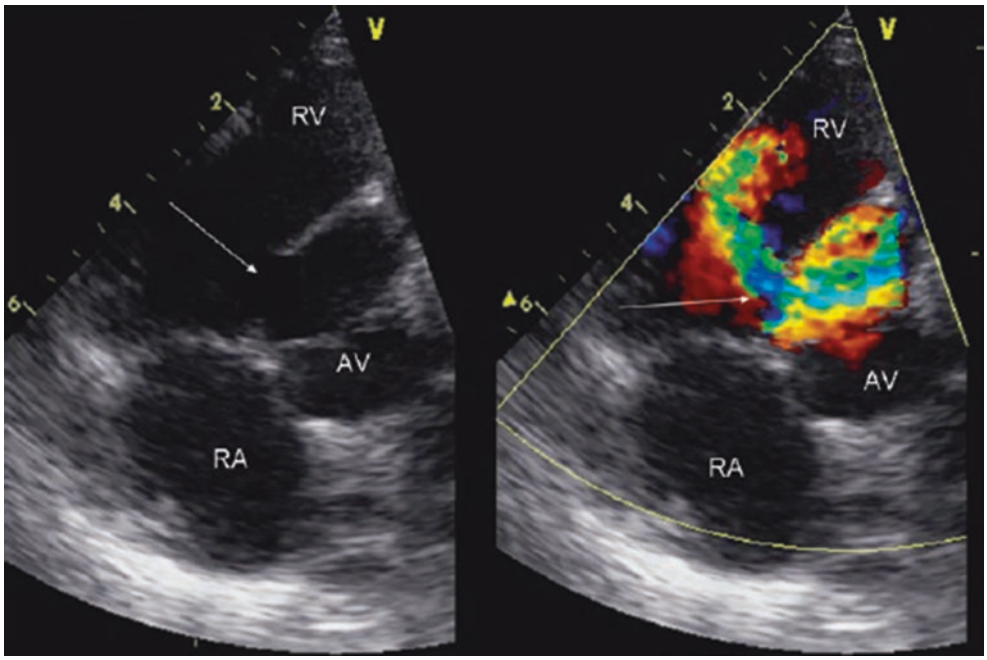


Fig. 6.3 Parasternal short axis image in a patient with pulmonary atresia/VSD who acutely decompensated. White arrows demonstrate the large residual VSD than resulted when a patch dehisced. RA right atrium, RV right ventricle, AV aortic valve

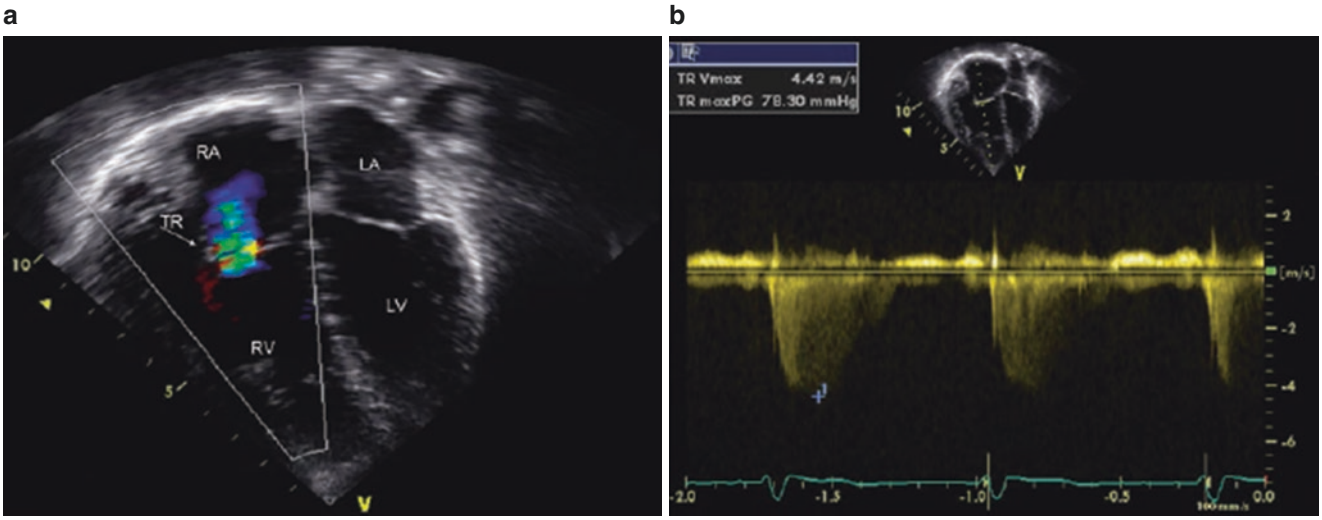


Fig. 6.4 (**a**) and (**b**): Four-chambered view demonstrating color Doppler of tricuspid regurgitation and the corresponding spectral Doppler pattern. The velocity obtained by spectral Doppler may be utilized to estimate pulmonary artery pressures in the absence of downstream obstruction. A complete envelope by pulse wave or continuous wave Doppler provides the velocity of the regurgitant jet, which may be translated into pressure data using the equation $\Delta P = 4(\text{Vmax})2$. RA right atrium, RV right ventricle, LA left atrium, LV left ventricle

6.3.2 Apical Window

For clinicians not formally trained in echocardiography, the images obtained with the transducer in the apical position (Fig. 6.1c) are perhaps the most intuitive as it allows for visualization of all four chambers and valves in the heart with a simple left-to-right orientation. Imaging is begun in the four-chamber view, in which the anatomic right and left ventricles may be identified. Sweeps of the transducer from this position identify the posterior coronary sinus and may indicate abnormalities such as a left superior vena cava or unroofed coronary sinus. Proceeding more anteriorly to a five-chambered view, the atrial and ventricular septa may be visualized looking for defects and the left ventricular outflow tract and ascending aorta may be examined. The four chamber view allows for the examination of the anterior and posterior mitral valve leaflets and pulmonary veins as they enter the left atrium. By rotating the transducer counterclockwise to 90° from the four-chamber view, a two-chamber view of the left ventricle and left atrium can be obtained to evaluate the anterior and posterior left ventricular wall function.

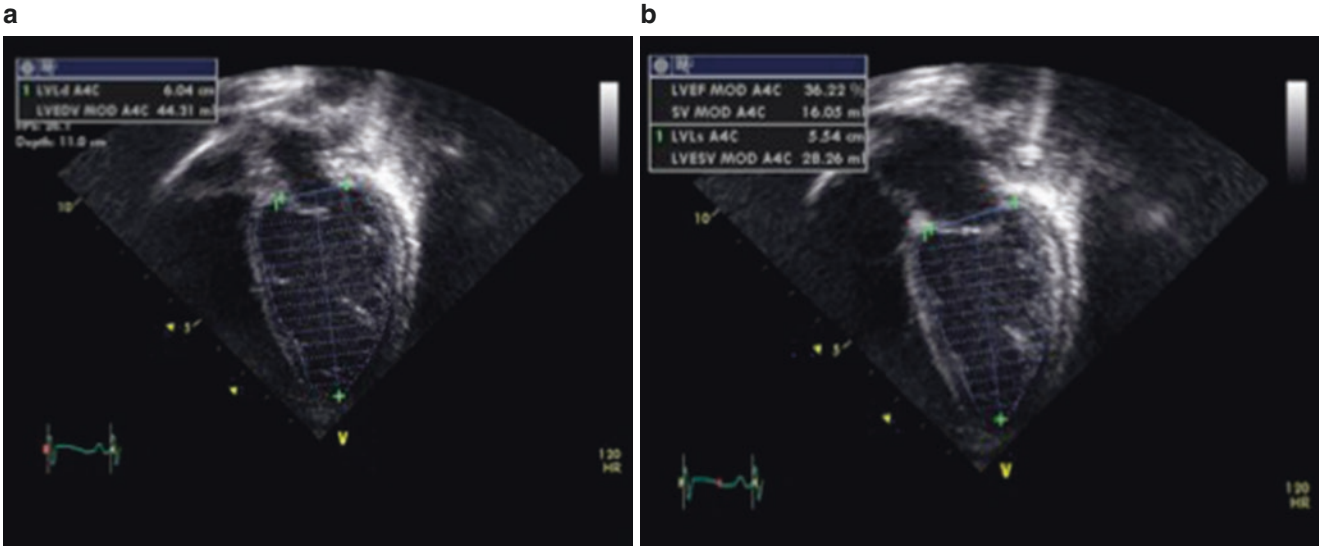


Fig. 6.5 Demonstrates 2D echocardiography from an apical four-chamber view with tracing of the LVEDV (**a**) and of the LVESV to allow for calculation of the ejection fraction (EF) using the Simpson's method (**b**). *LVEDV* left ventricular end-diastolic volume, LVESV left ventricular end-systolic volume, TR tricuspid regurgitation

6.3.3 Subcostal Window

For pediatric patients with complex cardiac anatomy, the subcostal position (Fig. 6.1d, e, f) provides the most detailed information and is often the best starting place. In order to obtain images in this position, patients are placed supine with the transducer in the subxiphoid position. In larger cooperative patients beyond the infancy period, image quality may be improved by having the patient participate in the examination with held inspiration that allows the heart to move downward toward the transducer. Initial views in this position should determine visceral situs, as well as the relationship of the inferior vena cava and aorta. Subsequent views and sweeps will provide detailed analysis of the atrial septum, as well as the images related to the ventricular septum, the atrioventricular valves, atrial and ventricular chambers, and drainage of systemic veins. With the rotation of the transducer, both ventricular outflow tracts may be visualized. Additionally in some patients, especially in the neonates and young children, the branch pulmonary arteries and the entire aorta may be examined from this position.

6.3.4 Suprasternal Window

The views are obtained in this position by placing the transducer in the suprasternal notch (Fig. 6.1g, h) with the neck extended. The suprasternal long- and short-axis views provide detailed information regarding arch sidedness, anomalies in the ascending and descending aorta and head and neck vessels, the size and branching of the pulmonary arteries, as well as anomalies of systemic and pulmonary venous systems.

6.4 M-Mode Imaging

One of the earliest applications of the ultrasound technology that remains an important tool in the evaluation of cardiac function, dimension, and timing, the M-mode echo provides an "ice-pick" view of the heart. An M-mode echo is obtained with the ultrasonic transducer placed along the left sternal border and directed toward the part of the heart to be examined. A single line of interrogation is repeatedly produced, and the resultant image is displayed with time along the x-axis and distance from the transducer along the y-axis (Fig. 6.2). M-mode obtains an estimate of ventricular function by measuring the fraction shortening (FS) and wall thickness in the parasternal short and long axis views.

6.5 Doppler Evaluation

Frequently in an intensive care setting, the clinician is concerned with new or residual flow disturbances from shunt lesions, an abnormal cardiac valve, or narrowing of a blood vessel. While 2D echocardiography determines anatomical relationships, additional information regarding movement of the blood or myocardium is provided by studying the Doppler shifts in the reflected ultrasound waves. The Doppler principle, first described by Johann Christian Doppler, states that for a stationary object, the frequency of ultrasound reflected is identical to the transmitted frequency. Inherently, the heart and the blood it pumps do not fit this basic definition. Therefore, when performing a cardiac ultrasound, the moving objects alter the frequency of the reflected signal (the Doppler shift) according

to the direction and velocity with which they are moving in relation to the fixed transducer [7].

Additional insights to intracardiac and vascular hemodynamics may be obtained when velocity data are collected. Doppler data are typically displayed as velocity rather than the actual frequency shift. The velocities can then be translated into pressure data using the modified Bernoulli equation:

$$P1 - P2 = 4\left(V_2^{\,2} - V_1^{\,2}\right)$$

$$\Delta P = 4\left(V_{\max}\right)^2$$

If one assumes that the level of obstruction and therefore the velocity of V_1 are negligible compared with the obstruction at V_2, the formula becomes even simpler: $DP = 4(V_{max})^2$. Although the modified Bernoulli equation can only be applied in appropriate situations, it does help predict the pressure drop across an abnormal valve or septal defect to give a general estimate of the severity of the lesion or pathophysiology, and this is particularly valuable in managing critically sick patients in the intensive care setting.

Of note, during Doppler imaging, it is clinically important to recognize the angle of interrogation of blood flow and its impact on the accuracy of our velocity measures. It is important when performing Doppler studies that the line of beam interrogation should be directly in the line of flow, resulting in as little distortion of data as possible. The more off angle the approach is, the increasingly more severe the underestimation of the true velocity will be. For practical purposes, an angle of interrogation less than 20° is essential to ensure clinically accurate information.

Two commonly used techniques are pulse wave (PW) and continuous wave (CW) Doppler. Pulse wave (PW) Doppler allows determination of direction and velocity at a precise point within the imaged cardiac field. However, it is limited in its maximum detectable velocity by the Nyquist limit, making it unusable for the quantification of high-velocity flow (e.g., as seen with severe obstruction). In contrast, continuous wave (CW) Doppler interrogates all points along a given beam. Continuous wave (CW) Doppler imaging is not constrained by velocity limits and can hence record velocities exceeding those of pulsed Doppler imaging. The drawback is that while the line of interrogation is identifiable, knowledge of anatomy must already be obtained to identify the precise location of the maximum velocity. Clinically these two techniques are commonly used sequentially to identify the area of interest and then to obtain the maximum velocity.

6.5.1 Color Flow Doppler

Color flow Doppler is a powerful technique for obtaining additional hemodynamic and anatomic data for patients undergoing echocardiography in the intensive care unit. Color flow Doppler allows velocity information to be overlaid on a 2D anatomic image, therefore, providing data regarding intracardiac and extracardiac shunts, valvar insufficiency or stenosis, and vessel obstruction. By convention, shades of red are used in identifying blood flowing toward the transducer and blue to indicate blood flowing away from the transducer. Therefore, color flow Doppler defines the presence and direction of shunts and is often used to grade the severity of valvar insufficiency.

6.6 Current Clinical Applications

Clinical applications of echocardiography within the intensive care unit may be divided into the following major areas:

1. The diagnosis and postintervention evaluation of anatomic lesions
2. Evaluation of cardiac function and hemodynamics
3. Diagnosis of intracardiac masses and extracardiac effusions
4. Guidance of intervention within the intensive care unit

6.7 Anatomic Lesions Pre- and Postintervention

Advances in technology have enabled most congenital heart defects to be diagnosed by echocardiography avoiding the risks, time, and cost of invasive cardiac catheterization [2–4]. In addition, for infants and pediatric patients admitted to an intensive care unit due to being succumbed to shock, echocardiography may be useful for differentiating anatomic causes of shock from functional causes. Patients with obstruction to outflow on the left side of the heart who go undiagnosed at birth frequently present with signs of diminished cardiac output (CO) or frank shock. These lesions, including aortic valve stenosis, coarctation of the aorta, and variations of hypoplastic left heart syndrome, may be identified and defined by echocardiogram alone.

Following surgical or catheter-based intervention, patients convalesce in the intensive care unit. Most patients undergo a postprocedural echo before getting discharged home to document adequacy of the repair and lack of significant complications. In postoperative patients, this assessment may prove more complicated as access to the patient and the correct windows may be severely compromised by dressings, intracardiac lines, and chest tubes. Occasionally, postoperative patients in the intensive care unit may be found to have unexpected residual lesions (Fig. 6.3). For example, following repair of septal defects, echocardiography may be useful

to screen for the presence of residual shunts, which may be less well tolerated secondary to myocardial changes following cardiopulmonary bypass [8]. Often the presence of a residual lesion is known in the operating room through transesophageal echocardiography or direct discussion with the surgeon. An important role of echocardiography is to distinguish those lesions with hemodynamic consequences from those whose presence has no impact on postoperative care. Transthoracic echocardiography may be used to diagnose and assess the hemodynamic sequelae of shunt lesions, residual stenosis, and function. The assessment of coronary flow, right ventricular dynamics, and distal obstruction following intervention is more complicated and technically challenging. In patients who are experiencing arrhythmias postoperatively, special attention should be paid to the flow within the coronary arteries to ensure that it has not been compromised or that a line or mass in the heart is not causing ectopy.

Unanticipated pulmonary arterial hypertension may slow the progress of a patient in the intensive care unit. In the absence of a Swan Ganz catheter or a direct pulmonary arterial monitoring, echocardiography may be used to estimate the pulmonary artery pressure [9, 10]. There are several methods that may be used to determine the pulmonary artery pressures. In a patient with tricuspid regurgitation, the velocity of the jet (VTR_{max}) estimates (using the modified Bernoulli equation) the difference in pressure between the right atrium and the right ventricle (Fig. 6.4). If there is no stenosis of the pulmonary arteries, pulmonary valve, or right ventricular outflow tract, the difference between the right atrial pressure (RAP) and right ventricular pressure (RVP) plus the right atrial pressure (RAP = CVP) provides an estimate of the systolic pulmonary arterial pressure (PAP):

$$\Delta P = \mathrm{RVP} - \mathrm{RAP} = 4\left(\mathrm{VTR}_{\max}\right)^2$$

$$\mathrm{RVP} = 4\left(\mathrm{VTR}_{\max}\right)^2 + \mathrm{RAP}$$

$$\text{Systolic PAP} = 4\left(\mathrm{VTR}_{\max}\right)^2 + \mathrm{RAP}$$

In the absence of tricuspid valve insufficiency, interventricular septal geometry may be used to help quantify the degree of pulmonary hypertension.

The same principle can be applied in patients with residual shunting through a ventricular septal defect (VSD) or through a patent ductus arteriosus (PDA). The velocity of blood flow through the defect reflects the pressure difference between the two cavities (between left ventricle and right ventricle for a VSD and between aorta and pulmonary artery for a PDA). Indeed, the higher is the velocity of the blood flow through the defect, the lower the systolic pulmonary artery pressure will be. The systolic PAP can be easily estimated by retracting the pressure gradient through the defect from the blood pressure (the BP is equal to the systolic LV pressure in the absence of LVOT obstruction) of the patient, using the following formula:

$$\text{Systolic PAP} = \mathrm{BP} - \left[4\left(V_{\max}\right)^2\right]$$

While estimating pressure using the Doppler method, the angle of insonation, namely the angle of interrogation between the blood flow and Doppler line, should be kept minimum and higher angle will underestimate the pressure gradient.

6.8 Analysis of Ventricular Function

One of the most frequent uses of echocardiography in the ICU is related to the evaluation of ventricular performance. Improvements in technology allow assessment of both systolic and diastolic function with increasing accuracy. Accurate and timely assessment of systolic function should be an integral part of the medical management of the hemodynamically unstable critically ill patient.

6.8.1 Left Ventricular Systolic Function

Visual assessment of left ventricular systolic function by "eyeballing" the contractility is probably the method of choice for nonechocardiographers and is often used in the intensive care setting. Ejection fraction is estimated visually using multiple echocardiography views. Left ventricular function is subjectively classified into normal function (EF $\geq$ 55%), mild dysfunction (EF 41–55%), moderate dysfunction (EF 31–40%), and severe dysfunction (EF $\leq$ 30%) [11].

Global assessment of LV contractility includes the determination of ejection fraction (EF), circumferential fiber shortening (FS), and cardiac output (CO). There are several methods that may be used to garner this information. Each has its limitations and assumptions, which are important to be understood prior to clinically applying the information gathered. For an assessment of the left ventricular function, perhaps the simplest quantitative approach is to use M-mode echocardiography (Fig. 6.2) in either the parasternal short axis at the level of the papillary muscles or in the parasternal long axis at the tips of the mitral valve leaflets to measure the left ventricular end-diastolic dimension (LVEDD) and left ventricular end-systolic dimension (LVESD) for the determination of the fractional shortening (FS) percentage. Fractional shortening is derived by the following:

$$\mathrm{FS}(\%) = \frac{\mathrm{LVEDD} - \mathrm{LVESD}}{\mathrm{LVEDD}} \times 100$$

Normal values for fractional shortening in children and infants vary slightly with age, falling typically between 28% and 44% [12–14].

Fractional shortening, therefore, provides a method of assessing circumferential change but has several obvious drawbacks. This method assumes that the ventricle being examined has a circular shape in the axis in which it is examined. As a result, changes in diameter may be mathematically related to circumferential fiber shortening providing an estimate of ventricular function. Therefore, anything that alters the circular shape of the left ventricle (anatomic abnormalities intrinsic to congenital heart disease, pre- and afterload changes, or ventricular–ventricular interactions) may affect the assessment of fractional shortening by altering the movement of the septum and causing an under- or overestimation of either the end-systolic or diastolic dimension.

A second method of assessing ventricular function is via ejection fraction. Ejection fraction is a volumetric appraisal of ventricular fiber shortening. Echocardiographically, the most common method of calculating ejection fraction is the biplane estimation of volumes from the apical four-and two-chamber views. One of the more commonly used mathematical algorithms is the Simpson method, in which the left ventricle is traced manually at the end diastole and end systole along the endocardium (Fig. 6.5). Using the method of disks, the left ventricle is divided into a series of parallel planes, and the resultant disks are individually summed up to create each volume [15, 16]. Ejection fraction is calculated using the left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) with the following equation:

$$\mathrm{EF}(\%) = \frac{\mathrm{LVEDV} - \mathrm{LVESV}}{\mathrm{LVEDV}} \times 100$$

Normal values for ejection fraction in children are 56–78%. Unfortunately, the determination of an accurate ejection fraction is also subject to ventricular shape with the left ventricle assumed to be its normal prolate elliptical shape. Variations from this shape, which occur frequently in pediatrics, significantly alter the relationship between fiber shortening and volume dependence when this equation is applied. In addition, patients in the intensive care environment frequently have suboptimal imaging windows making the endocardium difficult to distinguish and trace.

Not infrequently in active pediatric intensive care units, a patient's heart and/or lung function must be supported for a period of time. Two such modalities of support are extracorporeal membranous oxygenation and ventricular assist devices. Often the pediatric echocardiographer is asked to assist in the management of these patients by providing insight into the recoverability of cardiac function. This request can be one of the more challenging uses of echocardiography in an intensive care setting. As discussed above, many of the techniques commonly used to determine ventricular systolic function and CO are dependent on the loading conditions of the heart, as well as contractility. As a result, both of these support systems, which unload the heart in an effort to allow recovery time, severely limit echo's utility as a prognostic indicator.

Alternative parameters for the evaluation of left ventricular function should be considered, especially in patients with poor image quality in the intensive care setting. The Tei index represents an index of myocardial performance (myocardial performance index = MPI) that allows evaluation of both systolic and diastolic function [17]. The MPI has proved to be a reliable method for the evaluation of LV performance. It is calculated on a pulsed wave (PW) Doppler at the mitral and aortic valve or on a Tissue Doppler tracing at the lateral mitral annulus (Fig. 6.6) by dividing the isovolumetric

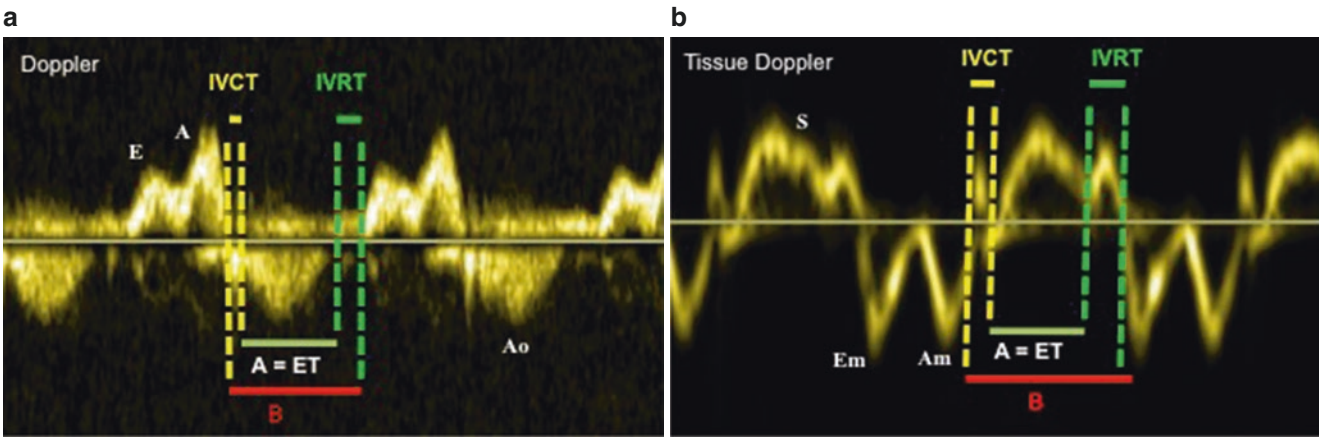


Fig. 6.6 Demonstrates how to calculate the Tei index from Doppler (**a**) through the left ventricular outflow tract with mitral E and A wave and aortic Doppler flow (Ao) and from Tissue Doppler (**b**) at the mitral annulus with mitral Em and Am waves and systolic (S) wave, allowing to obtain IVCT, IVRT, and ET. ET ejection time, IVCT isovolumic contraction time, IVRT isovolumic relaxation time, E Doppler mitral early diastolic wave, A Doppler mitral late diastolic wave, S TIssue Doppler mitral systolic wave, Em TIssue Doppler mitral early diastolic wave, Am Tissue Doppler mitral late diastolic wave

relaxation time (IVRT) plus the isovolumetric contraction time (IVCT) by the ejection time (ET):

$$\text{Tei index}\left(\text{MPI}\right) = \frac{\text{IVRT} + \text{IVCT}}{\text{ET}} = \frac{B - A}{A}$$

The Tei index is affected by the age during the first 3 years of life, showing a progressive reduction until the age of 3, and the values are significantly greater at lower ages (0.4 ± 0.09) [18]. There are no further changes from ages 3 to 18 years, with normal values of 0.33 ± 0.02 by pulse wave (PW) Doppler.

Several newer methods of determining myocardial function, including tissue Doppler imaging (TDI), strain and strain rate, color M-mode, calcium gating, and three-dimensional (3D) echocardiography, are entering the realm of echo in the intensive care unit. These newer modalities may prove to be more efficacious than current standard echocardiography is at present, particularly for tissue Doppler imaging (TDI), which allows the evaluation of myocardial velocities. Peak systolic annular velocity (S′) measured at the level of the mitral annulus reflects left ventricular contractility, and it has become a reliable measure of the global left ventricular function with normal values in adults >10 cm/sec.

6.8.2 Right Ventricular Systolic Function

Echocardiographic assessment of the right ventricle (RV) is more difficult because of its geometrical shape and its anterior position behind the sternum. The RV contraction differs from the left ventricle and is primarily determined by longitudinal shortening. There is little or no isovolumic contraction and relaxation, and the afterload on the RV is low [19]. Guidelines for imaging the right heart in adults have been published by the ASE in 2010 [20]. Several echocardiographic techniques have been used for the assessment of right ventricular size and function: M-mode, 2D, pulsed wave Doppler, Doppler tissue imaging, speckle tracking echocardiography, and 3D echo. The main echocardiographic views to image the right ventricle are the parasternal long and short axes and the apical and the subcostal views.

Qualitative evaluation of the RV ("eyeballing" technique) has long prevailed in the regular clinical setting. However, besides being echocardiographer dependent, it is imprecise and often insufficient. An approximate assessment of RV size can be made by comparing it with the LV size. RV is normal if it is less than 2/3 of the LV size, mildly increased if it is more than 2/3 of the LV, moderately enlarged when it is about the same size, and greatly enlarged when it is bigger than the LV [21]. RV function can also be evaluated qualitatively. The best view to assess the RV function is the parasternal short axis at the level of the papillary muscle to look at the RV free wall and the septal motion.

Tricuspid annular plane systolic excursion (TAPSE) is the measure of the excursion of the tricuspid annulus between early diastole to end systole. It is measured by placing an M-mode cursor through the lateral tricuspid annulus in a four-chamber view (Fig. 6.7). TAPSE measurement is simple to obtain, is a reliable parameter of RV function, and has been well correlated with RV ejection fraction by MRI [22].

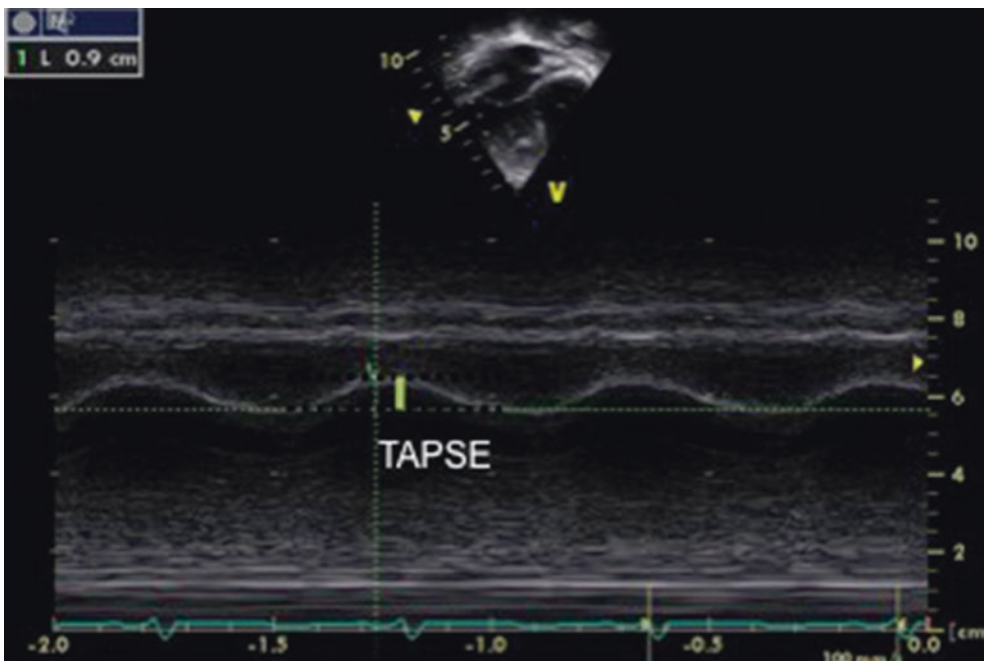


Fig. 6.7 demonstrates M-mode echocardiography with the cursor placed on the tricuspid annulus allowing to measure a decreased tricuspid annular plane systolic excursion (TAPSE)

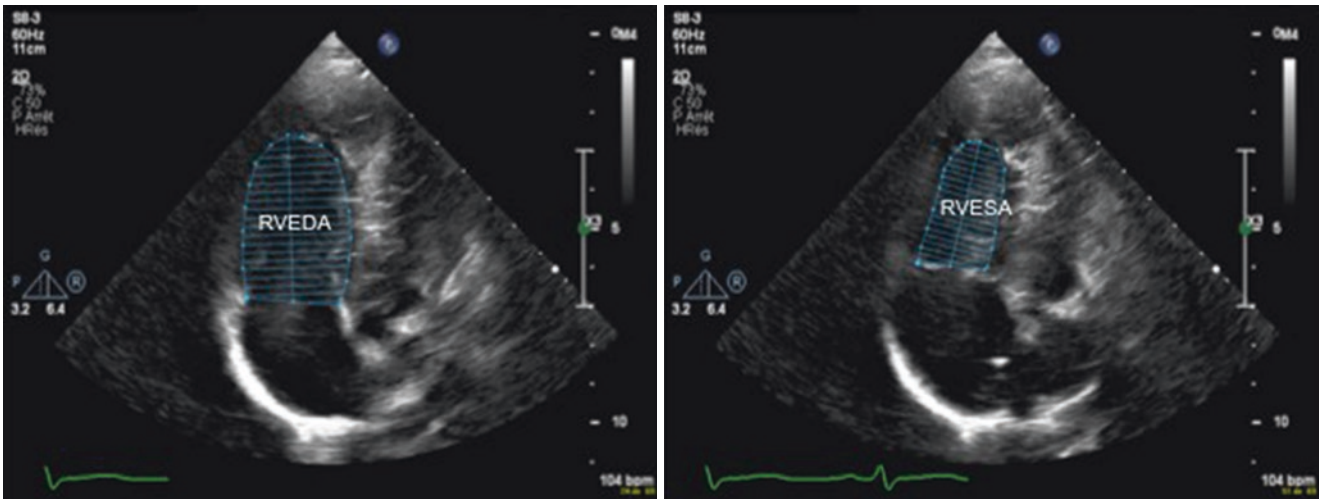


Fig. 6.8 demonstrates 2D-echocardiography with tracing of the RVEDA and RVESA to obtain the FAC of the right ventricle (Courtesy of N. Sekarski, MD). FAC fractional area change, RVEDA right ventricular end-diastolic area, RVESA right ventricular end-systolic area

Fractional area change (FAC) is probably the best assessment of RV systolic function by echocardiography and has been shown to correlate well with cardiac MRI. It is measured by using the following formula (Fig. 6.8) with normal values ranging from 43 ± 18%:

$$\text{RV FAC}(\%) = \frac{\text{RVEDA} - \text{RVESA}}{\text{RVEDA}} \times 100$$

6.8.3 Diastolic Function

Accurate assessment of diastolic function by echocardiography is an evolving field that has made great strides in the past few years. Diastolic heart failure and its impact on postoperative management also deserve consideration. Spectral Doppler evaluation is a relatively easy and useful method for evaluating diastolic function noninvasively at the bedside.

Spectral Doppler evaluation is for the quickest method to judge diastolic function at the bedside. A prominent pulmonary vein atrial reversal wave (a wave) is a marker of diastolic dysfunction. This finding represents marked flow reversal into the pulmonary veins during atrial systole in response to a noncompliant ventricular chamber. The mitral inflow Doppler pattern can also be a useful marker for diastolic dysfunction. Mitral inflow is composed of two waves—an E wave representing early passive ventricular filling (preload dependent) and an A wave representing active filling as a result of atrial systole. The E:A ratio, velocity of E wave deceleration and duration of the A wave, can be altered in patients with diastolic dysfunction. Age, arrhythmia, conduction disturbances, and changes in loading conditions may affect the Doppler signal and represent a major limitation particularly in critical care patients.

Tissue Doppler imaging (TDI) is a newer technique for assessing diastolic ventricular function. TDI allows recording of the low Doppler velocities generated by the ventricular wall motion and directly measures myocardial velocities. In spectral TDI, pulsed Doppler is placed along the myocardial wall (mitral, septal, or tricuspid annulus) recording the peak myocardial velocities. Three waveforms are obtained: a peak systolic wave (Sa), an early diastolic wave (Ea), and an end-diastolic wave (Aa) produced by atrial contraction [23]. The tissue Doppler systolic mitral annular velocity has been shown to correlate with global LV myocardial function [24]. TDI has also been used to estimate diastolic function and is relatively independent of preload condition [25, 26]. The pulsed Doppler peak early mitral inflow velocity (E) divided by the TD early diastolic mitral annular velocity (Ea) results in a ratio that correlates with the pulmonary capillary wedge pressure [27]. The E/Ea ratio is also useful in estimating mean LV filling pressure [28]. At this time, TDI represents one of the most accurate techniques to assess diastolic function and is therefore of particular interest in the critical care population in whom abrupt changes in preload and afterload are common, making Doppler evaluation of diastolic function less reliable.

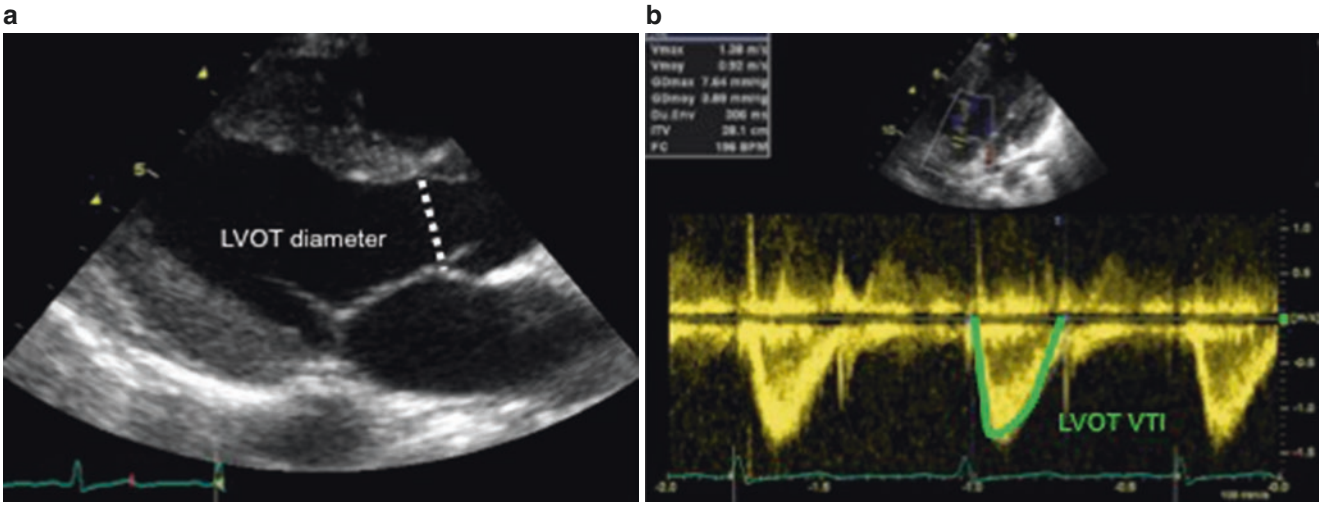


Fig. 6.9 Demonstrates how to measure the cardiac output (CO) from 2D echocardiography, with measurement of the LVOT diameter (CSA = πr^2; where r = diameter/2) (**a**) and from Doppler through the LVOT with measurement of LVOT VTI (**b**). LVOT left ventricular outflow tract, VTI velocity time integral, CSA cross-sectional area

6.9 Evaluation of Hemodynamics

6.9.1 Cardiac Output and Cardiac Index

The evaluation of cardiac output by echocardiography is well established in children and can be performed on bedside echocardiography, even in sick children in an intensive care setting. The cardiac output is the stroke volume multiplied by the heart rate and may be decreased in the presence of impaired ventricular function. Assessing cardiac output may help in targeting the specific treatment in critically ill children.

The echocardiographic assessment of cardiac output can be obtained by multiplying the cross-sectional area (CSA in cm^2) of the left ventricular outflow tract by the velocity time integral (VTI in cm/sec) of blood flow across the left ventricular outflow tract (Fig. 6.9) and by the heart rate (HR in beats/min) [29].

$$\mathrm{CO}\left(\mathrm{ml}/\mathrm{min}\right) = \mathrm{CSA} \times \mathrm{VTI} \times \mathrm{HR}$$

$$\text{where}\,\mathrm{CSA}\left(\mathrm{cm}^2\right) = \pi \times r^2\ \left(\text{with}\ r = \text{diameter}/2\mathrm{x}\right)$$

Cardiac index can be derived by dividing the cardiac output by body weight in kilogram or by referring the cardiac output to the body surface area (BSA) [30].

$$\mathrm{CI}\left(\mathrm{ml}/\mathrm{min}/\mathrm{m}^2\right) = \frac{\mathrm{CSA} \times \mathrm{VTI} \times \mathrm{HR}}{\mathrm{BSA}}$$

Despite various assumptions and limitations, the assessment of left ventricular output on echocardiography correlates strongly to the measurements acquired by other well-established techniques such as pressure measurement by cardiac catheter and Fick's dye dilution method. The published studies showed a bias under 10% [31].

The assessment of left ventricular output is reliable in children without shunts. The authors find the trend on serial echocardiography more useful than one absolute value in clinical practice. Because CSA for any patient doesn't change and HR can be calculated precisely at any time, serial assessment of VTI may help in studying the impact of any intervention on cardiac output in real time.

6.9.2 Ventricular Filling Pressure (Preload Assessment)

Right heart filling pressure can be evaluated by assessing the inferior vena cava (IVC) size and collapsibility with respiration (Fig. 6.10). When the right atrial pressure is normal, the IVC collapses during inspiration >50%. Decreased collapsibility <50% and dilated IVC >2.1 cm in end-expiration (in adults) is a sign of increased right heart filling pressure, suggesting a right atrial pressure (RAP) >10 mmHg. Dilation of the IVC is more difficult to assess in children because of age-related change in the IVC's size but can be related to body surface area.

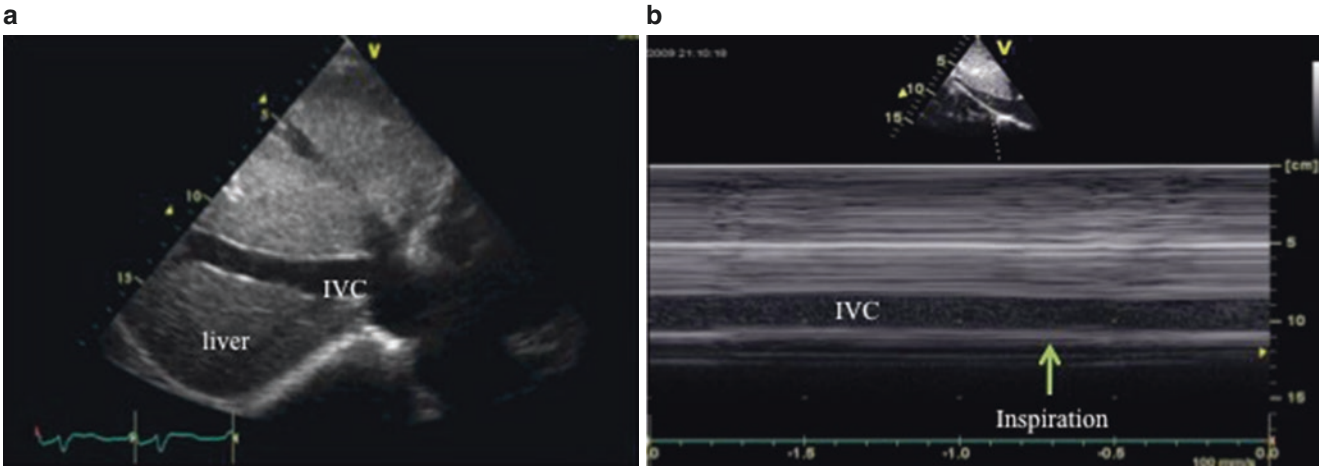


Fig. 6.10 Demonstrates 2d-echocardiography subcostal long-axis view with a dilated IVC (**a**) and M-mode echocardiography with no respiratory variation of the IVC size, suggesting high right heart filling pressure (**b**). IVC inferior vena cava

Signs of decreased right heart filling pressure include the presence of a small IVC <1.2 cm (in adults) with almost complete collapse during respiration. IVC distensibility is useful to evaluate for fluid responsiveness in patients with hypovolemic shock. Signs of positive response to fluid challenge are significant respiratory changes in IVC diameter with a distensibility index <18% and respiratory variation of stroke volume (aortic valve Doppler flow by echocardiography) of more than 20% [32, 33].

6.10 Detection of Intracardiac Masses and Extracardiac Effusions

An abnormal area of dense reflectance that is well localized within an echo may represent a mass, thrombus, or calcification. In the postoperative or critical care patient with multiple lines in place, especially in the setting of low flow, care must be taken to evaluate these areas for thrombus formation. Echo is the imaging modality of choice for elucidating and evaluating cardiac mass lesions [34]. Differentiating an area of concern from artifact can be challenging. Areas that move appropriately throughout the cardiac cycle and the presence of an abnormality in more than a single view suggest a mass rather than an artifact (Fig. 6.11a–d). These findings must in turn be distinguished from such anatomical variations as a prominent Eustacian valve or Chiari network.

Major factors that predispose a patient to the development of intracardiac thrombi are the presence of intracardiac lines, diminished CO, and localized stasis in addition to changes within the clotting cascade from sepsis, bypass, intrinsic clotting disorders, or heparin use. Echocardiographic evaluation of patients within the intensive care setting must include an awareness of the increased incidence of thrombus formation and a careful evaluation of areas predisposed to become a nidus for thrombus.

Following cardiac surgery, it is not uncommon for patients to develop small collections of fluid in the pericardial space (Fig. 6.12). Typically, this is of little concern to the clinician; however, in a postoperative patient experiencing tachycardia and/or hypotension, the necessity of recognizing the potential for and screening for cardiac tamponade becomes paramount. In young infants and children, it is frequently difficult to rely on the physical exam findings of increased jugular venous pressure or the late finding of pulsus paradoxus. In this instance, a directed and easily performed 2D and Doppler echocardiography can confirm the presence of an effusion and provide accurate assessment of its hemodynamic significance [35].

The size and extension of a pericardial effusion may be diagnosed from parasternal, apical, or subcostal windows. The apical view is the easiest for obtaining information regarding the effusions' hemodynamic significance. From the apical four-chamber view, both the mitral and tricuspid valve flow patterns are evaluated with the respiratory monitoring in place. Examining the changes in inflow hemodynamics with respiration allows for the evaluation of tamponade physiology. Greater than 25% variability in maximal E wave velocity of the mitral valve with inspiration or 50% of the E wave velocity of the tricuspid valve (Fig. 6.13a, b) is indicative of significant hemodynamic compromise resulting from the effusion [36]. Additionally, collapse (differentiated from contraction) of the free wall of the right and left atrium (Fig. 6.14a, b) when the pericardial pressure exceeds the atrial pressure may be seen from this view in a patient with a significant effusion [37–42].

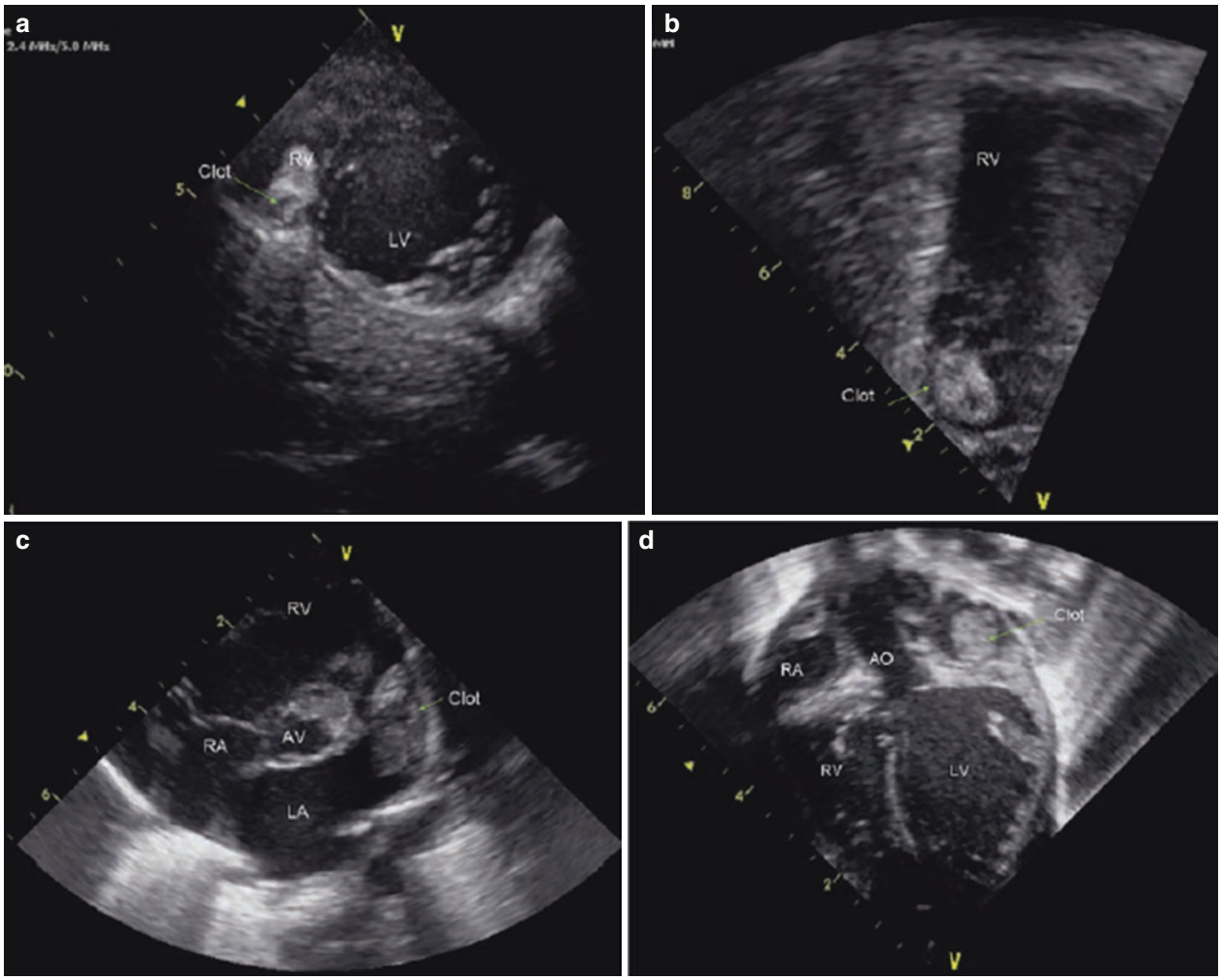


Fig. 6.11 Demonstrates a thrombus in the right ventricle seen in parasternal short axis (**a**) and modified four-chamber (**b**) views. *RV* right ventricle, *LV* left ventricle. (**c**) and (**d**): demonstrate a thrombus in the left atrial appendage in both parasternal short axis and a modified four-chamber views. RA right atrium, RV right ventricle, AV aortic valve, AO ascending aorta, LV left ventricle

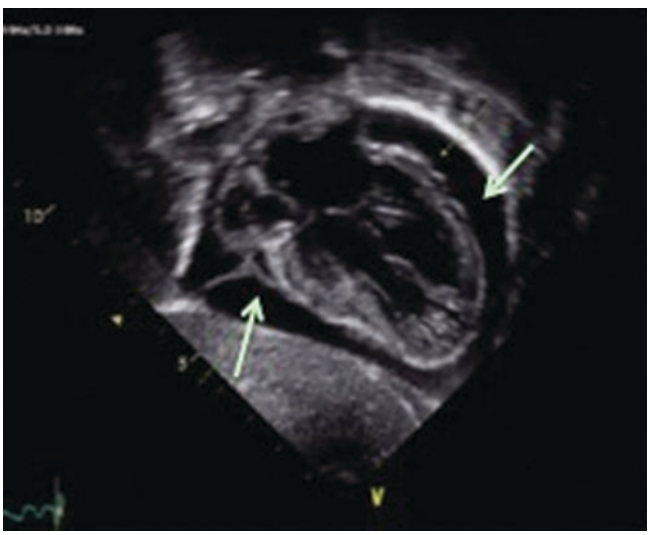


Fig. 6.12 Subcostal image demonstrating a large circumferential pericardial effusion (green arrows)

6.11 Echocardiography-Guided Procedures

6.11.1 Pericardiocentesis

Performing "blind" percutaneous pericardiocentesis as a treatment for significant pericardial effusion dates back to the early eighteenth century, and it is historically fraught with complications [43]. Improved techniques in the 1970s with the advent of 2D echo allowed more accurate localization of the fluid and the development of echo-guided pericardiocentesis [44]. Echo-guided pericardiocentesis (Fig. 6.15) has been found to be a safe and effective procedure with insertion of a catheter for drainage used to reduce the rate of recurrence found to complicate simple needle drainage and is considered the primary and often the definitive therapy for patients with clinically significant effusions [45, 46].

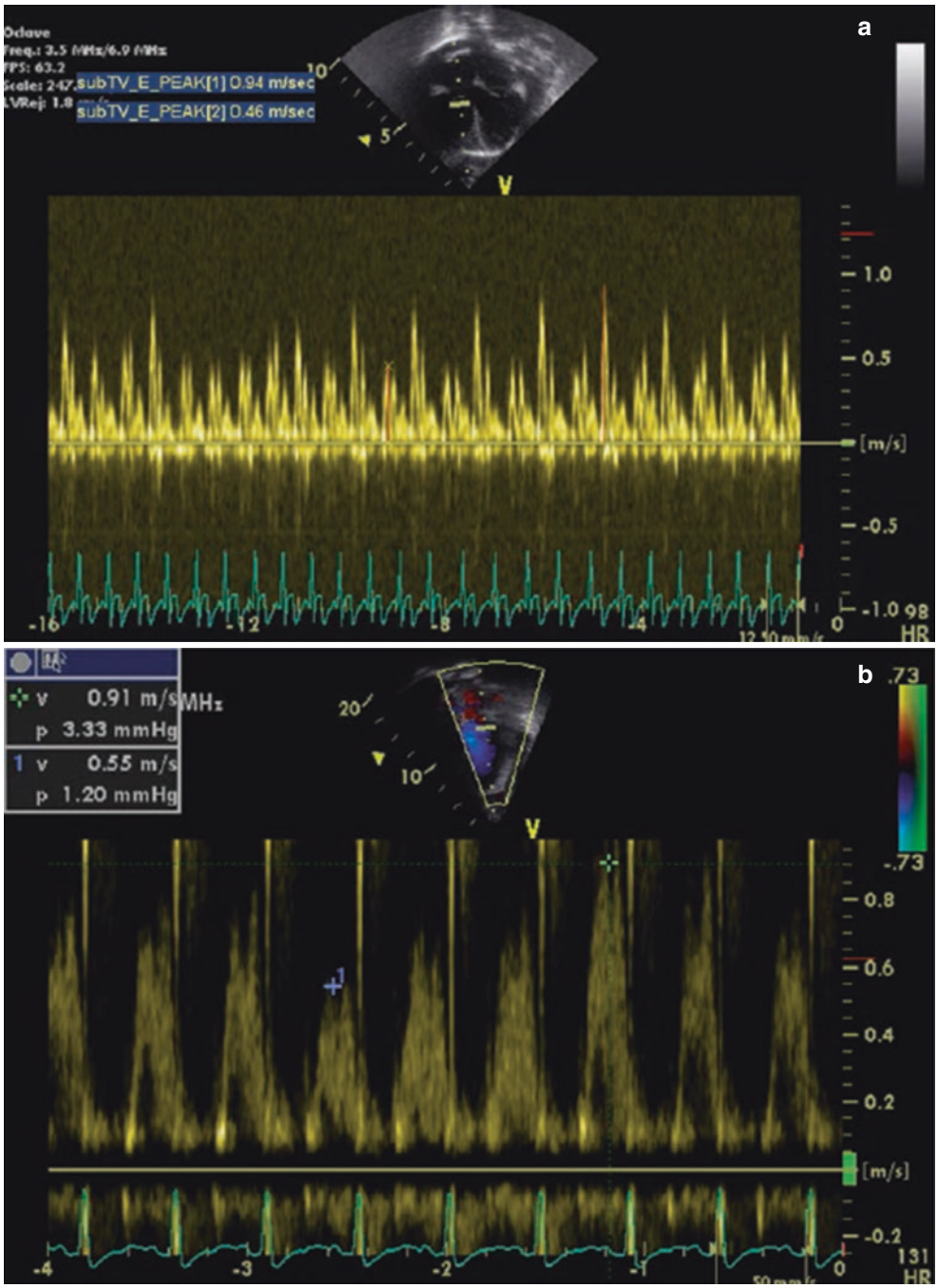


Fig. 6.13 (**a**) and (**b**): Respiratory changes in the mitral and tricuspid valve E wave Doppler patterns consistent with tamponade physiology. The tricuspid valve inflow demonstrates more than 50% variability between inspiration and expiration (**a**). During mitral valve inflow Doppler, the peak E wave velocity alters more than 30% between inspiration and expiration (**b**)

6.11.2 Balloon Atrial Septostomy (BAS)

Part of any echocardiographic assessment of a patient with congenital heart disease should include evaluation of the atrial septum. Cardiac lesions such as transposition of the great arteries, hypoplastic left heart syndrome, and tricuspid atresia require an adequate atrial communication. In the setting of a restrictive atrial septal communication or intact septum, a BAS is required to improve mixing and CO. In the past, the procedure, originally described by William Rashkind, was performed in the cardiac catheterization laboratory under fluoroscopic guidance [47, 48]. However, during the last decade, BAS has been routinely performed at the bedside in the intensive care unit under echocardiographic guidance (Fig. 6.16a–d). Most commonly either a subcostal view that includes a focused look at the atrial septum, pulmonary vein, and mitral valve or an apical four-chamber view is used. For the echocardiographer, the primary role is to provide continued visualization of the catheters and communicate well with the interventionalist.

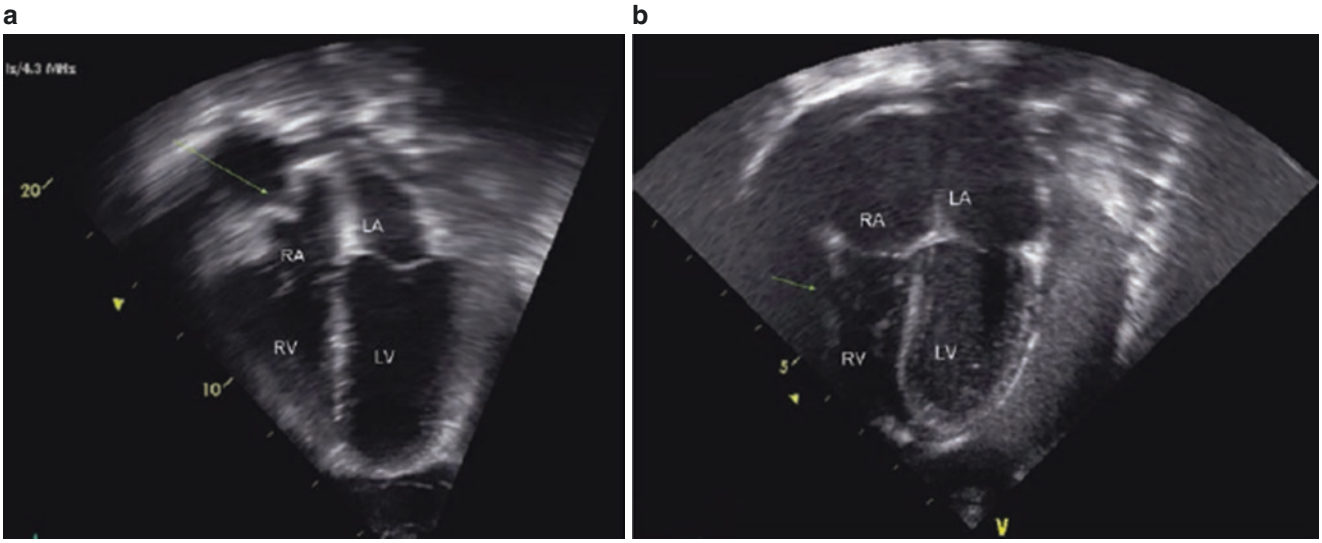


Fig. 6.14 (**a**) and (**b**): Four-chambered views demonstrating right atrial and right ventricular collapse (green arrows) as a finding of tamponade physiology. RA right atrium, RV right ventricle, LA left atrium, LV left ventricle

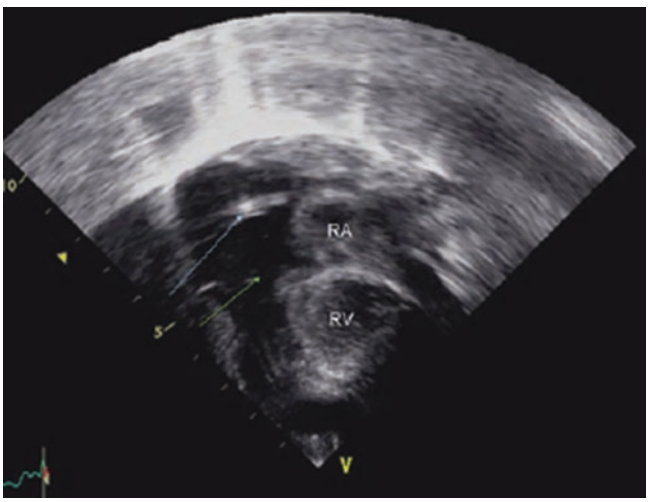


Fig. 6.15 Echoguided pericardiocentesis. Green arrow is in the pericardial space demonstrating the large fluid collection. Blue arrow is pointing to the needle that has been advanced into the pericardial space to drain the fluid collection. The large effusion allows the echocardiographer to direct the individual performing the pericardiocentesis away from areas that could lead to complications such as perforation of the myocardium

Advantages of this technique are multifactorial; echocardiography is superior to fluoroscopy during BAS due to a lack of radiation, the ability to perform the procedure at bedside rather than transporting to a catheterization laboratory, and direct, continuous visualization of the atrial septum, pulmonary veins, and mitral valve. The disadvantages of this technique include the potential for interference with maneuverability for both echocardiographer and catheter operator around a small neonate and therefore the risk of contamination of the sterile field. Additionally, there is the possibility of poor acoustic windows in an ill neonate who may be mechanically ventilated. However, with proper planning and communication, the limitations of transthoracic echocardiographic guidance of BAS may be minimized [49–52].

6.12 Future Directions

There are several areas of advanced imaging that are becoming more commonplace in the practice of pediatric echocardiography. Primary assessment of cardiac mechanics by evaluating myocardial motion, strain, and strain rate has been validated in healthy children and provides additional information regarding myocardial performance.

Three-dimensional real-time echocardiography has a growing role in evaluating anatomic defects, valves, and right and left ventricular function independently of geometric assumptions that constrained the previous methods.

6.12.1 Myocardial Mechanics

In the past several years, myocardial strain and strain rate have emerged as promising quantitative measures of myocardial function and contractility. Strain (ε) is a dimensionless parameter defined as the deformation (L) of an object relative to its original length (Lo) and is expressed as a percentage. Strain rate (SR) is defined as the local rate of deformation or strain (ε) per unit of time and is expressed in 1/s. Strain and strain rate measurements can be obtained from

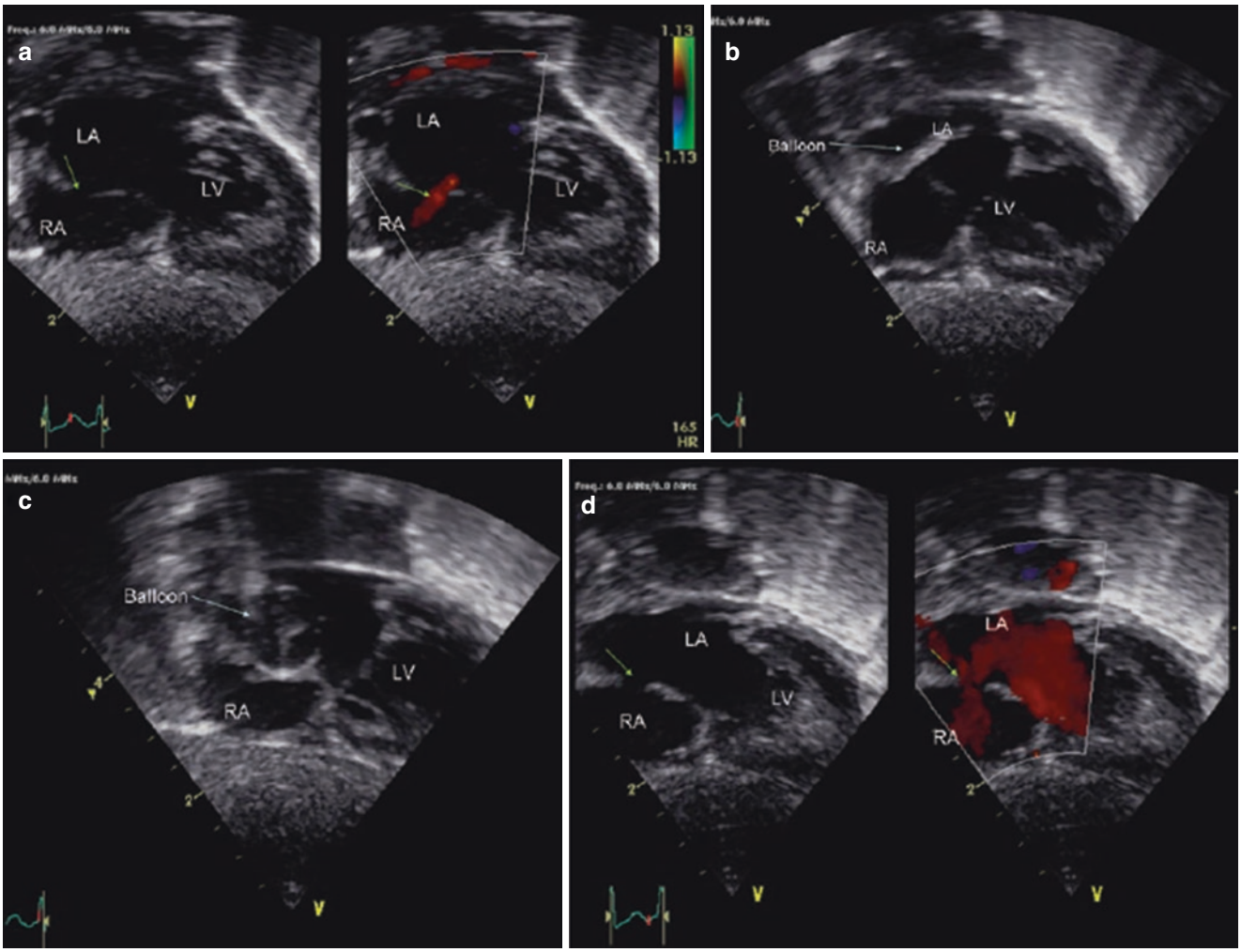


Fig. 6.16 Subcostal images demonstrating echo-guided balloon atrial septostomy (BAS). (**a**): shows the initial small atrial communication in both two-dimensional (2D) and color Doppler imaging. (**b**): reveals the deflated balloon that has been advanced across the atrial communication. It is important during this portion of the procedure for the echocardiographer to ensure that the balloon has not been advanced across the left atrioventricular valve. (**c**): demonstrates the inflated balloon within the left atrium. It is important to note the balloon's position away from the mitral valve and pulmonary veins. (**d**): demonstrates the atrial communication following septostomy using both 2D and color Doppler imaging. RA right atrium, RV right ventricle, LA left atrium, LV left ventricle, *Green arrows* atrial communication

data acquired by Doppler tissue imaging or 2D tissue tracking. Strain and strain rate should be of great help in the future in the evaluation of ventricular function since conventional M-mode and 2D echocardiography have limitations due to complex morphology of the right ventricle and altered left ventricle morphology that occurs in complex congenital heart defects [53]. Left and right ventricular values of strain and strain rate are available for healthy children [54].

6.12.2 3D Echocardiography

Off-line 3D reconstruction consists of acquisition of sequential 2D slices that are converted to a rectangular coordinate system for 3D reconstruction and provides accurate anatomic information suitable for quantitative analysis [55–58].

Left ventricular volume, mass, and function can be accurately assessed using RT3D independently of geometric assumption, and ejection fraction can be calculated. The wide-angle mode is often used to acquire the entire LV volume, from which further analysis allows determination of global and regional wall motion. Wall motion is evaluated from base to apex with multiple slices from different orientations. The advantage of 3D over 2D is the ability to manipulate the plane to align the true long axis and minor axis of the LV, thus avoiding foreshortening and oblique image planes. LV volume assessment by RT3D is rapid, accurate, reproducible and superior to conventional 2D methods [59] and is comparable to MRI, which represents

the gold standard [60–64]. Three-dimensional reconstruction of the tricuspid valve has been shown to be helpful for the anatomical assessment of Ebstein's malformation [65, 66] or after atrioventricular septal defect repair [67]. 3D echocardiography is a useful adjunct to standard 2D imaging and should be increasingly used in the future.

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Chapter 7
Cardiac Anesthesia

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Abstract Anesthesia for the patient with congenital heart disease (CHD) begins with a comprehensive preoperative evaluation to safely transition patients through different phases of the anesthetic. Anesthesiologists must optimize patient hemodynamics relative to the presence and degree of shunting, obstruction, and resistance of pulmonary and systemic vascular beds. This can be challenging given that all anesthetic agents have an impact on the cardiopulmonary system. Induction of anesthesia can be safely accomplished via intravenous or inhalation techniques. Prior to incision, airway management and vascular access must be reliable, secure, and accessible. Judicious fluid administration and use of vasoactive medications help maintain hemodynamic stability during incision, dissection, and preparation for cannulation. The anesthesiologist must anticipate the possibility of catastrophic hemodynamic collapse. Given the numerous perturbations of cardiopulmonary bypass (CPB), multiple methods are used to provide myocardial and neural protection. Separation from CPB occurs only after the patient is warm, ventilated, metabolically optimized, and maintaining a stable cardiac rhythm. Treatment of coagulation abnormalities associated with CPB must be individualized, and blood product administration is common. Transition of care from the operating room to the ICU can be particularly challenging in post-cardiac surgery patients who require the constant support of many life-sustaining devices.

Learning Objectives

1. Describe the preoperative evaluation for a patient with congenital heart disease presenting for congenital cardiac surgery
2. Recognize the physiologic effects that various anesthetic agents have on the cardiovascular system and the implications for patients with congenital heart disease
3. Compare methods of blood gas management styles between children and adults
4. Describe the evaluation process for deriving a post-operative plan for patients after congenital cardiac surgery

Questions and Answers

1. What ventilator settings could lead to cardiovascular collapse in a neonate with hypoplastic left heart syndrome presenting to the operative room for their Norwood procedure (Stage I palliation)?

   A: Neonates with hypoplastic left heart syndrome (HLHS) have ductal-dependent systemic blood flow. There is a considerable drop in pulmonary vascular resistance over the first several days of life, and as such, a higher proportion of blood will begin to go through the pulmonary vasculature at the expense of systemic output. After the induction of anesthesia in the operating room, if supplemental oxygen is given and/or the neonate is hyperventilated and become hypocarbic, this may lead to a relatively profound decrease in pulmonary vascular resistance, pulmonary over-circulation, and systemic hypotension potentially contributing to end-organ ischemia. The increased pulmonary over-circulation results in more blood return to the single right ventricle which could lead to dilation and eventual heart failure.

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2. What are the adverse effects of volatile anesthetic agents for neonates presenting to the operating room with critical aortic stenosis?

   A: Inhaled volatile anesthetics, such as isoflurane and sevoflurane, contribute to reduce systemic vascular resistance (SVR). Patients with fixed left-sided obstructions have little, if any reserve to increase their cardiac output. Thus, the decrease in SVR in the setting of a fixed obstruction can result in profound hypotension potentially leading to end-organ ischemia. Furthermore, the decrease in SVR with resultant hypotension can lead to a tachycardia, which will further reduce cardiac output due to decreased ventricular filling time. Hemodynamic goals are to maintain SVR and avoid tachycardia.
3. A 6-month-old female with an atrioventricular septal defect presents as an outpatient for complete repair scheduled at 8 A.M. At 3:30 A.M. she was given a bottle of breast milk fortified with infant formula. What implications does this have for induction of general anesthesia?

   A: As per the current nil per os (NPO) guidelines, if this infant only had breast milk at that time, she would be assumed to be safe for induction of anesthesia. However, because of the addition of infant formula, the NPO should be 6 hours, and this procedure should be delayed until at least 9:30 A.M. This is due to concerns of the gastric volume and the risk of aspiration during the induction of general anesthesia. NPO rules are observed as best they can be to minimize the risk of aspiration during induction; however, truly emergent cases should never be delayed due to last oral intake. In this circumstance, a rapid sequence induction with endotracheal intubation should be implemented.

7.1 Preoperative

7.1.1 Evaluation/Preoperative Optimization

Anesthesia begins with a comprehensive preoperative evaluation including patient history, physical exam, and a review of laboratory values and diagnostic investigations. It is important to note that the anesthesiologist does not "clear" the patient for surgery. The role of the anesthesiologist is to optimize the patient's medical comorbidities prior to the stress of a surgical intervention in order to minimize the risk of perioperative morbidity and mortality.

7.1.1.1 Preoperative Studies

Comprehensive preoperative evaluation of all patients with congenital heart disease (CHD) is essential for successful intervention in the setting of complex anatomic variations and unique physiologic consequences. Additional non-cardiac congenital defects should also be identified in order to prepare for unique physiologic requirements. Preoperative cardiac investigations may include electrocardiogram(s), Holter monitors, echocardiography, stress tests, and/or cardiac catheterizations.

Electrocardiogram (ECG) A baseline ECG should be reviewed for underlying rhythm or conduction abnormalities, chamber hypertrophy, and signs of preexisting ventricular strain or ischemia.

Holter Monitors Holter monitors can further delineate the patient's underlying rhythm along with intermittent conduction abnormalities, which may not be visualized on a single ECG since these only capture an isolated point in time.

Echocardiography Anatomic pathology is defined primarily by transthoracic echocardiography (TTE). A comprehensive TTE utilizes spectral and color Doppler interrogation to define blood flow along with the associated structures of interest. Further anatomic investigations can be done using magnetic resonance imaging (MRI) and computerized tomography (CT) with angiography when lesions are difficult to evaluate using TTE alone.

Catheterization Measurements of pressure and oxygen saturation along with pressure gradients, vascular resistance, and quantified shunting can clarify the physiologic impact of the congenital cardiac defect. Catheterization can delineate the ratio of pulmonary and systemic blood flow (Qp:Qs) in patients with shunting cardiac defects. This information is essential for the anesthesiologist to safely and effectively transition the patient from anesthesia induction to cardiopulmonary bypass by understanding the impact of altering the systemic and pulmonary vascular resistances. In addition, understanding the requisite Qp:Qs provides the anesthesiologist with hemodynamic goals for weaning from cardiopulmonary bypass.

Cardiopulmonary Exercise Testing (CPET) Stress testing is often used to identify exercise-induced arrhythmias and to monitor a patient's cardiac reserve as they age. This information can also predict a patient's response to the stress of surgery and anesthesia for both cardiac and non-cardiac surgery. Unlike adults, atherosclerotic coronary artery disease in children is rare. In addition to the information

obtained during exercise stress testing (heart rate, rhythm, ST segments, blood pressure), CPET provides metabolic information of the patient's hemodynamic status while in motion using dynamic parameters such as oxygen consumption, oxygen pulse, and the ratio of minute ventilation to CO_2 production [1]. This provides valuable information about the function of the heart and lungs. Future interventions, appropriate exercise recommendations, and medical management may be based on the information obtained during CPET.

Pacemakers and Internal Cardioverter-Defibrillators (ICDs) Many children with congenital heart disease have implantable pacemakers or ICDs for a variety of indications. Perioperative assessment should include pacemaker indications, cardiovascular pathology, and the presence of symptoms. Device interrogation prior to elective surgery is important to identify device settings and the underlying rhythm. It may be necessary to reprogram the device to avoid potential problems with pacemaker malfunction when exposed to electrocautery. Rate-responsive and anti-tachycardia modes should be deactivated due to the high risk of interference. It is often necessary to reprogram the pacemaker to an asynchronous, non-sensing mode (AOO, VOO, or DOO). Although most devices pace asynchronously when a magnet is applied, this is not universal. Use of a magnet is therefore not an acceptable alternative to device interrogation. Alternative pacing modalities should also be available in pacemaker-dependent patients.

ICDs are used in patients at high risk of sudden cardiac death such as long QT syndrome, Brugada syndrome, hypertrophic cardiomyopathy, and those with a history of malignant arrhythmias or near sudden death events. Perioperative management of the ICD relates to the risk of electromagnetic interference, particularly with the use of unipolar electrocautery. Magnet application deactivates most, but not all devices. While this can be done in emergent cases, devices should be interrogated preoperatively and may need adjustment or deactivation prior to elective surgery. Reevaluation should also occur following surgery. If the device is deactivated or reprogrammed, external cardioversion/defibrillation should be available.

7.1.1.2 Single vs Double

In the non-palliated single ventricle physiology, there is complete mixing of pulmonary and systemic venous blood at atrial or ventricular levels, and the ventricle then distributes blood to both systemic and pulmonary vascular beds. Flow distribution is therefore dependent on the vascular resistance at each location, and management decisions, such as oxygen administration, over- or underventilation, and vasodilatory medications, can have drastic influences on pulmonary blood flow and cardiac output. In univentricular patients who have undergone palliated reconstruction to decrease the degree of mixing, pulmonary blood flow may be passive and dependent on an adequate circulating blood volume. Different stages of palliation each have unique requirements, and it is imperative for the anesthesiologist to optimize cardiac output and oxygen delivery.

7.1.1.3 Mixing

Mixing lesions refer to defects which result in complete mixing of oxygenated and deoxygenated blood in the cardiac chambers or great vessels. Single ventricle CHD, truncus arteriosus, and anomalous pulmonary venous return are all mixing lesions. Mixing is due to unrestricted flow across a large intracardiac communication. Hypoxemia then leads to compensatory changes in order to increase oxygen carrying capacity. Increased hemoglobin and red cell mass increase blood viscosity, which can paradoxically decrease oxygen delivery due to compromised blood flow. In cardiac defects that result in systemic and pulmonary venous admixture, the resistance of the pulmonary and systemic vascular beds significantly affects the degree of intracardiac mixing. Anesthesia can result in perturbations of systemic and pulmonary vascular resistance via multiple mechanisms. Supplemental oxygen, arterial oxygen (PaO_2) and carbon dioxide ($PaCO_2$) concentrations, arterial vasodilation, venodilation, and myocardial depression can all affect the degree mixing.

7.1.1.4 Ventricular Function

Preoperative ventricular function must be defined prior to the administration of anesthetic agents as most agents produce varying degrees of myocardial depression. An already failing ventricle exposed to additional cardiac depressants can result in cardiovascular collapse. Changes in ventricular function or valve integrity should be noted by the anesthesiologist prior to induction of anesthesia, as this may be a sign of an insidious progression of heart failure.

7.1.1.5 Arrhythmias

Patients with underlying arrhythmias or arrhythmogenic myocardial tissue should have defibrillator pads placed prior to the induction of anesthesia. Those on maintenance antiarrhythmic medications should be instructed to maintain their dosing schedule in the preoperative time period.

7.1.1.6 Shunts, Obstruction

Flow through shunt lesions, either intracardiac or extracardiac, is affected by the size of the defect, the pressure gradient, and the resistance to blood flow on either side. Large (nonrestrictive) shunts are more affected by vascular resistance, and small (nonrestrictive) shunts are more dependent on pressure gradients. Left-to-right shunt lesions are the most common congenital cardiac defects and include PDA, ASD, VSD, and AV canal defects. Less common are double outlet right ventricle, partial and total anomalous pulmonary venous return, and truncus arteriosus. Increasing systemic vascular resistance (SVR) or decreasing pulmonary vascular resistance (PVR) results in excess pulmonary blood flow (high Qp:Qs) and increases the volume burden on the heart. This may lead to pulmonary edema, progressive pulmonary vascular occlusive disease (PVOD), decreased cardiac output, decreased oxygen delivery, and poor peripheral perfusion. Management focuses on lowering SVR and avoiding reduction of PVR. All cyanotic patients have some degree of right-to-left shunting, and it is important to know if the ductus arteriosus is necessary to maintain pulmonary or systemic blood flow. Increasing PVR or decreasing SVR may result in desaturation due to more right-to-left shunting. Optimal management maintains an appropriate Qp:Qs ratio allowing for sufficient pulmonary blood flow while maintaining systemic perfusion. Selective pulmonary vasodilation with inhaled nitric oxide (iNO), prostacyclins, and sildenafil may be necessary (Table 7.1).

Obstructive lesions increase the pressure load to proximal structures. This leads to chamber hypertrophy and/or dilatation. The increased oxygen demand places the hypertrophied myocardium at risk for ischemia. Right-sided obstruction reduces pulmonary blood flow, and all have the potential for right-to-left shunting with resultant hypoxemia. Left-sided obstruction leads to decreased cardiac output. Obstruction can be fixed or dynamic. Minimizing the degree of dynamic obstruction and increasing forward flow can be achieved with increased preload, decreased heart rate, and decreased contractility. When obstructive lesions coexist with shunts, the obstruction significantly affects the degree of shunting and in extreme cases may even change the direction of the shunt (Table 7.2). It is important to understand the location and degree of obstruction to optimize cardiac output and meet the increased oxygen requirement of the hypertrophied ventricle (Table 7.3).

Table 7.1 Treatment of elevated pulmonary vascular resistance

Hyperventilate (decrease $PaCO_2$)
Increase FiO_2 (increase PaO_2)
Correct acidosis
Correct hypothermia
Provide inotropic support
Promote pulmonary vasodilation (milrinone, iNO, sildenafil)
Decrease sympathetic stimulation (blunt stress response with opioids)
Avoid elevated airway pressures

Table 7.2 Hemodynamic management of shunt lesions

	Right-to-left	*Left-to-right*
Hemodynamic results	↓ Pulmonary blood flow ↑ LV volume LV dysfunction Hypoxemia and cyanosis	↓ Systemic blood flow ↑ LV volume LV failure
Management goals	↓ PVR Avoid ↓SVR Hyperventilation Hyperoxia	Avoid ↓ in PVR Avoid ↑ in SVR ↓ FiO_2 (hypoxic mixtures may be needed) Avoid hyperventilation

Table 7.3 Hemodynamic management of obstructive lesions

	Right-sided	*Left-sided*
Examples	Tetralogy of Fallot Ebstein's anomaly Pulmonary stenosis with intact ventricular septum Pulmonary atresia with intact ventricular septum Pulmonary atresia with VSD and multiple aorotopulmonary collaterals Eisenmenger's syndrome	Aortic stenosis (subvalvular, valvular, or supravalvular) Hypertrophic cardiomyopathy Coarctation Interrupted or hypoplastic aortic arch Shone's anomaly Mitral stenosis Cor triatriatum
Hemodynamic results	↓ Pulmonary blood flow RV hypertrophy and dysfunction Tricuspid insufficiency Hypoxemia	↓ Systemic blood flow ↓ Cardiac output Hypotension LV hypertrophy and dysfunction Decreased coronary perfusion
Management goals	Avoid ↑ PVR Avoid ↓ SVR Avoid hypoventilation Hyperoxia Maintain preload	Avoid ↓ PVR Avoid ↓ SVR Maintain preload
	Maintain ductal patency in ductal-dependent lesions	

7.1.2 Day of Surgery

7.1.2.1 Nil Per Os (NPO) Guidelines

Preoperative fasting in infants and children can lead to dehydration, hypovolemia, and hypoglycemia. This can be particularly problematic in blood volume-dependent lesions, such as in Fontan circulation. Current guidelines from the American Society of Anesthesiologists allow clears up to

Table 7.4 NPO guidelines for sedation and anesthesia

Ingested material	Minimum fasting[a]
Clear liquids[b]	2 hours
Breast milk	4 hours
Infant formula	6 hours
Nonhuman milk	6 hours
Light meal[c]	6 hours
Fried or fatty foods or meat	8 hours

Adapted from an Updated Report by the American Society of Anesthesiologists Task Force of Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration [3]
Minimum NPO recommendations in healthy patients of all ages undergoing elective procedures. Emergent situations should weigh the need for intervention with the increased risk of pulmonary aspiration
[a]Guidelines do not guarantee complete gastric emptying
[b]Clear liquids include water, juice without pulp, carbonated beverages, clear tea, and black coffee
[c]A light meal consists of toast and clear liquids. Any meat or fried/fatty foods may prolong gastric emptying time

2 hours preoperatively; breast milk up to 4 hours; formula, fortified breast milk, nonhuman milk, and light solids up to 6 hours; and solid foods (meat, fried, or fatty food) up to 8 hours preoperatively (Table 7.4) [2, 3].

7.1.2.2 Preoperative Sedation: Midazolam (Oral, Intravenous)

Benzodiazepines enhance the inhibitory effect of the $GABA_A$ receptor by binding to receptors in the central nervous system (CNS), thus increasing the frequency of chloride channel opening, which leads to sedation and amnesia.

Pharmacokinetics Midazolam is a water-soluble benzodiazepine. The bioavailability from greatest to least is: intravenous (IV) > subcutaneous > intramuscular > buccal > nasal > rectal > oral. While midazolam can be administered via all the above routes, oral administration is generally the form best tolerated in a child without preexisting IV access. The peak clinical effect after an oral dose occurs in 15–20 minutes, whereas the peak clinical effect after an IV dose occurs within 2–5 minutes. Midazolam is metabolized primarily by the liver's CYP3A4 enzyme. Other medications metabolized by CYP3A4 of the P450 enzyme system include fentanyl, lidocaine, and oral contraceptives. Erythromycin decreases the metabolism of midazolam, intensifying its clinical effect.

CNS In the CNS, midazolam produces sedation, hypnosis, anxiolysis, and anterograde amnesia. It also functions as an anticonvulsant and muscle antispasmodic. Possible side effects include hiccoughs, paradoxical reactions, postoperative nightmares, and fearfulness.

Cardiovascular Midazolam has limited clinical effects on the cardiovascular system if administered alone. It can cause minimal reduction in blood pressure, cardiac output, and vascular resistance. Heart rate may decrease, increase via vagolysis, or remain unchanged.

Respiratory Midazolam is associated with respiratory depression and a decreased response to CO_2 accumulation. This is usually insignificant unless coadministered with other respiratory depressions, especially opioids.

Reversal Flumazenil competitively antagonizes all benzodiazepines. Dosing is 0.01 mg/kg to a maximum of 0.2 mg/dose. Patients should be monitored for recurrence respiratory depression due to flumazenil's short duration of action, usually less than 60 minutes.

Premedication Preoperative anxiety or agitation has been associated with postoperative emergence delirium/agitation and behavioral changes weeks after surgery [4]. Premedication can be safely administered in patients with CHD. In the patient with CHD, minimizing distress allows the patient to maintain homeostasis with respect to pulmonary and systemic vascular resistance. Patient cooperation and a smooth induction of anesthesia can minimize the amount of right-to-left intracardiac shunting in certain congenital lesions.

There are several other premedications that may be considered; however their use may be more feasible when IV access has already been established. Fentanyl is a mu opioid receptor agonist. Fentanyl may not only lead to sedation but has analgesic effects as well. Ketamine acts as an N-methyl-d-aspartate antagonist and, similar to fentanyl, can result in both sedation as well as analgesia. Dexmedetomidine and clonidine are both alpha 2-adrenergic receptor agonists with dexmedetomidine being 800 times more selective for this receptor. Dexmedetomidine should be given cautiously in patients on digoxin therapy due to the risk of bradycardia.

7.1.2.3 Parental Presence

Benefits of parental presence during the induction of anesthesia may include reduction in the need for preoperative sedatives, reduced patient anxiety, increased compliance, and parental satisfaction [5]. Oral midazolam has demonstrated superiority to parental presence in both the reduction of patient anxiety and increasing the level of compliance [6]. One major objection to parental presence is the possibility of adverse parental reactions in either behavioral or physical manifestations.

7.2 Induction

7.2.1 Inhalational/IV

Regardless of the procedure, the goal throughout induction is to induce general anesthesia while maintaining adequate cardiac output and oxygen delivery. Given the variability of CHD, medication selections should be individualized. This depends on factors such as patient age, cardiac reserve, presence of an IV catheter, child preference, or potential for a difficult airway. Many children will not tolerate having IV access established while awake. In fact, the distressed or crying patient may develop alterations in systemic or vascular resistance with profound hemodynamic impact. It is therefore acceptable to perform a controlled inhalational induction prior to placement of an IV. Some older, more mature, children may prefer preoperative IV placement to the application of a mask, which can be distressing, albeit temporarily. Propofol is preferred in the setting of adequate cardiac function as it leads to superior intubating conditions, but the reduction SVR can lead to significant hypotension limiting its use in the compromised myocardium. In a patient with decreased cardiac function, etomidate, ketamine, or some combination of midazolam/opioid may be used.

Whether using IV or inhalational induction, hemodynamic monitoring is crucial as many anesthetic agents produce hypotension by decreasing SVR (Table 7.5). Preoperative diuretics exacerbate hypotension, and many patients are on diuretics to minimize symptoms of heart failure. During anesthetic induction, the combination of anesthetic-induced vasodilation and preoperative diuresis often require resuscitation with crystalloids or colloids.

7.2.2 Airway Management and Intubation

Airway management can occur using orotracheal or nasotracheal intubation. Nasal tubes are more readily secured to the face and may decrease the incidence of tube dislodgement by the transesophageal echocardiography (TEE) probe operator. Nasal tubes may also be better tolerated in the postoperative period for patients intended to be mechanically ventilated for several days (i.e., open chest after Norwood procedure). In older children, there is an increased risk of sinusitis from prolonged nasal intubation. The more commonly used orotracheal tubes can be placed more easily and rapidly.

Table 7.5 IV anesthetic agent impact on the cardiovascular system

Drug	Mechanism of action	Cardiovascular effect
Propofol	Allosterically ↑ binding affinity of GABA at the $GABA_A$ receptor	Dose dependent ↓ in BP and cardiac output ↓↓ SVR
Etomidate	↑ GABA affinity and depress the reticular activating system	Mild ↓ in SVR and BP No change or minimal ↓ in HR and cardiac output
Ketamine	NMDA antagonist with functional thalamic dissociation	Release endogenous catecholamines to maintain or ↑ HR and BP Direct myocardial depressant

7.2.3 Vascular Access

Congenital cardiac surgery necessitates invasive venous and arterial access that is secure, accessible, and reliable. Invasive vascular access displays beat-to-beat pressure waveforms, allows for frequent blood sampling, and can provide a means of early detection and intervention of pathologic processes. The invasive nature of vascular access brings with it a variety of possible complications including bleeding, infection, vascular injury or transection, vessel thrombosis, pneumothorax, and aneurysm/pseudoaneurysm formation. Vascular access can be particularly challenging in the very young, patients with multiple comorbidities, and those presenting for reoperation.

Arterial Access Percutaneous arterial access is usually accomplished by palpation, but ultrasound use has steadily been increasing in popularity. The radial artery is the preferred location to obtain an arterial waveform due to the ease of access and collateral blood flow to the hand by the ulnar artery. Brachial, axillary, ulnar, femoral, umbilical, dorsalis pedis, posterior tibial, and temporal arteries are all options for cannulation. When percutaneous access is unsuccessful, an arterial cutdown is an alternative method of obtaining arterial access. Despite the reliability and speed of access for a cutdown, there is a higher rate of bleeding, infection, distal ischemia, and vessel occlusion [7]. The role of pulmonary artery catheterization is limited in congenital heart surgery due to small vessel size and the presence of intracardiac shunting. Although rare, it can be utilized in patients older than 6 months undergoing left heart surgery if there is no intracardiac shunting.

Venous Access Peripheral IVs are used to infuse crystalloids, colloids, and blood products with minimal resistance to flow. During induction of anesthesia, prompt venous access is important to facilitate airway management via the administration of muscle relaxants. Central venous access is critical to obtain right-sided heart pressures and administration of vasoactive medications with minimal delay. The internal jugular vein is most commonly chosen due to its proximity to the heart, its ease of percutaneous access, and the ability to compress structures in the case of accidental arterial puncture. However, it is prudent to exercise caution when choosing the internal jugular vein in

single ventricle patients with cavopulmonary anastomoses, patients with prior jugular access for extracorporeal membrane oxygenation (ECMO) cannulation, and those at high risk for requiring heart transplant, which will necessitate frequent jugular access for endomyocardial biopsies. Other possible sites for central access include subclavian and femoral veins. Central access can be achieved through cannulation of the umbilical vein in the early postnatal period. Intracardiac lines can be placed intraoperatively for postoperative use. This facilitates earlier removal of percutaneous lines and preserves sites for future percutaneous access.

7.3 Maintenance

Anesthesia maintenance refers to the period between the induction of anesthesia and emergence from anesthesia. Immediately after induction of anesthesia and securing of the airway, the anesthesiologist prepares the patient for surgical incision through invasive access to circulation (see above), monitoring and adjustments of thermoregulation, placement of the TEE probe, and the application of additional monitors, such as cerebral/tissue oximeters. Prior to drape placement, great attention must be placed on patient positioning to minimize excess pressure to the skin, eyes, ears, nose, and genitals.

Arrhythmias, desaturation, and hemodynamic disturbances often occur during incision, dissection, and preparation for cannulation. Judicious fluid administration and use of vasoactive medications help maintain hemodynamic stability. Transesophageal echocardiography is also performed during this time, and access directly to the patient can be limited. For this reason, it is imperative that all monitors and vascular access be secure and reliable and that backup plans are in place should any of this fail.

7.3.1 Inhaled Anesthetics

Inhaled anesthetics act as CNS depressants in an unclear mechanism that leads to sedation. While sevoflurane, isoflurane, and desflurane all produce mild myocardial contractility depression via the L-type calcium channels, halothane causes significant depression as well as decreased SVR to produce significant hypotension. Sevoflurane and isoflurane also lower blood pressure, primarily by lowering SVR in a dose-dependent manner. Although all inhalation agents can cause QTc prolongation, sevoflurane has more often been associated with torsade de pointes [8–10]. During induction with desflurane, tachycardia and hypertension are commonly seen followed by mild reductions in heart rate and blood pressure.

Nitrous oxide produces minimal to no alterations in myocardial contractility or arterial pressure. It, however, is relatively contraindicated in the setting of increased FiO_2 requirements. Overall, mask induction using sevoflurane with or without nitrous oxide tends to be well tolerated, but concentration should be decreased as soon as possible to minimize hemodynamic perturbations.

7.3.2 IV Infusions

Regardless of the care and expertise exercised throughout the induction of anesthesia, catastrophic hemodynamic collapse can occur. It is therefore essential to have vasoactive medications immediately available in both bolus and infusion forms. A rescue infusion of epinephrine, dopamine, or dobutamine should be prepared to minimize the delay of its administration. Milrinone is also commonly used in congenital heart surgery due to its benefits of inotropy, chronotropy, lusitropy, and dromotropy. However, it can and does produce decreases in systemic vascular resistance, which may require another agent to maintain arterial blood pressure and coronary perfusion pressure.

Intraoperative infusions of dexmedetomidine may be suitable during cardiac surgery as part of a balanced general anesthetic. Dexmedetomidine is a highly selective alpha 2-adrenergic agonist that acts centrally to produce sedation. It also potentiates the analgesic effects of opioids. Because it acts centrally to decrease sympathetic nervous system activity, it causes a dose-dependent decrease in heart rate and blood pressure in a predictable manner. Minimal respiratory depression makes it possible to continue infusions through to extubation in the intensive care unit (ICU).

The stress response is a systemic response to injury affecting cardiovascular, metabolic, endocrine, and immune functions. Since this maladaptive response is linked to morbidity and mortality [11], outcomes improve when the stress response is attenuated with the use of high-dose opioid anesthesia [12, 13]. It is important to ensure adequate opioid anesthesia in prebypass, bypass, and postbypass phases. This can be accomplished with a continuous infusion or high-dose opioid administration at each stage. When used in combination, neuraxial anesthesia with or without opioids can also be used to suppress the stress response [14].

7.4 Cardiopulmonary Bypass

The basics of the cardiopulmonary bypass (CPB) circuit include a venous reservoir, an oxygen/heat exchanger unit, roller or centrifugal pumps, an arterial filter, suction, and cardioplegia. Size and location of cannula placement are

based on anatomic structures. Often, separate venous cannulas are necessary in both the IVC and SVC. An additional cannula may also be necessary in a persistent left SVC. Arterial cannulation occurs via the ascending aorta. In newborns with ascending aortic malformations, cannulation may occur at the ductus arteriosus and clamping of the pulmonary arteries to prevent runoff.

After heparinization, the venous cannula slowly decompresses the heart, draining into the venous reservoir. Maintaining the heart's ability to eject attenuates the hypotension of acute hemodilution with the initiation of CPB. Flow requirement is determined based on weight or body surface area and is greater than in adults. Compliant vasculature results in lower perfusion pressure on bypass. Hemodynamically relevant shunts may lead to circulatory steal, and higher flows are required until surgical control is obtained. Once CPB flow is established, ventilation is suspended.

Myocardial protection during CBP is of utmost importance as perioperative insults to the immature myocardium are poorly tolerated. The hallmark of myocardial protection is hypothermia, particularly in cyanotic infants with collaterals leading to washout of cardioplegia. Hypothermia is utilized for most congenital heart surgery. Cooling too rapidly may result in neurologic damage due to differences in regional cerebral blood flow. Cooling via the heat exchanger must occur slowly, evenly, and completely. Similarly, with rapid rewarming, hyperthermic overshoot can be very damaging.

7.4.1 Heparin

Anticoagulation prior to the initiation of CPB is necessary to inhibit thrombin generation, limit fibrinogen consumption, and minimize fibrinolysis. The action of heparin and its ease of neutralization with protamine make heparin the anticoagulant of choice for CPB. Heparin binds to antithrombin III (ATIII) accelerating ATIII inhibition of thrombin.

Heparin Reversal After a successful separation from cardiopulmonary bypass, the effects of heparin are antagonized with protamine (1–1.5 mg of protamine is given for every 100 units of heparin). Administration of protamine, however, should not delay treatment of postbypass coagulopathies. Individualized management of anticoagulation and its reversal has been shown to produce less coagulation activation, less fibrinolysis, and less need for transfusions [15]. Hypotensive protamine reactions are less common in children than adults but can present as true allergic reactions. Treatment includes calcium, volume resuscitation, inotropic support, and resumption of cardiopulmonary bypass.

7.4.2 TXA/Amicar

Congenital heart disease has been associated with coagulation abnormalities and accelerated fibrinolysis. The antifibrinolytics tranexamic acid (TXA) and ε-aminocaproic acid (EACA) competitively bind at lysine binding sites on plasminogen to prevent its activation to plasmin. This modifies the adverse effects of the CPB circuit on the coagulation cascade. Inhibition of plasmin activity may also play a role in suppressing pro-inflammatory cytokines after CPB [16]. TXA has both a longer half-life and is more potent than EACA.

Both TXA and EACA can reduce bleeding and transfusion in the pediatric patient undergoing cardiac surgery. The inhibition of fibrinolysis also helps to minimize platelet dysfunction due to products of fibrinolysis. This benefit is more significant in high-risk groups such as cyanotic patients, complex surgeries, and reoperations [17]. Investigations did not show a reduction in postbypass bleeding in indiscriminate children undergoing corrective surgeries. However, there was a significant bleeding reduction in children with cyanosis and those undergoing repeat sternotomies [18].

Thrombotic complications can occur when used incorrectly in the setting of hypercoagulable state and compensatory fibrinolysis, such as in disseminated intravascular coagulation [19]. New-onset seizures have also occurred with the use of antifibrinolytics, particularly with high doses of TXA [20, 21]. As such, lower doses are preferred.

7.4.3 Blood Gas: Alpha Stat vs pH Stat

In order to slow metabolism and oxygen consumption, hypothermia is often used during complex CHD repairs and palliations, in particular those involving the aortic arch. According to the ideal gas law, the amount of gas in solution increases proportionally to the decrease in temperature. As such, hypothermia decreases metabolic rate and increases the solubility of oxygen and carbon dioxide in blood and tissues.

As temperature drops, carbon dioxide becomes more soluble and its partial pressure decreases. In children, there is preservation of the cerebral blood flow response to CO_2 tension. If not corrected, the low $PaCO_2$ causes cerebral vasoconstriction, less efficient brain cooling, and less cerebral protection. In pH stat management, blood gases are managed by either decreasing CO_2 elimination or by the addition of CO_2 to the CPB circuit in order to obtain a goal of pH 7.4 and $PaCO_2$ 40 mm Hg at the patient's actual temperature. As such, a temperature-corrected arterial blood gas may appear profoundly acidotic with a high $PaCO_2$. This blood gas management style also helps to counteract the left shift of the oxyhemoglobin curve caused by hypothermia, thus improv-

ing oxygen delivery. Near-infrared cerebral oximetry values are higher with the use of pH stat management in cyanotic infants with aortopulmonary collaterals [22].

The pH stat management goal to preserve cerebral blood flow has led to an increased load of cerebral emboli in adults. For this reason, alpha stat tends to be the standard of care in this population. Conversely, the pediatric patient is much less likely to have emboli, and the primary injury mechanism is hypoxic/ischemic.

Alpha stat blood gas management adjusts the pH and CO_2 level based on the temperature-corrected values (i.e., goals of pH 7.4 and $PaCO_2$ 40 mm Hg at 37 °C). By doing so, the degree of histidine dissociation remains unchanged and enzymatic function is preserved. Thus, the blood gas at the patient's true hypothermic temperature may appear profoundly alkalotic with a low $PaCO_2$. In adults, alpha stat management is believed to better preserve cell function and autoregulation by maintaining a neutral pH at 37 °C.

7.4.4 Circulatory Arrest

Deep hypothermic circulatory arrest (DHCA) may be used to facilitate complex intracardiac and aortic repairs. Metabolic rate decreases by 64% by cooling from 37 °C to 27 °C. In addition to decreasing metabolic rate, DHCA decreases blood loss, protects the myocardium, and provides neuroprotection [23]. Disadvantages of DHCA include longer CPB times, increased postbypass coagulopathy, and disruption of cerebral autoregulation. Hypothermia does not increase postoperative recovery or the rate of wound infections. While DHCA is neuroprotective, it can also be associated with significant neurologic morbidity. The basal ganglia appear to be particularly vulnerable. While advances in technology over the years have decreased this risk, it still can occur. One way to decrease neurological morbidity is the use of pH stat management, as indicators of brain cell disruption begin to appear later than when using alpha stat management [24].

All of the following increase the safety margin during DHCA:

- Core body temperature 17–18 °C with ice applied to the head.
- Mild hemodilution to goal hematocrit 25–30% to balance oxygen carrying capacity and blood viscosity in the setting of hypothermia.
- Achieve systemic hypothermia slowly, over at least 20 minutes to ensure even cooling.
- pH stat management to improve even cerebral cooling and tissue oxygen unloading.
- Hyperoxia just before arrest improves oxygen unloading.
- DHCA divided into periods no longer than 20 minutes, allowing at least 2 minutes of reperfusion between arrest periods.
- Application of low flow CPB or selective cerebral perfusion.
- Cold reperfusion of the brain for 5–10 minutes may help restore cerebral autoregulation and washout of metabolites, which can partially counteract the postarrest increase in cerebral vascular resistance.
- Normoxemia after DHCA can decrease exacerbation of brain injury at reperfusion.

Neurologic monitoring, such as near-infrared spectroscopy, may further help to determine the safe time duration of DHCA.

7.4.5 Weaning from Bypass

During rewarming, ventilation is resumed and vasoactive agents are started. Depending on bypass duration, repeated doses of amnestics, analgesics, or muscle relaxants may be necessary. Separation from bypass occurs by slowly decreasing venous return to the pump only after the patient is warm, ventilated, and maintaining a stable cardiac rhythm (either intrinsic or via epicardial pacing wires). Prior to weaning, a blood gas is checked to optimize electrolytes and hematocrit. Goal hematocrit of 40% in small infants and palliated anatomies improves hemodynamic stability coming off bypass and allows for immediate correction of coagulation disorders using targeted blood product transfusion. Postbypass coagulopathies are common and present in forms of thrombocytopenia, platelet dysfunction, hypofibrinoginemia, fibrinolysis, and coagulation factor deficiencies. Exposure to CPB itself induces coagulopathy due to hemodilution, initiation of the inflammatory response, and non-physiologic contact and tissue factor activation. Platelet dysfunction is multifactorial and tends to be particularly common after CPB. Platelet activation, adhesion, and aggregation are all affected by exposure to the bypass circuit. Significant predictors of postbypass bleeding are age less than 12 months and weight less than 8 kg [25, 26].

Modified Ultrafiltration Modified ultrafiltration (MUF) at the end of bypass removes blood from the aortic cannula and guides it through a hemofilter and back into the right atrium after passing through the heater/oxygenator complex. Hemodynamic disturbances are common during this time, and the anesthesiologist manages blood pressure with volume and vasopressors as needed.

If the patient's hemodynamics can tolerate MUF, the benefits are numerous and include a reduction of pro-inflammatory cytokines and vasoactive active substances (interleukins, bradykinins, etc.), reduction of total interstitial fluid after bypass, increased stroke volume due to improved pulmonary blood flow, improved V/Q matching, and increased hematocrit due to free-water removal.

7.5 Emergence/Immediate Postoperative Period

Most patients go to the ICU following cardiac surgery, either corrective or palliative. Hemodynamics, rhythm, and ventilation will be continually managed in this setting. Many patients require continued resuscitation to maintain adequate preload due to ongoing fluid losses. Vasopressors are titrated to maintain adequate contractility and arterial pressure.

7.5.1 Decision to Extubate

Infants and children with CHD are particularly vulnerable to oxygen desaturation, hypercapnia, and hemodynamic instability. The decision to extubate integrates numerous considerations including length of surgery, airway edema, residual neuromuscular blockage, wakefulness, adequacy of oxygenation and ventilation, and hemodynamic stability. Reintubations are often technically more difficult than initial intubations due to edema, bleeding, and secretions. Patients who were difficult to intubate are less likely to be extubated in the operating room. When extubated, there must be a predetermined strategy for reintubation, should the need arise.

7.5.2 Extubation Criteria, Hemodynamics, Rhythm

In addition to the above factors, extubation is dependent on hemodynamic, rhythm, and coagulation stability in the patient with CHD. If the need for active resuscitation is ongoing, the patient is unlikely to tolerate extubation. Positive pressure ventilation is problematic for preload-dependent lesions and those with passive pulmonary blood flow as in the Glenn or Fontan circulation. However, the same physiology is also particularly vulnerable to changes in PaO_2 and $PaCO_2$. Furthermore, major surgery results in significant pain, treatment of which can lead to progressive sedation and hypoventilation. Neuraxial techniques have been used to facilitate extubation earlier by providing adequate analgesia and limiting the side effects of IV narcotics.

7.5.3 ICU Transport, Handoff

Transport from the operating room to the ICU can be particularly challenging in post-cardiac surgery patients who require the constant support of many life-sustaining devices. These vascular lines and therapeutic devices must continue to provide support to the patient while being transported from one location to another. Examples of this include multiple IV/arterial lines, medication infusions, blood product transfusions, endotracheal tube, ventilating circuit, urinary catheter, chest tubes, nitric oxide tank, rhythm and pressure monitors, and pulse oximetry. Occasionally, ECMO is also required for continued artificial hemodynamic support. The transport process must be cautious and methodical as the disruption of any device results in very real consequences.

Once arriving to the ICU, the patient is immediately attached to the ventilator if they are to remain intubated. All vascular lines and infusions are verified for accuracy. The surgical and anesthesia teams provide the ICU staff with important information regarding the patient's cardiac condition, their comorbidities, what was done during the procedure, and what complications are possible based on the intervention. It is important that all information and complications be shared at this time so the patient can be appropriately managed. All questions should be addressed in a non-judgmental manner, and physicians involved in the case should be immediately reachable for any additional issues which may arise.

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Chapter 8
A Pharmacokinetic and Pharmacodynamic Review

Carol G. Vetterly and Denise L. Howrie

Abstract Important pharmacodynamic and pharmacokinetic differences in drug handling are observed in newborns, infants, and children when compared to adult patients. Therefore, knowledge of pharmacokinetic and pharmacodynamic principles in the pediatric population may better ensure safe and effective medication prescribing.

8.1 Definitions

Pharmacodynamics is the study of the biochemical and physiological action or effects of drugs on living organisms. Pharmacokinetics is the study of the processes by which drugs move through the body, generally, referring to processes of absorption, distribution, metabolism, and excretion.

8.2 Absorption

Drugs that are administered extravascularly undergo absorption. The bioavailability of a drug is defined as the fraction of a given drug dose that is available in the systemic circulation to exert a pharmacologic effect. The extent or efficiency of systemic drug absorption is dependent upon characteristics including hydrophobic or hydrophilic properties, molecular weight, and drug ionization at biologic pH. Drug penetration through biologic membranes most often occurs through passive diffusion dependent upon drug concentrations. The absorption of a drug is also dependent upon the dosage form selected and the pharmaceutical characteristics of the formulation.

Orally administered medications require drug absorption in the gastrointestinal tract, determined by variables including surface area of the gastrointestinal tract, rates of stomach emptying and intestinal transit, pH of the stomach and small intestines, as well as blood flow to the absorption site [1]. There are important considerations regarding the use of oral medication and drug absorption in pediatric patients. For example, gastric pH in newborns is high, around 6–8 at birth, decreasing to a pH of 1–3 within 24 h of birth [2] and reaching adult values by 3–7 years of age. This is an important consideration when administering acid labile medications via the oral route. For example, higher serum concentrations of penicillin may be achieved in early infancy [1], while weak acids, such as phenobarbital or phenytoin, may require higher daily doses to achieve comparable serum concentrations due to pH values.

Medications may also be absorbed through the respiratory tract via the inhalation route. Water-soluble particles will be absorbed to a greater extent from the lung alveoli. Small particles (<1 μm) can penetrate into the tracheobronchial area. During respiratory administration of drugs, it should be noted that inadvertent swallowing of drug into the gastrointestinal tract may significantly contribute to systemic bioavailability.

The skin is also a route of drug absorption. The stratum corneum is the most important layer in the regulation of medication penetration. Cutaneous absorption of medications may be increased in children due to a greater relative body surface area to body mass ratio compared to adults [1, 3]. The topical route in infants and children has potential for a greater risk of systemic absorption as a result of a greater skin-surface-to-body-weight-ratio, a decreased subcutaneous fat layer, as well as a thinner stratum corneum and epidermis [1, 2].

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In pediatric patients, and specifically newborns, efficiency of intramuscular drug absorption may be decreased and unpredictable due to decreased muscle mass and tone, reduced muscle blood flow, and decreased muscle activity.

8.3 Distribution

Drug distribution is extensively altered in children when compared to drug handling in adults. Drugs are distributed throughout the body through tissues and fluids under the control of variables including body composition (body water, fat, bone, muscle, etc.), extent of plasma protein binding, and organ blood flow [4]. Total body water varies depending on the age of a pediatric patient. Total body water ratio, when compared to body mass progressively, decreases with age: preterm newborns 85%, term newborns 75%, infants approximately 78%, and a 1-year old approximately 75%, adults 60% [2, 3]. Variation in total body water content affects distribution of hydrophilic medications, so that higher loading doses and maintenance doses (when compared by body weight) may be required. For example, aminoglycoside daily dose requirements are increased: 7.5 mg/kg/day in infants and young children as compared to adult doses of 3–5 mg/kg/day to achieve similar therapeutic serum concentrations.

A hypothetical drug "volume of distribution" (*V*d) may be calculated, reflecting the extent of distribution into body fluids and tissues, and relates the amount of drug in the body to the measured plasma concentration. An apparent *V*d may be calculated as:

$$V\mathrm{d}\ \left(\mathrm{L/kg}\right) = \frac{\mathrm{Dose}\ \left(\mathrm{mg/kg}\right)}{\mathrm{Plasma\ \ concentration}\ \left(\mathrm{mg/L}\right)}$$

The larger the volume of distribution, the larger the medication dose needed to achieve a target drug concentration. For example, if the *V*d of a particular drug is 1 L/kg, and the therapeutic serum concentration is 20 mg/L, then the necessary loading dose of the medication would be 20 mg/kg. Phenytoin and phenobarbital loading doses in status epilepticus are examples of clinical applications of this pharmacokinetic principle.

Plasma protein binding is another important determinant of drug distribution, as many important drugs in pediatrics demonstrate high extent of binding to albumin and alpha-1-acid-glycoproteins. Lower serum albumin concentrations and decreased affinity of acidic drugs at albumin binding sites, most evident in newborns and young infants, result in higher free concentrations for drugs such as phenytoin, valproate, and salicylates with risks of enhanced toxicity and/or enhanced clearance and subtherapeutic effects. Drug displacement interactions may also be more evident in infancy where highly albumin-bound drugs such as ceftriaxone or sulfonamides, for example, may displace bilirubin and other physiologic substances from albumin binding sites, resulting in toxicity.

Plasma concentration of alpha-1-acid-glycoprotein, a carrier of basic drugs, is decreased in newborns, reaching approximately 50% of adult values during infancy and slowly increasing during the first year [3]. Effects of age-based changes may be important for agents such as lidocaine. Disease states can also affect changes in alpha-1-acid-glycoprotein, with elevations as an acute phase reaction caused by inflammation (e.g., myocardial infarction in adults). This could result in lower free concentrations of drugs, including quinidine, lidocaine, and propranolol, necessitating careful laboratory and clinical monitoring.

8.4 Metabolism

Drug metabolism is the process by which a substance is biochemically transformed through chemical reactions in the body. Primary route of drug metabolism is via the liver, but metabolism also may occur to lesser extents in the kidney, gastrointestinal tract, lung, blood, and kidney. Drugs may demonstrate "first-pass effects" in which metabolism of an orally administered medication occurs in the intestinal lumen and liver before reaching systemic circulation. Medications which demonstrate high first-pass effects include beta-blockers such as propranolol, opioids such as hydromorphone, isoproterenol, and nitroglycerin. It is important to note that when a drug has a high first-pass effect, the oral dose of the medication is considerably greater than the intravenous route, and dosing conversions from parenteral to oral routes or vice versa may result in errors.

Hepatic drug metabolism may occur through a variety of processes. Phase I reactions including oxidation (CYP450), reduction, and hydroxylation [3] allow formation of more polar, water-soluble molecules that can be more easily eliminated by the body. Rates of metabolism through Phase I pathways generally are approximately 50% of activity at birth and mature over time [3]. Phase II reactions, including conjugation, glucuronidation, sulfation, and acetylation, vary in activity from 20% to 70% at birth and mature with age [5].

The cytochrome P450 enzyme system is responsible for oxidative metabolism. Four major isoenzyme pathways are responsible for metabolism of approximately 95% of all drugs: CYP3A4, CYP2D6, CYP2C9, and CYP1A2. Knowledge of drug metabolism via these enzyme pathways is useful because significant drug–drug interaction may be anticipated.

The CYP3A4 enzyme pathway is responsible for metabolism of the greatest number of medications. Drugs may act as

substrates for this enzymes family; drugs may also act as inhibitors or inducers of this family. Examples of medications that are substrates include prednisone, dexamethasone, cyclosporine, tacrolimus, benzodiazepines, calcium channel blockers, "statins," and lidocaine [6]. Medications that are inhibitors of this enzyme pathway such as amiodarone, erythromycin, azole anti-fungals such as fluconazole and voriconazole, and diltiazem may produce significant drug–drug interactions through reduced drug metabolism of competing substrates. Medications that are enzyme "inducers" such as carbamazepine, phenytoin, rifampin, and phenobarbital would decrease substrate drug concentrations and, therefore, therapeutic responses. There are large differences reported in CYP3A4 activity with a 4–13-fold variations in clearance rates [7].

CYP2D6 isoenzyme family encompasses approximately 25% of medications. Substrates of this pathway include tricyclic antidepressants, opioids, mexiletine, flecainide, haloperidol, and beta-blockers. Dextromethorphan is the standard marker for efficiency of drug metabolism through this pathway. Examples of CYP2D6 inhibitors include amiodarone, haloperidol, and quinidine; inducers include phenytoin, phenobarbital, carbamazepine, and rifampin.

CYP2C9 enzyme substrates include omeprazole, phenytoin, S-warfarin, diazepam, and propranolol. Inhibitors include amiodarone, fluconazole, omeprazole, and topiramate. Inducers include phenytoin, phenobarbital, carbamazepine, and rifampin.

The CYP1A2 isoenzyme family is responsible for approximately 5% of medications such as theophylline, R-warfarin, and caffeine. Inhibitors include erythromycin, clarithromycin, fluconazole, and ciprofloxacin. Examples of inducer include phenytoin, carbamazepine, phenobarbital, and rifampin.

8.5 Excretion

Excretion of drugs and metabolites occurs primarily through the urine and feces, although other routes include saliva, sweat, respiratory tract, tears, semen, and breast milk. Renal excretion of drug proceeds via glomerular filtration, tubular secretion, and tubular reabsorption. There is age-specific maturation of renal processes of elimination that affects rates of drug elimination. For example, glomerular filtration function is reduced in premature infants and newborns, with progressive maturation by 8–12 months of age. Therefore, drugs such as vancomycin and gentamicin require extended dosing intervals in neonates due to immature renal function.

8.6 Describing Drug Pharmacokinetics Through Pharmacokinetic Models

Pharmacokinetic parameters expressed in mathematical terms may be used to generate visual descriptions of drug movement. The most simplistic model of drug movement is referred to as a single compartment model in which the body is a single compartment, there is no absorption phase, and the drug rapidly equilibrates through all tissues (Fig. 8.1). In this model, it is assumed that a drug follows first-order elimination when the amount of drug eliminated from the body in a specified amount of time is dependent upon the rate of elimination and the concentration of drug at that time. An increase in drug dosage results in increased serum concentrations and the amount of drug eliminated over that period (Fig. 8.2). For example, the amount of drug eliminated from the body may change, but the fraction of the drug removed over a period of time remains constant [8]. Aminoglycosides, cephalosporins, and vancomycin follow first-order elimination.

Pharmacokinetic models may reveal pattern of elimination best described as zero-order elimination, also referred to as nonlinear or Michaelis–Menten kinetics. Zero-order pharmacokinetics describes drug elimination as a saturable process at the serum concentrations commonly achieved in patients. In zero-order elimination profiles, the amount of drug eliminated does not change with the amount (concentration) of drug in the body at a given time; however, the fraction of drug that is removed changes [8] (Fig. 8.2). Aspirin, phenytoin, and ethanol are example of medications that exhibit zero-order kinetics within recommended dosage regimens. The impact of this pharmacokinetic profile can be understood in its application to practice for phenytoin. A given patient may require a dosage increase to

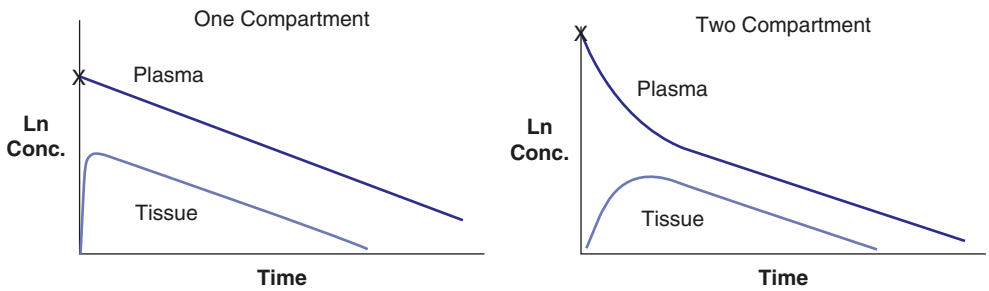

Fig. 8.1 Log of concentration vs. time for one and two compartment models

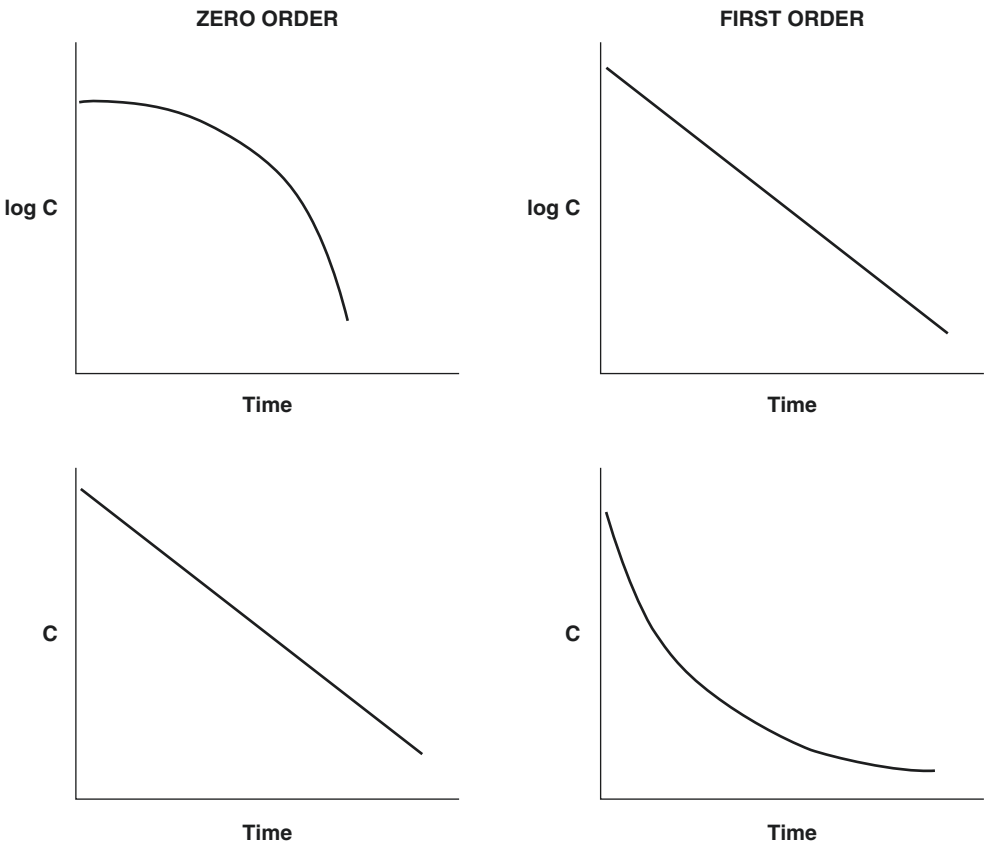

Fig. 8.2 Log of concentration vs. time for first- and zero-order pharmacokinetic models

achieve a targeted therapeutic plasma concentration. With zero-order elimination, phenytoin dose increases by 15% may result in a disproportionate increase in serum concentration, as much as two- to threefold, resulting in serious toxicity. In this setting, a fixed amount of drug is eliminated per hour regardless of serum concentration.

8.7 Drug Half-Life

Another important pharmacokinetic concept is half-life, defined as the time for drug concentration to decrease by one-half of its initial value. Clinical application of this value lies in the ability to predict timing of steady-state drug concentrations when the rate of drug administration equals the rate of drug elimination. For example, as serum steady concentrations are achieved at approximately four to five half-lives, dosage adjustments are best made at that time [8].

Nakau et al. studied the pharmacokinetics of bosentan and tadalafil in pediatric pulmonary hypertension. Pharmacokinetic variables differed from that of adult patients because the children in the study had a lower peak plasma concentration and shorter half-life [9].

In conclusion, understanding pharmacokinetic and pharmacodynamic principles for specific drugs and age-related differences in the pediatric population may aid in therapeutic decision-making. Anticipation of patient-specific variable, such as hepatic and renal function and drugs affecting the CYP450 enzyme system, enhances appropriate drug selection, dosage, and therapeutics.

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Chapter 9
Sedation and Analgesia

Garrett Roney, Edmund H. Jooste, Patrick M. Callahan, Steven E. Litchenstein, Peter J. Davis, and Phillip S. Adams

Abstract Management of sedation and analgesia in the pediatric patient after cardiac surgery and cardiopulmonary bypass is of particular importance in the setting of decreased cardiac function and increased metabolic oxygen demands secondary to inflammatory responses. Important considerations include the relief of pain and anxiety, attenuation of the stress response, and maintaining mechanical ventilation synchrony. Opioid and benzodiazepine medications have historically been the mainstay sedative and analgesic agents in the intensive care unit, and they do indeed still have an important role. Still, other agents, such as dexmedetomidine, ketamine, propofol, and neuromuscular blockers, will help to provide a more balanced and tailored sedative and analgesic plan in order to maintain a level of non-agitation and hemodynamic stability in a wide variety of pediatric patients with specific needs. Additionally, many pediatric patients with congenital cardiac disease will require extracorporeal membrane oxygenation, which presents many pharmacokinetic implications that will significantly alter the pharmacodynamic effects of some of these drugs. Thus, the understanding of these alterations and the ability to adapt the patient's sedative and analgesic plan to account for them is a necessity.

Learning Objectives

1. Describe the specific needs and considerations for sedation and analgesia in pediatric patients with congenital cardiac disease, especially after cardiopulmonary bypass.
2. Compare the mechanisms of action, the pharmacokinetic profiles, and dosing regimens of a variety of commonly used sedative and analgesic agents in the pediatric intensive care unit.
3. Apply the pharmacodynamic profiles of sedative and analgesic agents to the clinical needs of specific patients.
4. Describe the role of neuromuscular blocking agents in the management of pediatric patients with congenital heart disease.
5. Recognize the pharmacokinetic implications of extracorporeal membrane oxygenation in sedative and analgesic plans.

Questions and Answers

1. What factors contribute to sedation and analgesia strategies for patients that have undergone cardiopulmonary bypass compared with those who have not?

A: After cardiopulmonary bypass, patients are in a simultaneous state of decreased cardiac function and increased metabolic oxygen demands secondary to inflammatory responses; these inflammatory responses are of particular significance in neonatal populations. Working to attenuate metabolic oxygen demand while maintaining hemodynamic stability is of profound importance in these patients. Furthermore, postsurgical patients may have also experienced complications that may include heart failure, muscle weakness, pul-

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monary disease or pleural effusions, postoperative hemodynamic instability, hemorrhage, coagulopathy, phrenic nerve injury with diaphragm paresis, vocal cord injury or recurrent laryngeal nerve damage, or significant dysrhythmias.

2. Though opioid and benzodiazepine medications still play important roles in the management of sedation and analgesia in critically ill patients, why are they no longer used to their historical extent in favor of other medications, such as dexmedetomidine?

A: Tolerance and withdrawal syndromes are very commonly observed in pediatric ICU patients, some studies indicating that up to 57% of pediatric patients receiving fentanyl experience symptoms of withdrawal. Patients that have been sedated with opioids for 3 or more days seem to be at increased risk. Virtually 100% of patients who have received fentanyl infusions for greater than 9 days will experience withdrawal syndrome. Withdrawal is at the very least uncomfortable but also potentially dangerous to the patient. Benzodiazepine withdrawal is characterized by agitation, anxiety, nausea, and cognitive dysfunction, palpitations, psychosis, hallucinations, seizures, and suicidal ideation. Opioid withdrawal is characterized by irritability, hyperactivity of the autonomic nervous system, respiratory distress, gastrointestinal distress most commonly characterized by diarrhea, and, rarely, seizures. Management may require the long-term use of these medications.

3. Name the importance pharmacokinetic changes noted in some drugs associated with extracorporeal membrane oxygenation.

A: ECMO results in a larger volume of distribution secondary to an increase in circulating blood volume and free water. This necessitates larger loading doses of medications, specifically hydrophilic drugs. There is a decrease in the concentration of plasma proteins, resulting in an increased fraction of unbound drug, which may require less frequent re-dosing of medication. Lastly, adhesion of drug to the ECMO circuit may require larger doses of drugs and re-dosing of drugs during circuit changes.

9.1 Overview

The major goal for postoperative sedation and analgesia in pediatric patients having undergone cardiothoracic surgery is to provide a level of comfort and non-agitation to assist in the transition from the intensive care unit (ICU) to home. Important considerations include the relief of pain and anxiety, attenuation of the stress response, and, when applicable, maintaining mechanical ventilation synchrony [1]. Agents used for pediatric sedation vary with the medical needs of the patient. After cardiopulmonary bypass (CPB), cardiac function is decreased, while metabolic oxygen demands are increased secondary to inflammatory responses. This effect is even more significant in complex cases requiring longer CPB times [2]. Therefore, an ideal sedative agent should provide hemodynamic and cardiopulmonary stability, be nontoxic and noncumulative, have minimal interactions with other medications, and have a rapid onset and offset of action. Early extubation may be an appropriate goal following multiple pediatric cardiac surgeries, including uncomplicated atrial or ventricular septal defect repairs, and right or left ventricular outflow tract reconstructions. Furthermore, early extubation is desirable in patients for whom positive pressure ventilation may have detrimental effects, such as in cavopulmonary anastomoses. Factors other than type and length of cardiac surgery that influence the decision of whether or not to attempt early extubation include the preoperative evaluation of the patient and presence of heart failure, inadequate nutrition and concomitant muscle weakness, pulmonary disease or pleural effusions, postoperative hemodynamic instability, and the risk of intraoperative complications such as hemorrhage, coagulopathy, phrenic nerve injury with diaphragm paresis, vocal cord injury or recurrent laryngeal nerve damage, or significant dysrhythmias [3, 4]. Historically, intravenous (IV) midazolam, lorazepam, and opioids were the mainstay sedative agents used in pediatrics. Indeed, in newborn and infant populations, who tend to develop very significant stress responses post-CPB, high-dose opioid therapy continued into the postoperative period has been shown to reduce morbidity and, perhaps, mortality by attenuating the post-CPB stress response [5, 6]. However, respiratory depression, tolerance, and withdrawal syndromes frequently complicate their use. Another study suggests that routine profound sedation in neonates after major cardiac surgery may not prevent low cardiac output syndromes better than targeted sedation strategies [7]. More recently, the use of alpha-2 agonists, the administration of IV opioids, and the intraoperative placement of neuraxial opioids have been used for postoperative sedation and analgesia.

9.2 Opioids

Fentanyl, remifentanil, sufentanil, and morphine are the most commonly used opioids during general anesthesia and are continued in the postoperative period for sedation. Opioids provide analgesia but at higher doses result in anesthesia. Sedation is also provided, but this is seen more significantly in morphine as opposed to the synthetic opioids. Opioids are not associated with amnestic effects. They are seldom used as a sole agent except when used in high doses during certain cardiac procedures or with critically ill patients [7, 8]. Intermittent opioid doses may be effectively used after cardiac surgery, but this can result in periods of under- and oversedation when compared to a continuous infusion.

9.2.1 Mechanism of Action

Opioids bind stereospecifically to various opioid receptors located throughout the central nervous system, as well as in peripheral tissues. The major classes of opioid receptors involved in analgesia are μ, κ, and δ. The μ_1 receptor primarily produces analgesia, whereas the μ_2 receptor produces mild analgesia and is responsible for hypoventilation, bradycardia, constipation, urinary retention, muscle rigidity, and physical dependence. The κ receptor produces sedation and spinal analgesia in the substantia gelatinosa, as well as dysphoric or hallucinogenic effects. The δ receptor produces analgesia, may be epileptogenic and may modulate the physical dependence and respiratory depressant effects of the μ receptor. Each receptor is coupled to a G protein. Opioid binding causes inhibition of adenylyl cyclase and consequently reduced intracellular cyclic adenosine monophosphate (cAMP). Inhibition of voltage-gated calcium channels and activation of potassium channels also cause cell membrane hyperpolarization and reduced neurotransmitter release [9, 10].

9.2.2 Pharmacokinetics

Opioids can be administered via different routes, including transdermally, intranasally, orally (PO), intramuscularly (IM), IV, or into the central neuraxial compartment. Increased dosing may be needed in patients already taking long-term opioids due to physiologic tolerance. After IV administration, the onset of action is within minutes (initial distribution time for most opioids is 5–20 minutes), with greater lipid solubility resulting in quicker onset [11]. The main metabolism is by the liver with the inactive metabolites being excreted by the kidneys. Morphine's onset is reasonably rapid (15–30 minutes) after IV and IM administration and lasts up to 4 hours. This slower onset is due to its relatively poor lipid solubility which slows down its penetration into the CNS and gives it a smaller volume of distribution. Its elimination half-life is 115 minutes. It is metabolized in the liver by conjugation to glucuronic acid to form morphine 3-glucuronide, an inactive metabolite, and morphine-6-glucuronide, which is an active metabolite. The morphine-6-glucuronide metabolite may accumulate in patients with renal disease leading to a prolonged morphine effect and potential respiratory depression.

Fentanyl is an extremely potent synthetic opioid, roughly 100 times as strong as morphine. Its rapid onset and shorter duration of action is due to its high lipid solubility. However, when dosed as an infusion or in high doses, it saturates inactive sites and becomes a long-acting opioid similar to morphine. Fentanyl's elimination half-life of 180–220 minutes is actually slightly longer than that of morphine, primarily due to its large volume of distribution. It is metabolized in the liver, and its breakdown products can accumulate in renal failure which may result in poor pain control and delirium.

Since tolerance to opioid medications and escalation of dosing is common in patients requiring long ICU stays or multiple surgical procedures, patients are at increased risk of opioid withdrawal as these medications are discontinued. For this reason, methadone has been employed to both provide long-acting, more continuous analgesia (half-life of 19 hours in patients older than 1 year of age) as well as provide a means for weaning opioid therapy. Methadone, interestingly, also has N-methyl-D-aspartate (NMDA) antagonistic activity that further increases its analgesic potential. However, a systematic review has found that evidence is insubstantial to recommend one weaning strategy over another, including those that implement methadone [12].

9.2.3 Pharmacodynamics and Side Effects

Central Nervous System Opioids result in significant analgesia, sedation, euphoria, and, in large doses, unconsciousness (Table 9.1). Opioids mildly decrease cerebral blood flow and oxygen consumption, as well as intracranial pressure (ICP). Opioids stimulate the chemoreceptor trigger zone of the medulla which may result in nausea and vomiting. Prolonged or repeated doses of opioids may result in tolerance, after

Table 9.1 Typical doses of commonly used opioids

Opioid	Acute pain	Continuous infusion	Prolonged analgesia
Fentanyl	1–2 μg/kg IV q10 min	1–5 μg/kg/hour IV	25–100 μg transdermal patch q72 h
Morphine	0.03–0.1 mg/kg IV q20min	0.04–0.06 mg/kg/hour	–
Methadone	–	–	0.05–0.08 mg/kg IV

which larger doses of opioids will be required to achieve the same analgesic effect. Physical dependence and addictive behavior are other adverse effects. Opioid-induced hyperalgesia, characterized by allodynia, may also result from prolonged exposure to opioids.

Cardiovascular Opioids generally have few cardiovascular side effects, but large doses can be associated with a decrease in sympathetic reflexes, resulting in bradycardia and decreased systemic vascular resistance (SVR). The histamine release associated with some opioids, particularly morphine, can result in a large decrease in SVR.

Respiratory Opioids may induce a dose-dependent respiratory depression resulting in a decreased response to $PaCO_2$, apnea, and hypoxia, as well as decreased cough reflex. Large bolus doses may result in centrally mediated muscle contraction in the abdomen and chest wall and can lead to an inability to ventilate. Muscle rigidity can be treated by the administration of neuromuscular relaxants or opioid antagonist.

Gastrointestinal Opioids bind to receptors in the gut, resulting in decreased peristalsis and constipation; tolerance does not develop to constipation, so all patients must be placed on a bowel regimen. Sphincter of Oddi contraction or biliary spasm may produce symptoms similar to symptomatic cholelithiasis but is reversible with opioid antagonism.

Urinary Contraction of the vesicle sphincter may result in urinary retention [11, 13, 14].

9.2.4 Patient-Controlled Analgesia (PCA)

In patients who are awake, continuous opioid analgesia may result in oversedation during periods that are relatively unpainful (rest and sleep), yet may undertreat their pain in more intense situations (procedures, coughing, or position changes). A patient-controlled titration of opioid medications may provide a better treatment of their pain by utilizing bolus doses of medication when they perceive it to be necessary (Table 9.2). The patient should be developmentally older than 6 or 7 years of age and be educated on the use of the computerized machine, demonstrate the ability to use the machine, and must agree to take responsibility to control their pain. Parents and other family members must be instructed to never activate drug delivery themselves as this can lead to overdose and respiratory depression. For instances when a patient may not be competent to effectively manage their own PCA, clinician boluses can be programmed into the device, which can then be delivered by bedside staff. In some patients who are tolerant to opioid medications, a continuous basal rate may be employed, but this carries with it increased risk of side effects such as respiratory depression and should be used with caution [15, 16].

Table 9.2 Common PCA dosing regimens [17]

Opioid	Bolus dose (mcg/kg)	Typical lockout interval (min)	4-hour limit (mcg/kg)
Morphine	15–25	8	300–400
Fentanyl	0.25–0.5	15	50–80
Hydromorphone	3–5	8	4–10

9.2.5 Withdrawal

Opioid withdrawal is a fairly common iatrogenic phenomenon in the pediatric ICU, with some studies indicating that up to 57% of pediatric patients receiving fentanyl experience symptoms of withdrawal. Patients that have been sedated with opioids for three or more days seem to be at increased risk [18]. Virtually 100% of patients who have received fentanyl infusions for greater than 9 days will experience withdrawal syndrome. Though patients will exhibit varying degrees of symptoms, opioid withdrawal is generally characterized by irritability, hyperactivity of the autonomic nervous system, respiratory distress, gastrointestinal distress most commonly characterized by diarrhea, and, rarely, seizures. Withdrawal is difficult to evaluate in neonatal populations, and evaluation of the patient's cry, respiratory rate, hours of sleep, stooling, and Moro reflexes become important clinical indicators. As previously mentioned, longer-acting opioids, such as morphine and methadone, are first-line treatment. Some studies have found success using non-opioid medications such as phenobarbital and clonidine. Still, of the many weaning strategies that have been studied, one does not seem to be superior to another [19].

9.2.6 Reversal

The most common opioid antagonist is naloxone. It is structurally similar to morphine and oxymorphone and provides competitive antagonism at the μ, κ, and δ opioid receptors. In adults, the peak effect is at 1–2 minutes with a half-life

of 64 minutes. Studies have varied on the half-life of naloxone in neonates (anywhere from 70 minutes to >230 minutes, depending on the route of administration), but it does seem to be increased when compared to adults. Bolus dosing of 0.01 mg/kg IV, repeated every 2–3 minutes, is recommended for reversing opioids after anesthesia [20–22]. Additionally, a low-dose infusion of 0.25 mcg/kg/hour has been shown to attenuate side effects such as pruritus and nausea in children receiving prolonged morphine use [23].

9.3 Benzodiazepines

Benzodiazepines are useful in the setting of cardiac disease because of their ability to display minimal cardiac depressant effects even at large doses. At lower doses, either as a bolus or as a continuous infusion, benzodiazepines produce anxiolysis, sedation, and amnesia. Unconsciousness can be achieved with larger induction doses.

9.3.1 Mechanism of Action

Benzodiazepines consist of a benzene and seven-member diazepine ring. They bind to the gamma-aminobutyric acid (GABA) receptor, increasing the frequency of chloride ion channel openings, essentially facilitating the binding of GABA to its receptor, as well as enhancing its effect [24].

9.3.2 Pharmacokinetics

Benzodiazepines can be safely administered IV, IM, PO, intranasally, buccally, and sublingually (Table 9.3). While midazolam is not approved for PO administration, it has been widely used in the pediatric population for premedication prior to general anesthesia. All benzodiazepines are highly protein bound (90–98%) and moderately lipid-soluble, and redistribution is fairly rapid with an initial redistribution half-life of 3–10 minutes. The imidazole ring of midazolam results in water solubility at low pH. Of note, the lipid solubility of lorazepam requires IV preparations to be made with propylene glycol, which can irritate blood vessels. Lorazepam undergoes glucuronidation in the liver, while midazolam undergoes hepatic oxidation, and their elimination half-lives depend on their volume of distribution and hepatic extraction ratio. Lorazepam has a low hepatic extraction ratio resulting in an elimination half-life of approximately 15 hours, although clinical effects may be prolonged secondary to high affinity to the receptor. Midazolam has a large volume of distribution, but an increased hepatic extraction ratio, resulting in an elimination half-life of approximately 2 hours. These relatively long elimination half-lives may cause sedative effects that prolong mechanical ventilation and intubation, making them especially suited for cases where prolonged sedation is desired [24, 25].

Table 9.3 Common dosages of benzodiazepines [27]

Benzodiazepine	Dosing	
Midazolam	*Oral premedication:*	0.5–1 mg/kg
	Intranasal:	0.2–0.3 mg/kg
	Sublingual:	0.1 mg/kg
	Intravenous bolus:	0.01–0.1 mg/kg
	Continuous infusion:	0.05–0.1 mg/kg/hour
Lorazepam	*Sedation:*	0.2–0.1 mg/kg

9.3.3 Pharmacodynamics and Side Effects

Central Nervous System Benzodiazepines produce no analgesia but are useful for their sedative, amnestic, and anxiolytic properties. They may also be of use in patients with intracranial pathology due to their ability to reduce cerebral oxygen consumption, ICP, and cerebral blood flow; they also can both treat and prevent seizure activity.

Cardiovascular A major advantage of benzodiazepine administration is their minimal effect on cardiovascular hemodynamics. There may be a slight decrease in SVR and cardiac output. When administered with opioids, there may be a synergistic effect that produces hypotension and direct myocardial depression. Midazolam may result in an induced vagolysis, characterized by a reduction in variability of heart rate during continuous infusions.

Respiratory Benzodiazepines depress the ventilatory response to carbon dioxide similar to opioids, albeit to a lesser extent. These effects are most pronounced after IV administration and with concurrent administration of other respiratory depressants, such as opioids. Doses should be carefully titrated to effect and respiratory status should be monitored closely with the ability to resuscitate if necessary [26, 27].

9.3.4 Withdrawal

Acute benzodiazepine withdrawal syndromes can be uncomfortable and dangerous for patients, which has tempered the frequency of benzodiazepine administration in ICU settings for prolonged sedation. In addition to agitation, anxiety, nausea, and cognitive dysfunction, the patient may also experience palpitations, psychosis, hallucinations, seizures, and suicidal ideation. Increased weaning times may be required in order to attenuate withdrawal symptoms, and longer-

acting benzodiazepines like lorazepam may be indicated. In mechanically ventilated patients, administration of a propofol infusion prior to extubation has been shown to effectively prevent agitation associated with withdrawal symptoms and facilitate the extubation process [28, 29].

9.3.5 Reversal

In oversedated patients or in patients experiencing adverse effects of benzodiazepines, reversal may be necessitated. Flumazenil is a competitive antagonist of benzodiazepines at the GABA receptor. Side effects include nausea, vomiting, anxiety, seizures, and benzodiazepine withdrawal syndrome [30]. Because of its short half-life of 0.7–1.3 hours, re-sedation is common. Typical flumazenil dosing is 0.01 mg/kg (0.2 mg maximum) titrated to effect up to a total dose 0.05 mg/kg or 1 mg maximum (whichever is lower) [31, 32].

9.4 Alpha-2 Agonists

Because of their opioid-sparing effects, blunting of sympathetic responses to surgical stress, and preservation of respiratory drive, alpha-2 agonists have emerged as an attractive sedative agent in the critical care setting, particularly dexmedetomidine. It may aid in preventing emergence delirium and facilitate the management of opioid withdrawal [33].

9.4.1 Mechanism of Action

Alpha-2 adrenergic receptors are composed of G proteins consisting of three isoreceptors (alpha-2a, alpha-2b, and alpha-2c), which bind both agonists and antagonists with similar affinity [34]. The receptors are present in both the central and peripheral nervous system at autonomic ganglia and at pre- and postsynaptic sites. Activation of the central nervous system leads to sympathetic inhibition, while binding of alpha-2 agonists in the spinal cord results in analgesia. Central nervous stimulation and sympathetic stimulation in the locus ceruleus in the brain stem affect sedation and anxiolysis [35, 36].

9.4.2 Pharmacokinetics

Dexmedetomidine has been administered safely as IV, IM, and PO and intranasally as a sedative premedication as well as an IV bolus or infusion. Dexmedetomidine is heavily protein bound (94%). It has a rapid onset and has a rapid initial redistribution half-life of 6 minutes with a terminal half-life of approximately 2 hours. Dexmedetomidine is metabolized in the liver through glucuronidation and the cytochrome P450 system with ultimate renal elimination. Though pediatric studies are lacking, there appears to be no difference in pharmacokinetic profile in pediatric patients [37–39].

9.4.3 Pharmacodynamics and Side effects

Central Nervous System Dexmedetomidine's alpha-2 agonism provides both sedation and analgesia. Dexmedetomidine appears to have little effect on ICP, but there is a decrease in mean arterial pressure, and as a consequence, cerebral perfusion pressure may decrease [40, 41]. Cerebral vasoconstriction will decrease cerebral blood flow. Dexmedetomidine also lowers intraocular pressure [42]. Dexmedetomidine has been reported to have both pro- and anticonvulsant properties. Lastly, dexmedetomidine lowers the shivering threshold and has been reported to be effective in treating postoperative shivering, which will reduce metabolic oxygen consumption in hypothermic patients [43].

Cardiovascular System There is generally a biphasic response to IV dexmedetomidine administration. The initial increase in blood pressure and the decrease in heart rate result from stimulation of peripheral postsynaptic alpha-2b adrenergic receptors which results in vasoconstriction with reflex bradycardia. The second phase of the decrease in blood pressure and heart rate results from the central presynaptic alpha-2a adrenergic receptor stimulation. Decreased cardiac output, bradycardia, and sinus arrest have all been reported. Myocardial oxygen consumption may decrease. Dexmedetomidine has also been reported for its antiarrhythmic effect in the context of junctional ectopic tachycardia, although atrial fibrillation can be seen as a side effect [44]. Overdose can be associated with hypo- or hypertension, hypoxia, and first- or second-degree atrioventricular block. Caution should be used when dexmedetomidine is used in conjunction with other drugs that decrease heart rate or cardiac output. Abrupt withdrawal after longer infusions (>24 hours) may result in withdrawal syndromes similar to those typically seen with clonidine.

Respiratory System Dexmedetomidine increases resting $PaCO_2$ and decreases minute ventilation both at rest and in response to a CO_2 challenge. However, these changes are modest compared to other sedative modalities and its minimal respiratory effects make it an advantageous drug to use in the critical care setting [45]. Nonetheless, respiratory depression may be seen as a synergistic effect when administered with other respiratory depressants. Additionally,

the sedative effects of the medication may still result in obstructive sleep apnea in at-risk patients [46–48].

9.4.4 Dosing

- *Loading dose*: 0.5–1 mcg/kg over 10 minutes
- *Maintenance*: 0.2–1 mcg/kg/hour

Dosing will be dependent upon the variable hemodynamic stability of the individual patients, as large bolus dosing will be associated with greater effects of bradycardia and initial hypertension.

9.5 Ketamine

The hemodynamic stability and preservation of respiratory drive, as well as its analgesic properties, have made ketamine an attractive drug to use in ICU settings, especially for procedural sedation (Table 9.4).

9.5.1 Mechanism of Action

Ketamine is an NMDA receptor antagonist and binding will inhibit postsynaptic spinal cord reflexes and effects of excitatory neurotransmitters throughout the brain. Ketamine is a dissociative anesthetic that functionally dissociates the thalamus from the limbic cortex, effectively preventing the relay of sensory impulses from the reticular activating system to the cerebral cortex [49].

9.5.2 Pharmacokinetics

Ketamine has been administered safely via many routes, including PO, intranasal, and rectal but is usually only given IM or IV. Ketamine is lipid-soluble with low protein binding, resulting in rapid brain uptake and then redistribution to peripheral compartments with a distribution half-life of 10–15 minutes. Ketamine is biotransformed in the liver into multiple metabolites with norketamine being a somewhat active metabolite. The relatively high hepatic extraction ratio results in a short elimination half-life of approximately 2 hours ending with renal elimination [50].

Table 9.4 Common ketamine dosages

Analgesia/short-term sedation:	0.5 mg/kg IV bolus
Induction:	1–3 mg/kg IV 3–5 mg/kg IM
Continuous infusion:	2.5-15 μg/kg/min

9.5.3 Pharmacodynamics and Side Effects

Central Nervous System Ketamine will induce analgesia, amnesia, and unconsciousness in patients. Patients appear conscious but lack the ability to process the input of sensation. Historically, ketamine has been associated with an increase in cerebral oxygen consumption, cerebral blood flow, and ICP, which has made it a poor sedative choice in patients with head trauma or space-occupying lesions. Recent evidence seems to indicate that this elevation of ICP is not seen when midazolam is co-administered. Myoclonus may be observed. Lastly, hallucinations, nightmares, delirium, and other psychotomimetic effects may be seen, but these are less commonly observed in the pediatric population and may be attenuated with the administration of midazolam [50].

Cardiovascular Ketamine is a sympathomimetic drug that centrally stimulates the sympathetic nervous system and inhibits postganglionic catecholamine uptake, resulting in an increase in heart rate, blood pressure, and cardiac output. Large doses, however, may result in direct myocardial depression secondary to inhibition of calcium signaling systems, especially in patients with depleted stores of endogenous catecholamines or blockade of the sympathetic nervous system, such as spinal cord transection. For this reason, ketamine should be used cautiously in patients with low myocardial reserve. The effects of ketamine on pulmonary vascular resistance (PVR) are controversial. Some studies suggest that ketamine can increase PVR in patients that are predisposed to pulmonary hypertension, but others indicate that there are minimal effects on PVR in children either spontaneously breathing or mechanically ventilated [51, 52]. Therefore, ketamine should be used judiciously in at-risk patients but may still be administered safely if hypoventilation and hypercarbic effects are avoided.

Respiratory Racemic ketamine (the only formulation available in the United States) produces potent bronchodilation, and upper respiratory reflexes are left intact. This makes ketamine a particularly attractive sedative in patients with bronchospastic disease. When ketamine is administered with opioids, apnea may occur. There is an increase in airway secretions, which may cause laryngospasm, bronchospasm, or airway obstruction in some patients; however, this effect can be ameliorated with administration of an anticholinergic medication such as glycopyrrolate [53, 54].

9.6 Propofol

Propofol is a drug commonly administered for both induction and maintenance of anesthesia, as well as an effective sedative agent in the ICU, but its prolonged use is limited secondary to significant decreases in SVR and myocardial depression. However, its rapid clearance and short duration make it useful for invasive procedures and rapid weaning to extubation.

9.6.1 Mechanism of Action

Propofol binds allosterically to $GABA_A$ receptors increasing the affinity of GABA for the receptor, thereby facilitating the inhibitory effects of GABA neurotransmission.

9.6.2 Pharmacokinetics

Propofol can only be administered IV and has a rapid onset of action with an initial distribution time of 2–8 minutes. Propofol is mainly conjugated in the liver and excreted renally, but its rapid clearance may be due to possible extrahepatic metabolism as well. Propofol infusion syndrome has been noted in patients, especially young adults and children, when it has been used for long-term sedation at very high doses. This syndrome is characterized by metabolic acidosis, rhabdomyolysis, cardiac failure, kidney failure, lipemia, and even death. Treatment of suspected propofol infusion syndrome consists of stopping any further propofol administration and supportive therapies [55, 56].

9.6.3 Pharmacodynamics and Side Effects

Central Nervous System Propofol will decrease cerebral blood flow and ICP, but a concomitant decrease in SVR may decrease cerebral perfusion pressure. Propofol also has anticonvulsant properties and has been used in the treatment of status epilepticus, even though common side effects include muscle twitching and opisthotonus. Patients do not develop tolerance to propofol, even after long-term infusions.

Cardiovascular Propofol causes a significant decrease in preload and SVR and also has direct myocardial depressant effects on the heart. Heart rate is usually preserved, if not slightly decreased, but more severe bradycardic effects may be noted in neonates, patients taking beta-blockers, or patients with pre-existing ventricular dysfunction [mm].

Respiratory Propofol is also a strong depressant of both hypoxic ventilatory drive and the ventilator response to hypercarbia, making apnea a very common side effect. Airway reflexes are also blunted, assisting in the manipulation of the airway but putting the patient at risk for aspiration [57, 58].

9.6.4 Dosing

- *Induction*: 1–3 mg/kg
- *Sedation*: 25–100 mcg/kg/min

9.7 Muscle Relaxants

Muscle relaxants can be used to great effect in patients with limited cardiorespiratory reserve, as they aid in reducing myocardial oxygen demand. Succinylcholine, a depolarizing muscle relaxant, is beneficial for tracheal intubation, but its rapid clearance and short duration of action do not make it an effective choice to maintain muscle relaxation in mechanically ventilated patients. However, non-depolarizing muscle relaxants, such as the intermediate-acting cisatracurium and rocuronium, provide longer periods of muscle relaxation to facilitate mechanical ventilation and decrease work of the heart (Table 9.5). These medications may be titrated to effect and also monitored with train-of-four stimulation.

9.7.1 Mechanism of Action

Non-depolarizing neuromuscular blockers act as competitive antagonists to acetylcholine at the alpha subunits of the acetylcholine receptors. Acetylcholine is prevented from binding and no end-plate potential develops, resulting in muscle paralysis [59].

9.7.2 Pharmacokinetics

Cisatracurium undergoes Hofmann elimination independent of any organ, making it an ideal muscle relaxant for patients with renal or hepatic dysfunction. An active metabolite is

Table 9.5 Common dosages of non-depolarizing neuromuscular blocking agents

Neuromuscular blocking agent	Induction (mg/kg)	Maintenance bolus (mg/kg)	Continuous infusion (μg/kg/min)
Rocuronium	0.6–1.2	0.15	9–12
Cisatracurium	0.2	0.02	1–2

laudanosine, which may rarely cause central nervous system excitation. Rocuronium has a more rapid onset of action than cisatracurium, does not undergo metabolism as it is mainly eliminated unchanged in the bile, and therefore has no active metabolites. It is cleared primarily by the liver and slightly by the kidneys, causing it to have a prolonged duration of action in those with severe liver failure. Both of these drugs have minimal other pharmacodynamic effects [60].

9.7.3 Reversal

When reversal of neuromuscular blockade is warranted, perhaps in preparation for extubation, administration of a cholinesterase inhibitor can be used to increase the concentration of acetylcholine at the receptor site, competing against the rocuronium. Since this effect is not permanent, there is potential for recurrence of neuromuscular blockade after reversal if rocuronium is still at the receptor. For this reason, the presence of T2, if not T4 as suggested by more recent studies, should be observed on train-of-four nerve stimulation testing. Neostigmine is the most commonly used reversal agent [61]. Use of a cholinesterase inhibitor may cause cholinergic effects throughout the body, such as bradycardia, so a comparable dose of an anticholinergic drug should be given simultaneously. Typical doses of neostigmine include 0.04–0.07 mg/kg with 0.2 mg glycopyrrolate per mg of neostigmine.

Alternatively, sugammadex, a recently approved, highly selective drug for binding aminosteroid neuromuscular blocking drugs, can be administered as an antidote to reverse rocuronium [62]. Sugammadex can be administered for the rapid reversal of aminosteroid muscle relaxant regardless of the proximity in time of the muscle relaxant dose. Sugammadex is only effective for the aminosteroid-type muscle relaxants, such as rocuronium and vecuronium, and will not antagonize agents like cisatracurium. There was a concern that concomitant exogenous steroid administration would reduce the efficacy of sugammadex; however, this has not been observed in human trials. Also, women of childbearing age should be informed if they receive sugammadex due to its ability to bind contraceptive agents. Typical dosing is 2 mg/kg for the presence of T2, 4 mg/kg for at least 1–2 post-tetanic counts, and 16 mg/kg for an immediate reversal after a single dose of rocuronium. Bradycardia and hypersensitivity reactions have been recorded [63].

9.7.4 Implications of Extracorporeal Membrane Oxygenation

In patients with congenital cardiac disease either prior to cardiac surgery or after CPB, they may experience states of persistently low cardiac output or refractory hypoxia requiring extracorporeal membrane oxygenation (ECMO). ECMO introduces many implications in the sedative and analgesic strategies that must be employed in the treatment of these patients (Table 9.6). In most cases, these patients will require invasive monitoring, airway intubation with mechanical ventilation, and maintenance of a deep level of sedation. Care must be taken in the initial transition from spontaneous ventilation to positive pressure ventilation which can, in some clinical scenarios, prompt cardiac arrest and circulatory collapse. Therefore, medications with stable hemodynamic profiles, including muscle relaxants and opioids, should be used, and the care team should be prepared for resuscitation measures.

Table 9.6 ECMO effects on pharmacokinetics and clinical significance

ECMO implication	Pharmacokinetics	Clinical significance
Adhesion of drug to circuit	Decreased bioavailability	Loss of drug in circuit changes Need for increased doses
Increased circulating volume	Increased volume of distribution	Need for increased loading doses, especially hydrophilic drugs
Decreased plasma proteins	Increased unbound drug	Less frequent need for re-dosing

At times, it may be difficult to assess whether the pharmacokinetic changes in patients requiring ECMO are due to the patient's underlying illness or the physiology of the ECMO circuit itself. That being said, several pharmacokinetic shifts result from the implementation of ECMO, which typically result in a larger volume of distribution and a decreased clearance for many medications. The circulating blood volume is increased secondary to the extracorporeal circuit, and intracellular water content also increases. These changes largely result in an increase in the volume of distribution, which will necessitate larger loading doses of medications, particularly in hydrophilic drugs such as non-depolarizing muscle relaxants. A subsequent decrease in plasma concentration of proteins is also seen, resulting in an increase in plasma concentrations of free drug [64, 65].

Additionally, drug binding to the ECMO circuit itself will decrease the bioavailability of the drug, requiring larger or more frequent doses. It has been suggested that as the technology of ECMO circuits has improved, the degree of drug-binding has decreased. However, it has been shown that even in newer systems, some drug levels decline in ECMO circuits when compared to control values. One study found that 17.2% of midazolam, 41.3% of lorazepam, and 32.6% of fentanyl remained in the ECMO circuit when compared to control values. Interestingly, this same study did not find a decline in morphine levels. This finding, combined with its long duration of action, may make morphine an optimal opioid to choose for sedation and analgesia in patients undergoing ECMO [66].

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Chapter 10
The Effects of Cardiopulmonary Bypass Following Pediatric Cardiac Surgery

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Abstract Despite many advances since Gibbon's first cardiopulmonary bypass (CPB) in 1953, end-organ damage and neurologic dysfunction remain a challenge in the management of pediatric patients undergoing cardiac surgery. A comprehensive understanding of the inflammatory process caused by CPB has led to intraoperative strategies that intend to minimize such responses.

Exposure of blood to the CPB circuit induces a complex systemic inflammatory response (SIRS), which involves the activation of multiple, interdependent cellular and humoral pathways. The coagulation and complement pathways are activated when the plasmatic proteins are exposed to the circuit material. Once cellular activation occurs, released proinflammatory cytokines, adhesion molecules, and chemokines are responsible for the amplification of the inflammatory cascade.

Each of the inflammatory cascade components has an important role in a process that ultimately results in vascular injury and end-organ damage.

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10.1 The Inflammatory Response to CPB

The activation of Factor XII is the first step in the inflammatory cascade response that occurs with CPB. Factor XII regulates the production of kallikrein, thrombin, and bradykinins as well as the conversion of plasminogen to plasmin, promoting fibrinolysis, and the activation of the complement system, a key component of the overall inflammatory response in which a series of proteins are assembled into the so-called membrane attack complex (MAC) and create transmembrane channels that allow influx of water and ions into the intracellular compartment, disrupting the osmotic and chemical equilibrium and ultimately leading to cellular edema and apoptosis [1, 2].

Additionally, complement activation stimulates leukocyte and platelet expression of endothelial adhesion proteins, causing vascular occlusion, decreased organ perfusion, and subsequently, ischemia [3].

Activation of the coagulation system will, in turn, enhance the upregulation of cytokine and chemokine production induced by the complement system. Cellular effects include the production of oxygen-derived free radicals, decrease in nitric oxide release, and increased exocytosis of histotoxic mediators, amplifying the inflammatory process. The release of these substances into the circulation will have a key role in the pathophysiology of ischemia/reperfusion injury [4–7].

In summary, the inflammatory response after CPB encompasses the activation of different pathways resulting in chemokine production, endothelial damage, organ ischemia, and cellular edema. The resultant inflammatory milieu and the disruption of the endothelial-cellular barrier are the mediators of the pathophysiologic process that results in multiorgan failure [8, 9]. A counter-regulation of the inflammatory process then takes place as a compensatory mechanism. This process plays an important role in determining the individual degree of the inflammatory response to CPB and end-organ compromise and it is likely regulated by genetic factors [1, 3].

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10.2 Physiologic Responses to CPB in the Pediatric Population

The inflammatory response can be amplified in pediatric patients due to several factors:

1. Major hemodilution of the blood components due to lower body surface area compared to the circuit area, smaller patients require higher prime volumes, exposing them to more blood products
2. Abrupt changes in temperature in order to perform the procedure affect the coagulation process
3. Need for higher perfusion rates due to higher metabolic demand, increased shear stress, and higher risk of hypoperfusion
4. Proportionally longer CPB times with extensive or complex repair
5. Use of low flows and circulatory arrest to allow surgical visualization
6. Immaturity of the organs and systems with increased susceptibility to injury

10.3 Specific Organ Effects of Pediatric CPB

The development of the pulmonary system is not complete until the second to the third year of life. During this critical period, the pulmonary vasculature is more susceptible to injury. The inflammatory response induced by the exposure to CPB will cause damage to the alveoli-endothelial barrier. Activated leukocytes adhere to the endothelial lining and migrate to the interstitium where protease secretion mediates the development of pulmonary edema; concomitant decrease in nitric oxide production will lead to pulmonary vasoconstriction.

Reperfusion injury is caused by the accumulation of cytokines, in addition to the release of oxygen-free radicals imposing significant damage to the delicate alveolar membrane. There are also changes in the composition and the activity of the alveolar surfactant, resulting in hypoxemia, atelectasis, decreased pulmonary compliance, and functional residual capacity [4, 5]. Establishing protective strategies of ventilation after exposure of pediatric patients to CPB is key to avoiding further damage.

Myocardial injury can be caused directly by ischemia following cross-clamp or surgical trauma and aggravated indirectly by the reperfusion inflammatory response. Proteases, inflammatory cytokines, and chemokines have a direct negative inotropic effect.

Metabolic myocardial stress occurs during ischemic arrest with cardioplegia and is associated with inadequate compensatory metabolic activity suppression. The first structural change after cardioplegia is an increase in capillary permeability, resulting in edema. This occurs early on and can be seen immediately after aortic clamping. The lesions involve both endothelium and the myocytes. More severe irreversible changes in the myocardium are the consequence of ischemia with an imbalance of sodium and calcium ions [10]. Significant global dysfunction may be present in infants and neonates due to the accumulation of interstitial fluid causing a decrease in the compliance with subsequent diastolic dysfunction.

The renal inmaturity and higher renal vasculature resistance predispose pediatric patients to an increased risk of renal injury during CPB. The mechanisms of renal dysfunction are multifactorial. However, the low perfusion pressure and lack of pulsatility during CPB may play a central role in kidney damage. The activation of the renin-angiotensin-aldosterone system after the exposure to CPB will increase renal vasoconstriction and fluid retention. Additionally, prolonged CPB with high flows and high-velocity suction may induce hemolysis contributing to further kidney injury.

The brain is not innocuous to the effects of the CPB. Hypoperfusion during CPB seems to be a factor of postoperative neurologic injury. The neonatal brain is especially susceptible to the inflammatory response which leads to the disruption of the hemato-encephalic barrier.

The interstitial edema in the brain may be a consequence of the ischemia–reperfusion injury. Oxygen-derived free radicals produced at multiple sites within the CNS, including leukocytes, endothelium, mitochondria, and local inflammatory cells cause cellular apoptosis. After periods of ischemia and reperfusion, some areas remain without perfusion in a process called the "no-reflow" phenomenon. There are two main components of the "no-reflow": "physiologic" – related to sustained vasoconstriction after injury – and "mechanical," caused by obstructed capillary beds [11, 12].

Younger patients with complex surgery and prolonged deep hypothermic circulatory arrest (DHCA) or those with circulatory support prior to surgery have an increased risk for postoperative neurologic injury. Early neurologic complications include stroke, cerebral bleeding, and seizures. Adverse long-term outcomes include impairment in neurodevelopmental activities such as abnormal school performance, learning disabilities, and behavioral issues [13].

The monitoring of cerebral perfusion during surgery may be achieved with the use of Near-Infrared Spectrometry (NIRS). However, diverse strategies for brain monitoring have been used in different institutions with variable outcomes.

It is important to note that what determines the individual response to the CPB and neurologic outcomes is not totally established. In addition, many patients with congenital heart disease may have a neurologic impairment prior to the exposure to CPB.

The hematologic system is greatly affected during CPB. Hemodilution and hypothermia produce significant effects on coagulation factors. Antithrombin III may be deficient in neonates with subsequent resistance to heparin. Inadequate anticoagulation during CPB leads to fibrinolysis and consumption of the coagulation factors, producing excessive bleeding. Careful monitoring of anticoagulation is achieved by measuring activated clotting time (ACT) during CPB; the goal is variable between institutions but usually maintained above 400–480 seconds [14].

Finally, the exposure to CPB imposes a generalized metabolic and endocrinologic response with the release of catecholamines, vasopressine, cortisol, and other endogenous hormones. These hormones may cause a significant increase in peripheral and pulmonary vascular resistances with consequences of hypoperfusion and organ damage. There is also an increase in insulin resistance after exposure to hypothermic CPB, leading to hyperglycemia.

10.4 Pharmacological and Non-Pharmacological Strategies Used During CPB to Decrease Inflammatory Response

10.4.1 Anti-Inflammatory Strategies

The use of steroids during CPB seems to reduce the production of inflammatory cytokines. However, there is a lack of evidence in the definitive benefit from its use. Moreover, there are no established guidelines regarding agent, dose, and timing of administration. This strategy is highly variable between institutions.

There are several pharmacologic agents used in practice and at the experimental level that have shown a reduction of the inflammatory response, including phosphodiesterase inhibitors, dopexamine, aprotinin, free radical scavengers and antioxidants (such as allopurinol, N-acetyl-cysteine, mannitol), ketamine, angiotensin-converting enzyme inhibitors, H2 antagonists, and specific C5a monoclonal antibodies, among others. However, evidence of the effectiveness of these therapies still requires further studies [15].

Other techniques have been developed to decrease the amount of hemodilution. Some of these techniques include miniaturization of the CPB circuit, conventional hemofiltration, and modified ultrafiltration (MUF).

Other techniques to reduce the amount of inflammatory components and interstitial edema include the use of heparin-bounded circuits that limits the activation of specific inflammatory pathways, improving biocompatibility, and the use of leukocyte filters that decreases the amount of activated neutrophils. Additionally, these techniques seem to reduce the amount of blood transfusions.

Specific strategies to identify and block specific targets of the inflammatory cascade are in the process of being investigated.

10.5 Neurologic Protection and Selective Perfusion

Neuronal injury is caused by the activation of leukocytes and the release of accumulated metabolic products during reperfusion. Factors associated with neurologic outcomes include:

1. Type of perfusion strategy
2. Temperature management
3. pH management
4. Hematocrit management
5. Glucose management
6. Oxygenation strategy
7. Use of pharmacological protection
8. Systemic inflammatory response

10.5.1 Perfusion Strategy

Several strategies have been developed to achieve neurologic protection. In 2001, Pigula et al. reported on the application of selective cerebral perfusion during prolonged periods of deep hypothermic circulatory arrest (DHCA) [16]. Both cerebral hemispheres were perfused through the right innominate artery using low-flow techniques. Since then, several modifications have been made according to the surgical group's preferences. In general, those techniques include:

10.5.1.1 Intermittent Perfusion (IP)

This technique involves the use of full pump flow for 2 min every 20 min during DHCA. The required rate is 80 mL/kg/min. Intermittent systemic recirculation during DHCA

prevents cerebral anaerobic metabolism. Experimental studies demonstrated that IP reduces astroglial changes and no-reflow phenomenon when compared to DHCA.

10.5.1.2 Regional, Continuous Low-Flow and Selective Cerebral CPB

Selective cerebral perfusion (SCP) has evoked renewed interest in recent years, and has become the primary brain protection method in many centers. Regional low-flow perfusion (RLFP) can be used to limit or exclude the use of circulatory arrest. This strategy involves the direct cannulation of the innominate artery and selective clamping of the proximal innominate, left carotid, and left subclavian arteries, achieving continuous regional brain perfusion. Flow rates may vary between 20 and 70 mL/kg/min.

Continuous low-flow and SCP are associated with the preservation of cerebral energy stores, improved cerebral perfusion, histologic outcome, and neurologic function when it is compared with prolonged DHCA (60–120 min).

The incidence of neurologic impairment ranges from 2% to 30% independently of the neurologic protection strategy used.

Several studies have demonstrated that low-flow bypass is superior in preserving high-energy phosphate, cerebral oxygen metabolism, cerebral blood flow, cerebral vascular resistance, and lowering levels of lactate on the brain. The minimum safe level of low flow has not been established.

10.5.2 Hypothermia and Deep Hypothermic Circulatory Arrest

Effects of hypothermia:

1. Decrease in cerebral metabolism and energy consumption (cerebral metabolic rate decreases 5–7% for each degree Celsius decrease in body temperature).
2. Reduction in the extension of degenerative processes including the excitotoxic cascade, microglial activation, oxidative stress, and inflammation.
3. Suppression of specific pathways of the apoptosis, such as cytochrome C release, caspase activation, and DNA fragmentation.

These properties of hypothermia help in the process of organ protection, especially when low flow or non-flow is necessary for surgical exposure. However, excessively low temperatures in the myocardium may cause a sudden release of intracellular calcium, increasing the resting myocardial tone interfering with the recovery function during the rewarming. Hypothermia may be conducted at three different levels: mild (30–34 °C), moderate (23–29 °C), and deep (13–22 °C).

DHCA was introduced 30 years ago, it involves the complete cessation of the CPB flow when the temperature is close to 15–18 °C. It is used when the cannulas require to be removed for the surgical repair, such as aortic arch repair or in the creation of neoaorta. This technique allows to have a surgical field free of blood for easier visualization.

The cooling should occur slowly with a difference between arterial and venous temperature of no more than 4–6 °C. During the rewarming phase, the temperature gradient between the venous and the arterial blood should be not more than 10 °C. Time on DHCA is also an important factor; prolonged exposure (more than 40 min) is directly correlated with worst neurologic outcome.

The Boston Circulatory Arrest Trial prospectively observed the neurological outcome of 171 neonates with D-transposition of the great arteries that were randomized either to DHCA or to low-flow CPB for the arterial switch operation. In the immediate postoperative period, the incidence of seizure activity was higher in the DHCA group. One year after surgery, children of the DHCA group had a higher risk of delayed motor development compared with the low-flow CPBP group, and the risk of neurologic abnormalities increased with the duration of the circulatory arrest. In the same study, investigators found a nonlinear relationship between the duration of DHCA and neurodevelopmental outcomes; however, there was no significant decline in the neurologic outcomes in children subjected to a period of DHCA lasting less than 41 min. After 8 years of surgery, there were no differences in neurologic development between the groups [17].

10.5.3 pH Management During CPB (pH-Stat–Alpha-Stat)

The optimal pH management strategy for cardiovascular procedures using the cardiopulmonary bypass and hypothermia is unknown. The two main strategies used are *alpha-stat* and *pH-stat*.

Changes of the Acid–Base Status with Temperature:

During cooling, the CO_2 increases in solubility and produces a decrease in the $paCO_2$ resulting in a metabolic alkalosis.

Body temperature of poikilotherms or cold-blooded animals directly varies with the ambient temperature. They permit an increase in their blood pH when they are at a lower temperature, which approximates alpha-stat management. Conversely, deep hibernators or warm-blooded animals do

not drop temperature more than a few degrees during the winter season. In spite of its low body temperature, the hibernating animal retains a remarkably rigid control of its internal environment; its pH remains at 7.40. It requires an increased total body CO_2 content to maintain neutrality. This is achieved with a relative acidification of the intracellular fluids produced by the adoption of a modified breathing pattern that is typified by periods of apnea lasting up to 2 h that are interspersed with 3–30 min intervals of rapid ventilation. This approach is pH-stat management.

For pH management during CPB, these two strategies have been adopted. When the *alpha-stat* strategy is used, the pH is allowed to freely arise without performing any correction to the arterial blood gas. With *pH-stat* strategy, the arterial blood gas is mathematically corrected for the actual temperature and carbon dioxide is added to reach a normal pH (7.40).

pH-stat strategy: causes cerebral vasodilatation above metabolic demands (loss of autoregulation) and a more homogenous cooling. Defenders of the pH-stat management argue:

1. Improvement in oxygen delivery by counteracting the leftward shift in the oxyhemoglobin dissociation curve associated with alkalosis.
2. Increased cerebral blood flow.
3. Suppression of cerebral metabolic rate.
4. pH-stat is particularly beneficial in cyanotic neonates and infants because it shifts more CPB flow away from the aortopulmonary collateral circulation and toward the cerebral circulation, both improving cerebral cooling and oxygen supply.

During cooling the addition of CO_2 could potentially improve the distribution of the cold to perfuse deep brain structures.

However, while pH-stat facilitates earlier peri-operative return of electroencephalographic activity, developmental and neurological outcomes revealed no significant differences attributable to pH management strategy. Other disadvantages include that low intracellular pH results in impaired intracellular enzymatic function.

Alpha-stat requires that neutrality is maintained only at 37 °C, and permits the hypothermic alkaline drift. Thus, additional CO_2 is not needed and cerebral autoregulation is maintained.

Defenders of the *alpha-stat* argue:

1. Preserves cellular transmembrane pH gradients, intracellular electrochemical neutrality, protein functioning, and enzyme activity are more normal when the pH is allowed to drift alkaline in parallel with the temperature. This concept is based on the notion that the pK of the histidine imidazole group changes with temperature in a manner nearly identical to physiologic blood buffers. Therefore, the ionization state of this group stays the same, irrespective of temperature. Ionization state is a determinant of intracellular protein function.
2. Relatively alkaline pH is beneficial before the ischemic insult of circulatory arrest. Despite considerable laboratory and animal research into these mechanisms, substantial controversy remains.

Some studies have shown significantly higher cerebral oxygenation when a pH-stat strategy is used at the end of cooling and during early rewarming. However, the higher cerebral blood flows associated with pH-stat also have a higher risk of embolization. In addition, the relative acid load induced by pH-stat had a negative effect on the enzymatic function after cerebral rewarming.

Results from several studies favor the pH-stat strategy during neonatal cardiopulmonary bypass. Data also suggest that pH-stat management results in better outcomes with shorter ventilation times and intensive care unit stays after pediatric cardiac surgery. In 2000, the group from Duke proposed the use of a combined strategy with pH management during cooling, followed by an *alpha-stat* strategy before the initiation of cardiac arrest. Currently, the use of moderate hypothermia may reduce the importance in the management of these strategies [18–20].

10.5.4 Hematocrit and Hemodilution

Hemodilution during CPB was introduced in the 1950s to decrease homologous blood, and to improve microcirculatory flow. During moderate hemodilution, total body oxygen delivery is maintained because of reduced blood viscosity and vascular resistance, resulting in an increased tissue blood flow.

The adequate hematocrit level during pediatric cardiac surgery is not clearly defined. Physiologically important changes in cerebral oxygen supply might occur at hematocrit levels of 12% at 18 °C, 15% at 28 °C, and 18% at 38 °C under CPB conditions [21].

Higher levels of creatine kinase-BB (CK-BB), a marker of brain injury, are seen in children with low hemoglobin levels during the first hours after DHCA. In addition, children with low hematocrit had worse peri-operative outcomes with decreased cardiac index and higher serum lactate levels. Evidence of better neurologic protection has been demonstrated with a hematocrit level of 30% [21].

10.5.5 Aorto-Pulmonary Collaterals

Aorto-pulmonary collaterals decrease the rate of cerebral cooling, blood flow, and increase cerebral metabolic imbalance after DHCA. Their presence has been associated with high incidence of choreoathetosis.

10.5.6 Oxygenation Strategy

At low temperatures, the quantity of dissolved oxygen is increased. Hyperoxia may be beneficial because the brain uses mainly dissolved oxygen during profound hypothermic cardiopulmonary bypass.

10.5.7 Glucose Management

Causes of hyperglycemia during heart surgery:

1. Glucose-containing fluids
2. Stress response
3. Changes in insulin secretion and resistance

The correct glucose level during cardiac surgery is not known.

During cerebral ischemia, hyperglycemia may increase the release of excitatory neurotransmitters. By contrast, in the adult population, hyperglycemia is not associated with neurologic impairment; instead, hypoglycemia is deleterious and should be avoided [21].

10.6 Composition of the Cardiopulmonary Bypass

The cardiopulmonary bypass is basically composed per cannulas that allow the blood coming from and to return to the heart, a venous reservoir that collects the blood from the patient's body, a pump system that gives the mechanics to maintain the blood flowing through the system, an oxygenator that allows the exchange of respiratory gases, and a heat exchanger that controls the temperature of the system.

Additional parts of the system include the cardioplegia system which delivers the cardioplegia solution to arrest the heart, the cardiotomy reservoir which receives the blood coming from the field, suctions, and the filters all along the system designed to decrease the risk of embolism.

The blood is returning through the venous cannulas and the suction cannulas to the venous reservoir and cardiotomy reservoir, moved by gravity or with the help of a negative pressure system, then the blood is driven with the help of the pump to the oxygenator and the heat exchanger. Finally, the blood returns to the body through the tubing connecting the aortic cannula.

10.6.1 Circuit

Circuitry for pediatric perfusion is challenging because of the wide range of patient sizes and corresponding blood volumes. Congenital defects are no longer limited to neonate, pediatric, and adolescent populations. Adult congenital populations are living longer and require ongoing care making it essential that prescriptive approaches for circuit design be employed [22]. The design in tubing circuitry and component selection is aimed at decreasing the overall prime of the heart-lung machine circuitry or total blood volume that is sustained outside of the patient's natural blood volume [23, 24]. Neonates and infants have a dynamic response to extracorporeal circuitry design. The ratio of patient blood volume to extracorporeal circuit prime is dynamic. Opportunity for decreasing the prime using various tubing lengths and diameters, along with creative component choices support overall circuit primes as low as 90–176 cc. Bloodless circuit designs offer a host of clinical advantages [23, 25–27].

10.6.1.1 Cannulation and CPB Initiation

Cannula selections are based on blood flow requirements, placement and operative procedures. Pressure drop versus flow demands are aimed at creating variable flow dynamics that limit hemolysis. While surgeons focus on operative cannula placement limitations, perfusionists focus on adequate end-organ perfusion and circuit line resistance. Vacuum assist can be used to augment venous drainage, decrease circuit prime, and optimize drainage away from the operative field. Cannula selection is aimed at blood flow ranges between cardiac indexes of 1.8 to 3.0 L/min/m^2 that assure adequate perfusion at variable temperatures and metabolic needs. Cardiovascular teams meet cannulation requisites based on these surgical and circuit considerations. There are several choices in the marketplace with corresponding water chart flow rates that estimate pressure drop based on blood flow. Table 10.1 is a custom chart used at Children's Hospital of Pittsburgh of UPMC for a variety of arterial and venous cannula choices, based on kilogram weight, cardiac index and cannulation site, for CPB. This chart attempts to simplify and establish a routine for cannula selection.

Table 10.1 CPB chest cannulation selections for Children's Hospital of Pittsburgh of UPMC based on body surface area (BSA) calculation [(4 × kilogram weight) + 7/ (90 + kilogram weight)] multiplied by a 3.0 L/min/m^2 cardiac index

Kilogram weight	Arterial	Superior & inferior vena cava	Dual stage venous	Single venous
1 and 2	6 Fr.	8 Fr./10 Fr.	—	12 Fr.
3	8 Fr.	10 Fr./12 Fr.	—	12 Fr.
4	8 Fr.	10 Fr./12 Fr.	—	14 Fr.
5	8 Fr.	12 Fr./14 Fr.	—	14 Fr.
6–8	10 Fr.	12 Fr./14 Fr.	—	14 Fr.
9	10 Fr.	14 Fr./16 Fr.	—	14 Fr.
10 and 11	10 Fr.	14 Fr./16 Fr.	—	16 Fr.
12	12 Fr.	14 Fr./16 Fr.	—	16 Fr.
13	12 Fr.	16 Fr./18 Fr.	—	16 Fr.
14–16	12 Fr.	16 Fr./18 Fr.	—	I8 Fr.
17–19	12 Fr.	18 Fr./20 Fr.	—	18 Fr.
20–22	12 Fr.	18 Fr./20 Fr.	—	20 Fr.
23–25	14 Fr.	18 Fr./20 Fr.	—	20 Fr.
26–28	14 Fr.	20 Fr./24 Fr.	—	20 Fr.
29–35	14 Fr.	20 Fr./24 Fr.	—	24 Fr.
36–41	16 Fr.	20 Fr./24 Fr.	—	24 Fr.
42–43	16 Fr.	20 Fr./24 Fr.	29/37 Fr.	24 Fr.
44–52	I8 Fr.	20 Fr./24 Fr.	29 37 Fr.	24 Fr.
53–62	18 Fr.	20 Fr./24 Fr.	29/37 Fr.	28 Fr.
63–69	20 Fr.	24 Fr./28 Fr.	29/37 Fr.	28 Fr.
70–87	20 Fr.	24 Fr./28 Fr.	33/43 Fr.	—
88–120	22 Fr.	24 Fr./28 Fr.	36 46 Fr.	—

Chest cannula selections based on weight, blood flow, and procedure type using Medtronic DLP® Pediatric One-Piece Arterial Cannula, EOPA® Arterial Cannula, DLP® Single Stage Venous Cannula with Right Angle Metal Tip, and/or MC2® Two-Stage Venous Cannula selections (Medtronic, Inc., Minneapolis, MN)

Venous Cannulation

Venous cannulae design attempts to mimic the natural flow characteristics of the vessel that is drained, as well as, considerations for insertion ease, reduction of turbulence, decreased thrombus formation, and minimizing trauma to the blood elements [28]. When bicaval cannulation is necessary, the cannulation is commonly performed using right-angle cannulae into the superior vena cava and the inferior vena cava. These cannulae decrease the risk of flow obstruction and allow for complete cardiopulmonary bypass. Special considerations are required when there is a presence of a left superior vena cava or interrupted inferior vena cava. Venous cannulation may also be achieved with a single cannula inserted into the right atrium. This type of cannulation is preferred if the atrium does not need to be opened or when deep hypothermic circulatory arrest (DHCA) will be used during the repair.

Arterial Cannulation

Arterial cannulation is performed with a single cannula into the aortic root (some cases require a different position according to the surgery). The size of the arterial cannula should be wide enough to provide adequate flow without causing obstruction or trauma to the aorta. The greatest resistance in the cardiopulmonary bypass (CPB) circuit is the smallest opening for blood flow, which often is the arterial cannula. Cannula selection is based on adequate blood flow estimations in concert with controlled pressure drop values. As with venous cannulation, adequate position of the cannula is crucial.

When the arterial and the venous cannulae are in adequate position, they are connected to the circuit. The venous blood is drained by gravity and/or controlled vacuum into the venous reservoir and then using either a roller or centrifugal pump, pumped through the oxygenator which has an integrated heat exchanger and arterial filter back into the systemic circulation through the arterial cannula (Fig. 10.1).

The development of new reservoirs and oxygenators has reduced the amount of priming volume used in pediatric extracorporeal circuits. Hemodilution produces a comprehensive effect over all systems, including impairment in hemostasis. This effect requires the use of blood products that increase the risk of infection, allergic reactions, or immunologic responses. In the past several years, CPB design using prescriptive low prime circuit components controls priming volumes that control the effects of hemodilution [2].

10.7 Components of CPB

10.7.1 Pumps

Currently, there are two types of pumps available for pediatric cardiac surgery: *Roller* and *centrifugal*.

Roller pumps are preferred to control low-flow when needed. Moreover, their compatible circuit requires the lowest prime volume. Each revolution propels the blood forward in the tubing (Fig. 10.2). This raceway of tubing is also referred to as the "boot line." Variable boot line selections offer adjustable blood flow ranges. Sequential compression of the tubing propels blood forward. Based on the tubing diameter and corresponding preload, varying the revolutions per minute (RPM) estimate the corresponding cardiac output of the pump. RPMs should be limited to 100 for that given tubing boot or an RPM that can be supported with a back-up hand crack. Tubing compression in the raceway is set using occlusive setting that regulates fluid drops of 2.5 centimeter per minute when the fluid-filled outlet tubing is held to a height of 75 centimeters above the volume in the reservoir. Over or under occlusion risks hemolysis and/or inadequate forward blood flows. The roller is turned against a pressure transducer and clamped line creating 200 mmHg of pressure. The conclusiveness is adjusted from 200 mmHg to

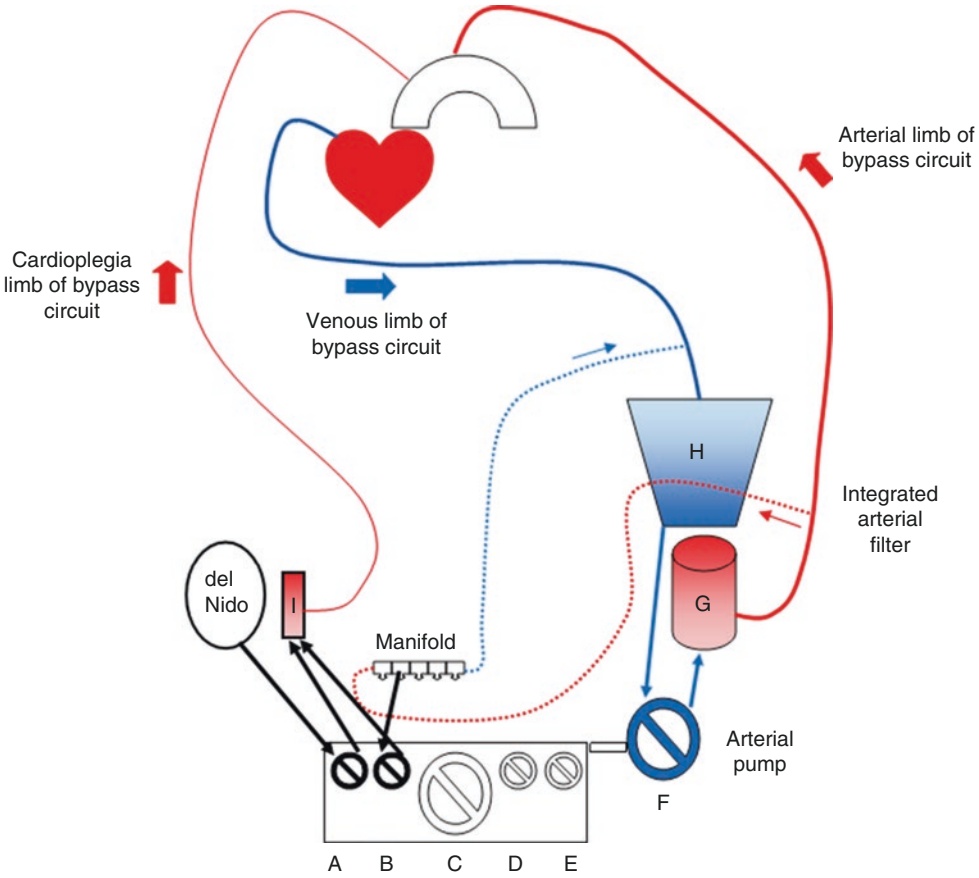

Fig. 10.1 Schematic diagram of cardiopulmonary bypass circuit that includes six roller pumps; two cardioplegia pumps (A & B), one suction pump (C), two vent pumps (D & E), and a systemic pole mounted roller pump. Oxygenator (G), reservoir (H), and dual cardioplegia circuit (I) for del Nido cardioplegia delivery

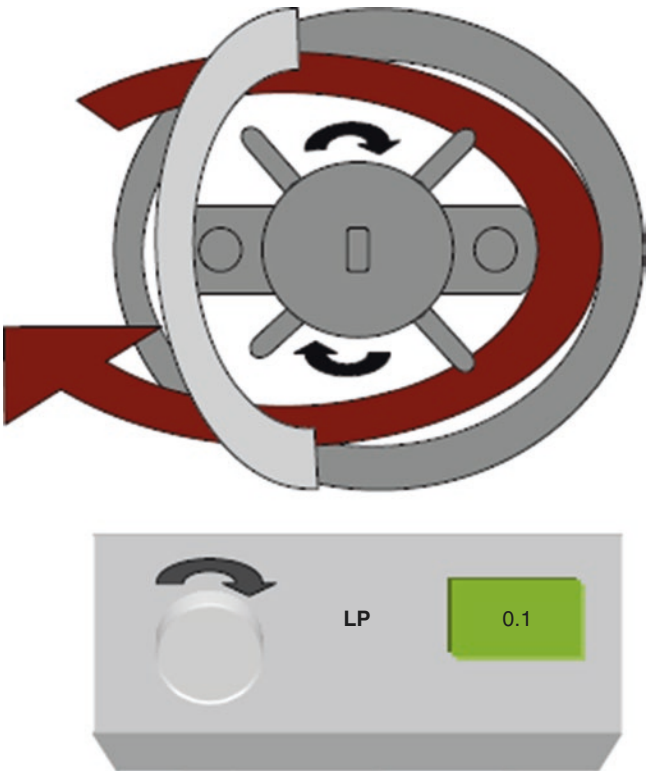

Fig. 10.2 Roller pump design. A positive displacement pump with a stationary raceway and rotating twin roller pumps

100 mmHg within 1 min. Like the fluid drop method, both roller occlusions are tested.

An alternative method for setting pump occlusiveness can be adjusted using pressure measurement. This method was developed by Tamari et al. [24, 29]. The occlusiveness measured is made by monitoring the pressure drop with the pump stopped.

Servo-regulated pressure monitoring distal to the outlet of the raceway prevents over-pressurization of the extracorporeal circuit and circuit connection rupture [2]. Mast mounted pumps offer the opportunity of getting CPB circuit components and circuitry close to the surgical field. This reduction in distance from circuitry components to the cannulation sites is an opportunity to further reduce the prime [30].

Centrifugal pumps entrain the blood into the pump by a high-speed rotor, spinning impeller blades, or rotating cones. Centrifugal pumps operate on a principle of moving fluid by creating a pressure gradient between the inlet and outlet of the pump [2].

The centrifugal pump amasses fluid movement by the addition of kinetic energy to the blood through the forced turning of the impellor or cone in the constrained container [28].

An analogy used to better understand the flow characteristics of a constrained vortex pump is a tornado. If we could create a twister in a cup using a spoon, the intensity of the

vortex is based on the intensity spinning the spoon. The faster the spoon is rotated the intensity of the vortex increases. The edges of the fluid in the cup climb and often spill over the top of the cup. Centrifugal pumps, called constrained vortex pumps, are a vortex in a closed container. Placing a lid on the cup, still having access to turn the spoon at a variable rate, generates pressure within the container. An inlet placed on the lid and an outlet on the side of the cup provide pathways for flow. Centrifugal pumps create low and high pressure areas leading into and out of this vortex. Design of the spinning pump head differentiates each of the centrifugal pump choices. The design of a rotary pump is the focus of potential hemolysis and emboli production. The centrifugal force and corresponding heat generation transcend to heat energy imparted into the blood. Still centrifugal pumps offer many advantages to roller head pumps [2].

Centrifugal pumps are afterload and preload sensitive. They are pressure dependent and overload sensitive. Unlike roller pumps they cannot generate excessive negative or positive pressures. Despite these advantages, centrifugal pumps have a higher prime than roller head boot lines. Centrifugal pumps have an advantage of controlling macroscopic air that may enter the extracorporeal circuit. Over-pressurization of the circuitry with corresponding connection rupture is innately controlled. Although centrifugal pump use in the adult population is well documented, its use for infant and pediatric CPB is limited with roller pumps continuing to be the preferred choice.

10.7.2 Biocompatibility and Tubing

There are two types of clinically relevant heparin-coated circuits:

1. Heparin-releasing surfaces
2. Heparin-immobilizing surfaces

The first subgroup, heparin-releasing surfaces, is bound so that it may be slowly released into the circulation directly from the surface. The second subgroup, heparin-immobilizing surfaces, includes those surfaces with heparin covalently immobilized on the polymer surface.

A third new group of biocompatible surfaces uses properties of modified protein adsorption, which secondarily influence biocompatibility. It is believed that the addition of alternating hydrophilic and hydrophobic regions modifies fibrinogen adsorption, thus changing its ability to interact with circulating platelets.

Custom tubing packs for cardiopulmonary bypass offer routine and set-up efficiency. A congenital program may have 3–4 base tubing configurations and a variety of arterial venous loop selections. Used in concert they offer a prescriptive approach that controls hemodilution [24, 31]. Circuitry design is aimed at minimizing the static blood prime, that is "outside" the body, with awareness for safety.

10.7.3 Oxygenators

Oxygenators are devices that have several integrated parts. They include the oxygenator bundle, heat exchanger, venous reservoir, cardiotomy reservoir, and arterial filter. In past years, arterial filter placement was beyond the oxygenator and not integrated within the oxygenator. Most pediatric oxygenators developed for use in cardiac surgery offer choice in heat exchanger and oxygenator performance that is in parity with an infant or neonate size. The goal continues to be an overall small prime with appropriate oxygenation, carbon dioxide removal, and heat exchange capability. Reduced prime, with these performance factors, separates the marketplace choices.

Micro-porous membranes or hollow fiber oxygenators are a type of oxygenators made up of polypropylene fibers, which are porous, offer powerful gas exchange, and afford simplicity setting-up and operating. Oxygenators are smaller and allow variable blood flow ranges and high gas transfer rates. Microporous membrane bundles are important in the removal of air. Used in concert with an inline or integral arterial filter they offer a heightened ability to remove air from the circuit. Technology directed at the method of fiber bundle construction and blood flow effect air removal [32, 33]. Oxygenators are normally qualified for 6 h of support. Use beyond this limit rarely suggests failure or fatigue [34]. The pressure drop across the membrane is listed with other performance values. Devices that offer low pressure drop, high heat, and gas exchange are favored. The overall goal is sustaining an acceptable level of all performance values, without damaging the blood components or increasing the effects of hemodilution [35].

The overall surface area in the CPB circuit is greatest in the integral oxygenator, thus biocompatible surface coating applied to the oxygenator is beneficial for preservation of blood components.

10.7.4 Venous Reservoir

The venous reservoir is the component of the CPB where blood is collected from the venous line at the initiation of extracorporeal support. Venous and shed cardiotomy blood is collected in a separately filtered hard shell reservoir. Venous blood enters through a separate port than cardiotomy blood with different filtration mediums.

Transfusion products, crystalloid solutions, and blood obtained from suction systems (which aspirate blood and air from the field and the heart chambers) drain into the cardiotomy. Most pediatric centers utilize hard-shell open reservoirs. Closed CPB systems incorporate a bag design for venous return. Closed systems limit blood and air interfaces which decrease the inflammatory and hematologic disturbances [14].

The venous reservoir is integrally used to remove air from the CPB circuit [33]. Cardiotomy filtering mediums exceed venous reservoir specifications because of the air and blood mix requisites.

Vacuum-assisted venous drainage (VAVD) is a technique used to augment venous return. When used, the venous reservoir is sealed and not vented to the atmosphere. Careful monitoring and vacuum regulation is key as not to cause reduced venous return and/or gas embolization. Pressurizing the venous reservoir because of an obstruction of the vent or suction regulation can escalate causing a massive embolization retrograde up the venous line from the sealed venous reservoir. VAVD entails the application of a regulated amount of negative pressure to a nonvented venous reservoir. The amount of negative pressure applied enhances venous return from the heart or blood vessel. Table 10.2 summarizes essential features needed to safely employ VAVD during CPB [14, 23, 28]. Vacuum should be discontinued if there is no forward blood flow through the oxygenator as not to pull air across the microporous membrane. VAVD should not be applied until after initiation of CPB. The venous reservoir should be open to air when VAVD is not in use (prevent pressurization of the reservoir).

VAVD offers CPB support without the requisites of gravity return circuit height and tubing configurations. Venous reservoir placement can be at any level; cannula selections can be smaller and tubing circuit lengths/diameters can be reduced. Benefits include improved surgical visibility and hemodilution control. VAVD may increase gaseous microemboli (GME) counts caused by air entrainment into the venous line [28].

Table 10.2 VAVD critical safeguards

VAVD essentials
Approved VAVD regulator
Approved venous reservoir
High positive and low negative pressure relief valve affixed to the venous reservoir
Reservoir positive pressure monitoring (servo-regulated control) set at 1–2 mmHg with visual and audible alarms
Reservoir negative pressure monitoring regulated to <40 mmHg with 0 & audible alarms
Venous line negative pressure monitoring set to <100 mmHg (gravity & applied vacuum)
If using a centrifugal pump incorporate a one-way valve between the venous reservoir and oxygenator
Eliminate any venous air entrainment
Single use sputum moisture trap assembly with connecting Y tubing
Open empty bag on rapid prime line

10.7.5 Cardioplegia Delivery System

This system is connected to an independent roller pump to drive blood from the cardioplegia solution into the aortic root. The system also has an independent heat exchanger, and the pressure and temperature are also independently monitored. Blood from the oxygenator is mixed with the crystalloid cardioplegia solution before transfer to the aortic root (Fig. 10.3).

10.7.5.1 Venting of the Left Heart

The left ventricle normally receives venous blood flow from the bronchial and Thebesian veins during CPB, this flow is collected in the right superior pulmonary vein. Bronchial blood flow is increased in cyanotic patients and abnormal blood flow to the left ventricle is present in patients with left superior venous cava, PDA, or aortic regurgitation. Adequate drainage of the left ventricle prevents distension, decreases wall tension, improves subendocardial perfusion, and improves surgical exposure. The decreased wall tension and improved subendocardial perfusion are essential to the pediatric population where the compliance of the small chambers is decreased.

10.7.5.2 Filters and Bubble Traps

Inline arterial line filters (ALF) and integral ALF trap air and filter debris, decreasing the risk for embolization. They are generally located at one of two sites through the CPB circuit. Screen filters have arterial pore sizes that range from 25 to 40 microns. Inline ALF are positioned distal to the oxygenator and below the level of the venous reservoir. This traditional position offers a level of safety because it is the last component before arterial blood reaches the patient. Many perfusionists prefer this traditional location because of safety [31, 32]. Inline ALF offers a higher overall amount of static prime to the CPB circuit than integral ALFs.

Integral ALF can be incorporated into the design of some oxygenator systems. They offer filtration capabilities as traditional inline ALF with decreased static prime but the debate related to macro and micro air removal is disputed [31].

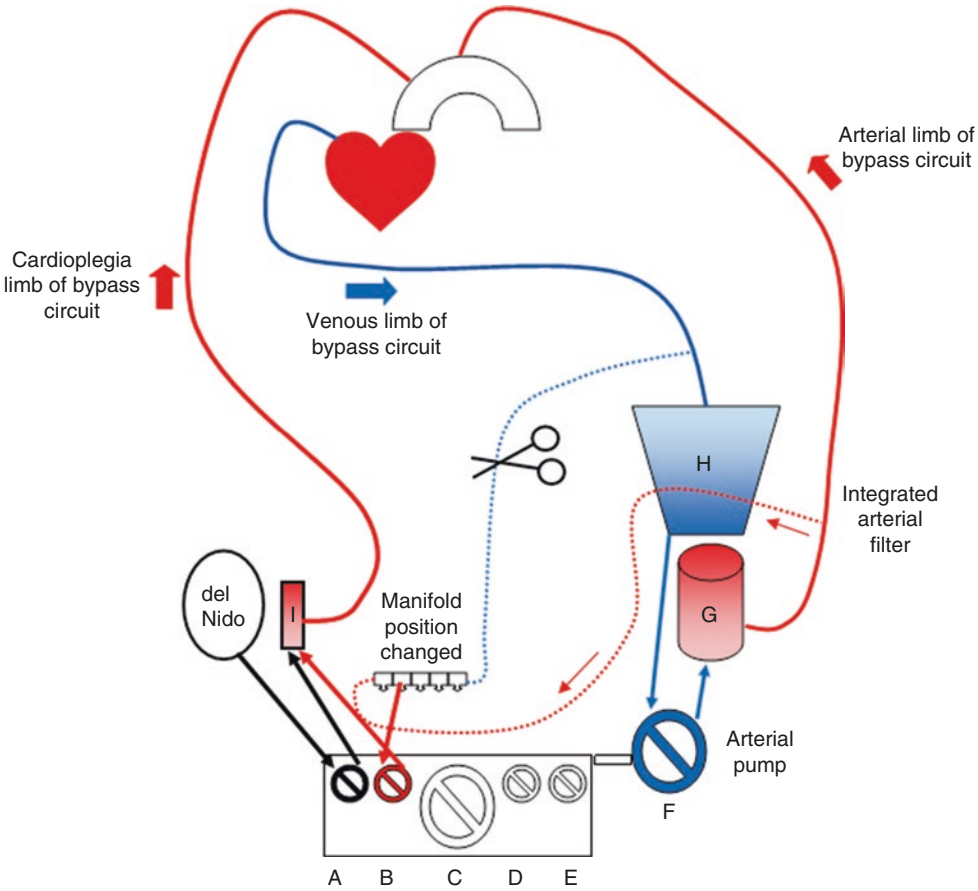

Fig. 10.3 Noncirculating cardioplegia delivery system for use in the blood to crystalloid mixed solutions. Roller pump A delivers crystalloid with a servo regulated second roller pump with arterial blood. This configuration uses del Nido cardioplegia at a ratio of one part blood to 4 parts crystalloid (1:4). Schematic diagram of cardiopulmonary bypass circuit that includes six roller pumps: two cardioplegia pumps (A & B), one suction pump (C), two vent pumps (D & E), and a systemic pole mounted roller pump. Oxygenator (G), reservoir (H), and dual cardioplegia circuit (I) for del Nido cardioplegia delivery

10.7.5.3 Circuit Miniaturization

Current advances in the design of the CPB circuit helps to reduce the use of peri-operative blood products. Recent studies in neonates have shown clinical benefit with its use, which includes reduction of the postoperative edema, improvement of the systolic blood pressure, and reduced mechanical ventilation time [36–38]. Table 10.3 is a prescriptive approach for circuit design based on kilogram weight and blood flow. Pediatric circuit design can become a routine based on patient size, blood flow requisites, and procedure type. The latter may offer analysis for patient sizes that are near component recommended limitations. The overall strategy customizing circuitry is meticulous when factors of VAVD use, cannulation, procedure type, and blood flow ideals are all considered. The culture of these choices and perfusion department algorithms works toward overall circuit prime reductions. Using the rated blood flows through various tubing choices in concert with reservoir and oxygenator choices is multifactorial. Unique combinations of custom tubing configurations are practice-specific with corresponding clinical value [31, 39].

Table 10.3 CPB component and tubing choices for Children's Hospital of Pittsburgh of UPMC

Circuit components	Oxygenator, pump, and tubing	Weight and blood flow (kg)
Oxygenator with hard-shell reservoir and integral arterial line filter	Capiox 1CX∗FX05RW	0–15
	Capiox 3CX∗FX15RW	15–70
	Capiox 3CX∗FX25RWC	>70
Custom tubing pack	3/16	0–4
	¼ inch raceway	4–15
	3/8 inch raceway	15–25
	Centrifugal pump	>25
Table lines	3/16 × 3/16 AV loop	0–4
	3/16 × ¼ inch AV loop	5–7
	¼ × ¼ inch AV loop	8–13
	¼ × 3/8 AV loop	14–22
	3/8 × 3/8 AV loop	23–70
	3/8 × ½ AV loop	>70

10.7.6 Hemoconcentrators and Ultrafiltration

Hemofiltration and ultrafiltration are techniques used to remove water from the circulatory blood flow. This effect is achieved through the filtration of water across a

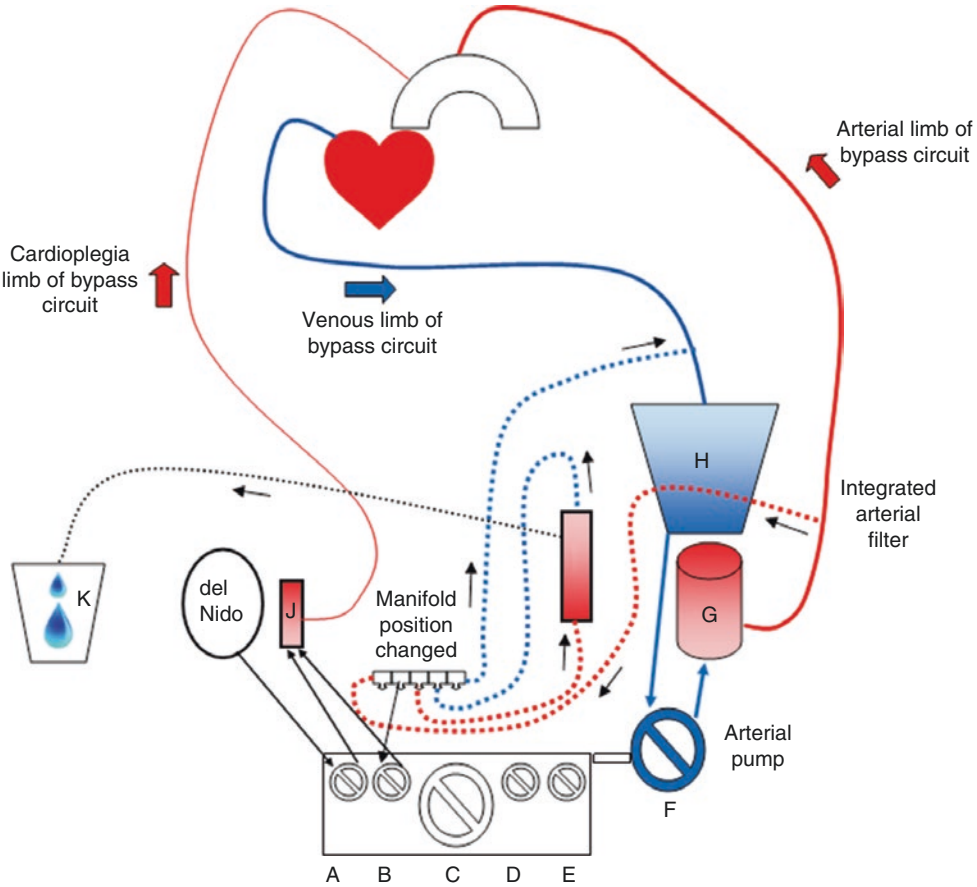

Fig. 10.4 Conventional ultrafiltration (CUF) system. Schematic diagram of cardiopulmonary bypass circuit that includes six roller pumps: two cardioplegia pumps (A & B), one suction pump (C), two vent pumps (D & E), and a systemic pole mounted roller pump. Oxygenator (G), reservoir (H), and dual cardioplegia circuit (J) for del Nido cardioplegia delivery. The CUF system (I) transmembrane pressure gradient is achieved with a shunt connection on the arterial limb of the circuit through a manifold that extends to the venous limb of the circuit. Effluent (K) is removed passively or actively with regulated suction

semi-permeable membrane as the result of a hydrostatic pressure gradient. The blood flows through a hemoconcentrator creating a positive pressure that drives water across the membrane through an ultrafiltration reservoir system (Fig. 10.4).

There are three approaches to ultrafiltration in pediatric cardiac surgery that occur before, during and after CPB.

1. Ultrafiltration of the prime (PBUF) (before the onset of the CPB)
2. Conventional ultrafiltration (CUF) (performed during the CPB)
3. Modified ultrafiltration (MUF) (after termination of the CPB)

PBUF is used to prepare prime if blood products are introduced into the solution [14]. PBUF is used to remove "free water" from the prime. Red blood cells (RBC), fresh frozen plasma (FFP), and medications can be balanced to enhance any physiologic effect with the initiation of CPB. Laboratory values testing of the prime validate the level of ultrafiltration needed to sustain normal physiologic values.

In 1991, Naik et al. reported the use of MUF [39]. It is initiated after separation from CPB; the blood from the aortic cannula is pumped through the hemofilter and then warmed by a heat exchanger and returned through the cardioplegia circuit to the patient's venous cannula(s). There is not a global consensus about the amount to be removed, but in general, the fluid is removed depending on arterial pressure, CVP, and left atrium pressure and available volume remaining in the CPB circuit. This technique is generally used for patient less than 10 kg of weight.

The major advantage of ultrafiltration is to remove excess fluid from patients, which leads to an increase in the hematocrit level and coagulation factors. MUF decreases the level of low-molecular weight inflammatory mediators and other deleterious substances [40].

Several clinical trials have demonstrated the clinical benefits of CUF and MUF after pediatric cardiac surgery; however, controversy remains regarding the optimal ultrafiltration strategy. MUF and CUF reduce blood loss, blood transfusion, and mechanical ventilation time. Other demonstrated effects of the use of MUF include:

1. Improvement in the postoperative hemodynamics
2. Improvement in the alveolar–arterial oxygen difference
3. Decreased pulmonary vascular resistance
4. Decrease the incidence of pleural effusions (after superior cavopulmonary connection and Fontan procedure)
5. Decreased myocardial edema
6. Improvement in the left ventricular function

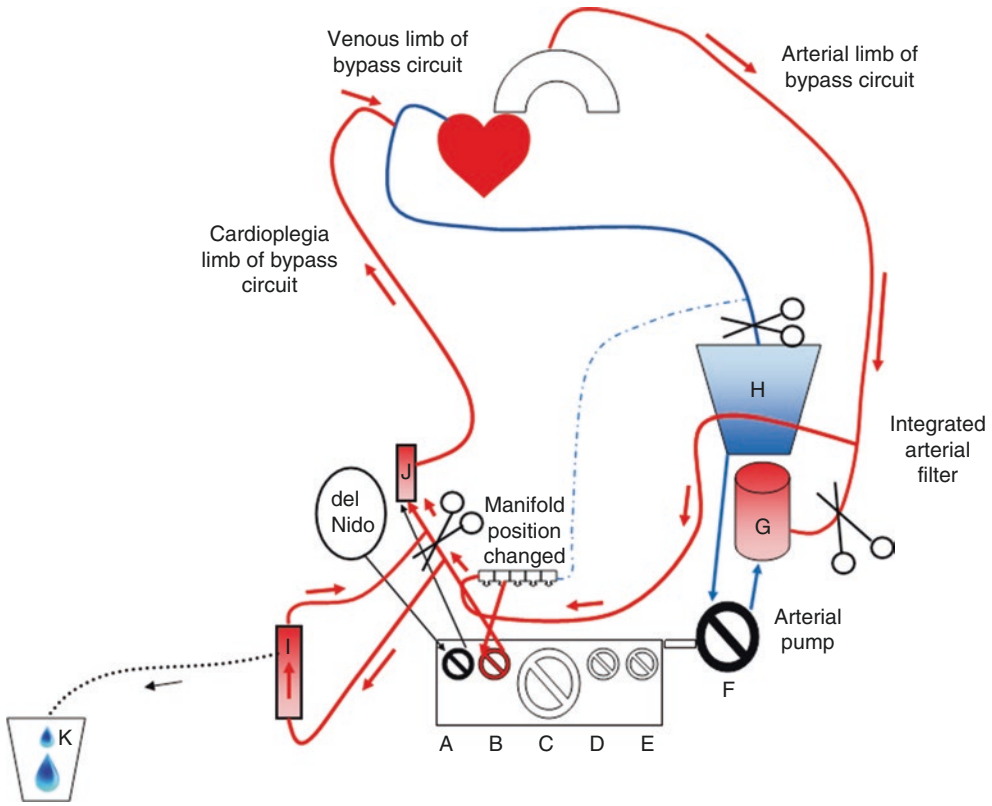

Fig. 10.5 Arterial Venous Modified Ultrafiltration (AVMUF) system through a cardioplegia heat exchanger (J). Schematic diagram of cardiopulmonary bypass (CPB) circuit that includes six roller pumps: two cardioplegia pumps (A & B), one suction pump (C), two vent pumps (D & E), and a systemic pole mounted roller pump. Oxygenator (G), reservoir (H), and dual cardioplegia circuit (J) for del Nido cardioplegia delivery. The AVMUF system (I) transmembrane pressure gradient is achieved using the cardioplegia arterial blood pump (B) that has been cleared of any residual del Nido crystalloid and temperature corrected to 37° Celsius. Effluent (K) is removed passively or actively with regulated suction. The systemic pump can be used to transfuse residual volume post CPB

There is lack of consensus in the type of MUF (arteriovenous, venovenous), duration of ultrafiltration during CPB, volume of ultrafiltrate, and the type of hemofilter to be used, leading to difficulty in the interpretation of the published studies and the definition of the best method of filtration [30].

Arteriovenous (A-V) MUF is performed by aspirating blood from the aorta and reinfusing it through the right atrium (Fig. 10.5). Veno-arterial (V-A) MUF is performed by aspirating blood from the right atrium and reinfusing it through the aorta (Fig. 10.6). Both methods concentrate the remaining pump volume and remove excess fluid from the patient's blood. However, A-V MUF specifically targets the lungs and pulmonary capillary beds. The blood coming from the hemoconcentrator has a higher oncotic pressure than the rest of the blood in the body. As this high oncotic blood returns to the right atrium and goes to the lungs it pulls excess fluid from the lungs. This reduces pulmonary vascular resistance, improves gas exchange at the alveoli and opens the micro airways.

A disadvantage of MUF systems that use cardioplegia systems, primed with patient blood, is the additional blood volume needed and manipulation of the CPB circuit [14]. Specific techniques performing MUF are unique and often not referenced in the literature. Continued miniaturization of the CPB circuits challenges the need and design for MUF [30].

Additional disadvantages include the potential for human and equipment error and increased plasma heparin concentration. The removal of blood from the systemic circulation may result in hemodynamic instability or impaired aortopulmonary shunt flow. High flow rates through the ultrafilter decrease cerebral blood flow velocities and cerebral mixed venous oxygen saturation during AVMUF.

10.8 Conduct and Medications Used During CPB

10.8.1 Priming the Pump

There is no universally agreed protocol for prime solution preparation; most centers have developed their own preferred regimen.

Priming of the circuit is performed with crystalloid solutions (Plasmalyte A) or blood products (packed red blood cells, plasma, or whole blood). In children, to avoid excessive hemodilution, homologous blood (packed red blood cells) is used, minimizing the amount of colloid and crystalloid transfused. Among natural colloids used in this group of patients, fresh frozen plasma is favored [41, 42].

Stored homologous blood has a deranged electrolyte and acid–base status. Priming the pump with blood results in a high concentration of potassium, especially if irradiated blood is used. However, children with impaired T-cell immunity do require irradiated blood. The citrate in citrate–phosphate–dextrose (CPD) (which is added to stored blood as an anticoagulant) binds to the serum Ca^2 producing

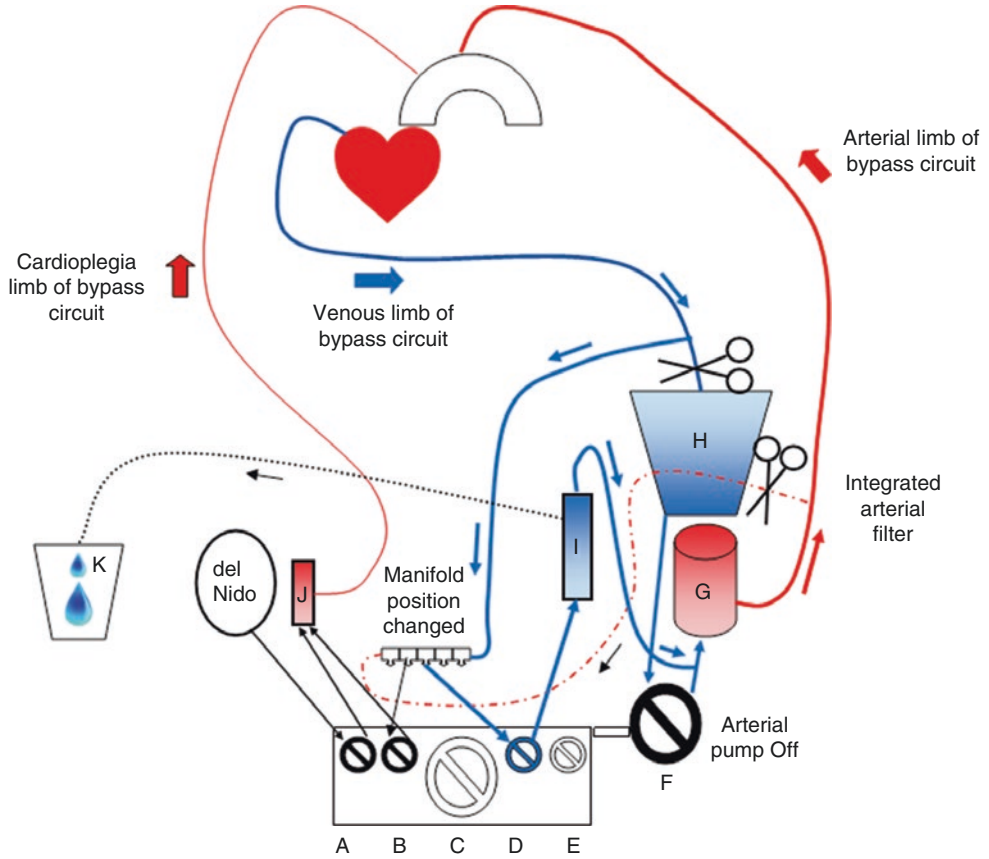

Fig. 10.6 Venous Arterial Modified Ultrafiltration (VAMUF) system. Schematic diagram of cardiopulmonary bypass circuit that includes six roller pumps: two cardioplegia pumps (A & B), one suction pump (C), two vent pumps (D & E), and a systemic pole mounted roller pump. Oxygenator (G), reservoir (H), and dual cardioplegia circuit (J) for del Nido cardioplegia delivery. The VAMUF system (I) transmembrane pressure gradient is achieved using an extra roller head blood pump (B). Blood is drawn from the venous limb of the cardiopulmonary bypass (CPB) circuit into the roller pump that is attached to ultrafiltration filter. Blood flow is directed to the inlet of the oxygenator (G) where heat exchange (37 °C), oxygenation, and filtration occur before the concentrated volume is returned through the arterial limb of the CPB circuit. Effluent (K) is removed passively or actively with regulated suction. The systemic pump can be used to transfuse residual volume post CPB

hypocalcemia. Due to the anaerobic metabolism of the red blood cells, the lactate and pyruvate levels are increased, making stored blood more acidotic [43].

The assessment to determine the type of fluid used for priming (crystalloid vs. blood products) depends on desired hematocrit. Despite recent advances in technology, the majority of neonates and infants still require peri-operative transfusion of homologous blood components.

Historically, whole blood (WB) was preferred due to the benefit of use of a single donor. WB also provides all blood components at the same time. Using packed red blood cells (PRBC) instead of WB has been shown to reduce mechanical ventilation time and intensive care stay [42, 44, 45].

Hemodilution decreases blood viscosity and increases the velocity of the blood flow through the capillary network. This decreases platelet activation and allows adequate flow.

Prime volume depends on the size of the circuit and size of the patient varying from 115 to 1500 mL in an adult circuit. Oncotic pressure is maintained with the addition of albumin. Steroids are used to decrease the inflammatory response. Mannitol is added to decrease platelet binding to the circuit surface and is used to increase diuresis.

Magnesium, calcium, and sodium bicarbonate are also added to the prime solution to maintain the electrolyte and acid-base equilibrium [46].

The addition of other medication is dependent on the surgical group's preferences. Other medications include antifibrinolytics such as aprotinin, tranexamic acid (TXA), or epsilon aminocaproic acid (EACA).

10.8.2 Pharmacokinetics and Pharmacodynamics of Medications During CPB

Changes in pharmacokinetics result from hemodilution, hypothermia, altered organ perfusion, acid–base status, and drug sequestration in the lungs and circuit.

1. *Hemodilution* of circulating carrier proteins produces an alteration of the free fraction of the medications and decreases their ability to bind to their target tissue. Most of the medications suffer a transient decrease, usually no more than 5 min. The free drug concentration increases as protein concentrations fall.
2. Change in perfusion pressure to the target organs produces an increase in the elimination of half-time due to a decrease in glomerular filtration rate. In addition, peripheral vasoconstriction produces a decrease in the drug absorption and consequently in the tissue distribution. There is also a decrease in the metabolic rate of the enzymatic reactions.
3. The reperfusion of the ischemic tissues releases sequestered medications increasing plasma concentrations of those during the rewarming period.
4. Heparin releases free fatty acids, which can displace drugs from protein-binding sites and increases free drug concentration for enhancing its pharmacologic effect.

The pharmacokinetics of infants and children vary greatly from adults. Neonates, infants, and children have different volumes of distribution, rates of metabolism, and immaturity of metabolic systems.

Fentanyl, midazolam, propofol, isoflurane, nitroglycerine, and vancomycin are some medications sequestered by the membrane of the oxygenator affecting the drug concentration. The effects of ultrafiltration and hemofiltration on drug concentration in children are not completely clear.

10.8.3 Pump Flow

The blood flow depends on physiologic parameters of perfusion (venous mixed saturation, lactate, and perfusion pressure). The amount of flow will determine the cardiac index. Normal cardiac index is maintained between 1.5 and 3 L/m^2, when temperature drops, metabolic demands decreases, and the cardiac index is lowered.

Currently, research in pulsatile perfusion demonstrated significant increases in vital organ blood flow and microcirculation. Furthermore, the use of pulsatile perfusion reduces systemic inflammatory response, decreasing inotropic support, intubation time, and hospital stay [47].

10.8.4 Anticoagulation

Adequate anticoagulation is essential to minimize the thrombin generation that occurs as response of the contact of the blood with the extracorporeal circuit. Thrombin formation is age-dependent. Children experience reduced thrombosis during CPB. Inadequate anticoagulation may cause both thrombosis and severe bleeding. However, the optimal dose of heparin in infants and children undergoing CPB is not well defined.

Children have low antithrombin III (ATIII) levels, which reduces the efficacy of heparin to neutralize thrombin generation during CPB. However, increased heparin levels have been associated with a decrease in the platelet function. In addition, the decreased level of fibrinogen in children overestimates the real anticoagulation level [48].

Monitoring of anticoagulation is performed with the measure of the activated clotting time (ACT). Hattersley introduced this method in 1966. Whole blood from the CPB is introduced into a tube or cuvette containing celite or kaolin as activators. A plastic stirring plunger is lifted up every 2 s until blood thickens sufficiently and the plunger is slowed.

Interpretation of the ACT is not adequate in neonates due to the lack of linear relation between ACT level and heparin level. Monitoring of heparin levels may provide a more accurate guide for the administration of heparin during neonatal CPB [49].

Thromboelastography (TEG) is an indicator of coagulability state. This tool is useful in examining the rapid phase of the clot formation indicating the platelet function and interaction of the coagulation factors.

Doses of alternative anticoagulants such as the direct thrombin inhibitors (argatroban and lepirudin) are not completely established in pediatrics, but may be useful in specific scenarios like a documented heparin-induced thrombocytopenia [50].

10.8.5 Monitoring

New monitoring devices permit real-time measurements of venous mixed saturation, hemoglobin, potassium, and blood arterial gases. Tympanic, nasopharyngeal, or esophageal temperature are monitored to give an approximation of the cerebral temperature and the lower side of the body is monitored using a rectal or bladder thermometer.

Several monitors have been studied as tools for neurologic assessment:

1. Bispectral index monitoring (BIS) detects cerebral hypoperfusion and cerebral air embolism.
2. Near-infrared monitoring (NIRS) detects cerebral ischemia.
3. Transcranial Doppler (TCD) ultrasound is a sensitive, real-time monitor of cerebral blood flow velocity (CBFV) and emboli during CHD surgery [51].

The NIRS displays a numeric value, the regional cerebral saturation index (rSO_{2i}), which is the ratio of oxyhemoglobin to total hemoglobin in the light path. The rSO_{2i} is reported as

a percentage on a scale from 15 to 95%. In the brain, the major source of tissue oxygen content is the saturation of blood in the microcirculation. Thus, rSO_{2i} reflects brain tissue oxygen content, which is influenced by cerebral oxygen delivery, oxygen consumption, and arterial/venous blood volume ratio [52, 53]. Cerebral oxygen saturation devices are currently used in some institutions to guide perfusion, oxygenation and transfusion therapy during CPB. However, the current evidence does not show definitive evidence in patient outcomes.

In general, CPB in neonates, infants, and children have a significant impact on outcomes, this is due to the important physiologic changes experienced secondary to hemodilution hypothermia and inflammatory response. Currently, the new technology and developed strategies are directed to improve neurologic outcomes.

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Chapter 11
Nursing Care of the Pediatric Cardiac Patient

Ashlee Shields, Ashley Cole, Alexandra Mikulis, and Erin L. Colvin

Abstract This chapter discusses skills and clinical knowledge nurses must have to care for congenital heart patients. In addition, there is emphasis on rapid assessment in emergency situations. Awareness is also drawn to neurodevelopmental growth in children with CHD.

11.1 Introduction

Neonates and children are admitted to the cardiac intensive care unit (CICU) for both medical (congestive heart failure, cardiomyopathy, or arrhythmias) and surgical (palliated or corrective surgery) treatment caused by acquired or congenital heart disease (CHD). Caring for this population requires a unique skill set of clinical expertise and remarkable assessment skills for prompt identification of a patients fluctuating clinical condition. Early recognition is pertinent to support and stabilize cardiopulmonary function. In addition to managing critically ill patients, nurses must practice family-centered care to ensure bonding and partnership while optimizing outcomes. This chapter outlines clinical knowledge needed to care for the pediatric medical and surgical cardiac patient. The developmental needs of children in the CICU and its importance will be discussed.

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11.2 Caring for the Congenital Heart Disease Patient

The pediatric cardiac nurse must have a strong foundation of cardiac anatomy, physiology, and the conduction system. In addition to understanding the normal heart, nurses must understand physiological changes in the first weeks of neonatal life, anatomy of the various defects, and physiology related to shunting of blood. A strong understanding of a normal cardiovascular assessment for the child's age and defect is necessary for the delivery of care. Each patient may have complex needs specific to his or her defect. While there are many obstacles that need to be addressed from admission to discharge, the discharge process should begin at admission, with the nurse providing ongoing education to primary caregivers.

It is essential for nurses to evaluate both subjective and objective clinical data including physical assessment, diagnostic studies, and laboratory values (Table 11.1). It is necessary to combine this information in conjunction with critical thinking to effectively manage the patient. Careful nursing assessment and synthesis of several data points are critical to recognizing inadequate oxygen delivery [1].

Understanding the child's defect and unique characteristics to their anatomy is essential in managing the patient during delivery of care. Treatment options and contraindications

Table 11.1 Critical data points to consider in cardiac CHD patient management

Heart rate and rhythm	Capillary refill time
Blood pressure	Presence of edema
Pulse oximetry	Urine output
Skin color	Near-infrared spectroscopy (NIRS)
Temperature	Mixed venous saturation
Blood gas	Electrolytes
Lactate	Coagulation studies

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associated with repairs specific to defects including medical, surgical, and palliative care should be taken into consideration. In addition, the nurse needs to understand both early and late complications associated with repaired versus unrepaired defects.

11.3 Preoperative Care

Caring for the neonatal preoperative patient includes consideration for major changes in pulmonary vascular resistance, closure of the ductus, and patent foramen ovale in the first days to weeks of life [2]. Regardless of age or defect, it is best to optimize hemodynamic and respiratory status prior to surgery.

11.4 Postoperative Care

After cardiac surgery, the patient will need ongoing assessment and evaluation of clinical data. Furthermore, careful consideration regarding performed surgical procedure, intraoperative diagnostic testing, and postoperative assessment needs to be continually evaluated to deter complications. Verifying the surgical procedure performed is pertinent to understanding how to manage physiology in the immediate postoperative phase. Intraoperative diagnostic testing, transesophageal echocardiography, gives the healthcare provider more information regarding cardiac output and success of the surgery. In addition to detailed assessment and management of the patient as mentioned previously, healthcare providers need to watch for hemorrhage, arrhythmia, and low cardiac output syndrome (LCOS). It is also important to consider end-organ function, which could be assessed through laboratory studies.

11.5 Neurodevelopmental

Awareness of neurodevelopmental care in the CICU is important for both physicians and nursing staff because children with CHD are at an increased risk for developmental delays. Stimulation provided by the medical team, CICU environment, and the patient's family influences the development of the child. Incorporating neurodevelopmental care practices into the nursing care can yield great developmental benefits. It is best to consider implementing a multidisciplinary neurodevelopmental rounding team on all CICU patients under 1 year of age. At a minimum, the team should include physical therapy, occupational therapy, nursing, a developmental specialist, researcher, and a child life specialist. The aim of this team should be to incorporate the bedside nurse and patient's family to devise a plan for neurodevelopmental care for the patient. Levels and types of stimulation, positioning and handling, feeding practices, developmental achievements, and goals should be discussed during rounds. Family-integrated care is imperative for neurodevelopmental outcomes. Ongoing follow-up is needed to better understand outcomes and can be performed by a developmental specialist throughout the first 2 years of their life to track their progress. The goal of developmental care is to provide multidisciplinary, individualized, and family-integrated care promoting optimal growth and development.

11.6 Emergency Situations

Patients with CHD are at risk for emergencies at any point during admission. There may be times where the likelihood of a cardiac arrest situation is imminent. Overall, it is important for healthcare providers to be aware of patients who have inadequate oxygen delivery or hemodynamic instability, as rapid deterioration can be inevitable. Rapid assessment of both the patient and laboratory data is crucial to timely intervention and avoidance of cardiac or respiratory arrest. During critical times, it is important that the healthcare team has defined roles to provide the most efficient care for decompensating patients. In the event that extracorporeal membrane oxygenation (ECMO) is needed, it would be important for the primary caregiver to consider the cardiac anatomy and optimal decompression and circulation after cannulation [1].

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Chapter 12
Cardiac Database and Risk Factor Assessment, Outcomes Analysis for Congenital Heart Disease

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Abstract Cardiac critical care has firmly established itself as a crucial subspecialty within the framework of a successful congenital heart center. Pediatric Cardiac Intensive Care Units (CICU) evolved from pediatric intensive care units, where pediatric patients with multitude of acute and chronic conditions were receiving care, into complex, highly subspecialized, technically sophisticated units focused on patients with congenital heart disease from infants to adults. The technological developments of pediatric clinical cardiology and cardiothoracic surgery have resulted in evolution of intensive care for congenital heart disease patients. Critical care has played a role in the significant improvements in morbidity and mortality after pediatric and congenital heart surgery observed in the modern era (Jacobs et al., Ann Thorac Surg 102:1345–1352, 2016).

Dedicated and highly trained bedside providers are required for CICUs to perform optimally. A nuanced understanding of congenital cardiovascular pathophysiology and surgical approaches is necessary to select effective therapies from various pharmacologic and non-pharmacologic domains according to the specific clinical situation including post-bypass low cardiac output syndrome, cardiogenic shock, acute and chronic heart failure, and arrhythmias, among others. Furthermore, patients in the CICU often have various complications such as respiratory failure, renal failure, multisystem organ failure, and CNS complications such as stroke and hemorrhage. Therefore, the medical staff in the CICU are also required to practice expert general pediatric intensive care.

The care of the patients with congenital heart disease is complex and degree to which CICUs impact outcomes of medical and surgical patients with congenital heart disease is not entirely clear. Over the past several years, pediatric ICUs throughout the country have partnered to improve general understanding, reporting, and benchmarking of cardiac critical care processes and outcomes. These collaborations have created a robust data infrastructure to foster development of new treatment approaches, quality projects, interventions, and research. Several databases now serve to accumulate and analyze data that could be used to measure performance of cardiac critical care teams (Vener et al., World J Pediatr Congenit Heart Surg 8:77–87, 2017).

Discovering successful strategies of high-performing CICUs and unveiling reasons for success or failure while aiming to improve care is a time-consuming process for any individual center. Collaborative learning presents a great opportunity to convert this existing information into a test subject on a larger scale and ultimately into actionable information that could drive improvement of healthcare for this vulnerable group of patients (Lannon and Peterson, Acad Pediatr 13:S69–S74, 2013)

This chapter starts with discussion of general approaches to measuring critical care outcomes and quality. Methods of quality assessment and risk adjustment are discussed. Two major clinical data repositories for cardiac critical care are presented: the Virtual PICU System (VPS, LLC, Los Angeles) database and Pediatric Cardiac Critical Care Consortium (PC^4) clinical registry. The chapter concludes with a discussion of some of the remaining challenges facing quality improvement collaboratives in the field of pediatric cardiac intensive care.

12.1 Measuring Outcome and Quality of Critical Care

Pediatric inpatient and critical care quality are complex phenomena. Historically, much of the focus of quality measurement focused on infant mortality and medication errors. In general, critical care remains a high-risk environment for hospitalized children owing to their innate vulnerabilities:

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development, dependency, different epidemiology, and representation in the society [1]. Quality research focused on cardiac critical care was challenged to standardize framework and language under which all care providers could operate.

The Agency for Healthcare Research and Quality (AHRQ), the federal authority for patient's safety and quality, and its Children's Health Advisory group selected 18 pediatric quality indicators (PDIs) in 2006. The selection was based primarily on expert input and analysis of data available from the federally funded Kids' Inpatient Database (KID). The PDIs apply to the special characteristics of a pediatric population and screen for problems that pediatric patients experience as a result of exposure to the healthcare system and that may be amenable to prevention by changes at the provider level or area level. Quality indicators were divided in two groups: provider-level indicators and area-level indicators. The quality indicators related to pediatric cardiac intensive care are listed below:

- PDI 01 Accidental Puncture or Laceration Rate
- PDI 02 Pressure Ulcer Rate
- PDI 03 Retained Surgical Item or Unretrieved Device Fragment Count
- PDI 04 Iatrogenic Pneumothorax in Neonates
- PDI 05 Iatrogenic Pneumothorax Rate
- PDI 06 RACHS-1 Pediatric Heart Surgery Mortality Rate
- PDI 07 RACHS-1 Pediatric Heart Surgery Volume
- PDI 08 Perioperative Hemorrhage or Hematoma Rate
- PDI 09 Postoperative Respiratory Failure Rate
- PDI 10 Postoperative Sepsis Rate
- PDI 11 Postoperative Wound Dehiscence Rate
- PDI 12 Central Venous Catheter-Related Blood Stream Infection Rate
- PDI 13 Transfusion Reaction Count

These quality indicators represent a significant step forward as they can be used by hospitals to help identify healthcare quality and safety problem areas that need further investigation, as well as for comparative public reporting, trending, and pay-for-performance initiatives. The PDIs also include risk adjustment where appropriate [2].

Hospital episode indicators are certainly most important to understanding patient-level outcomes, but these metrics do not inform improvement strategies because they do not necessarily provide granular information on the performance and quality of individual teams that separately care for a patient throughout the hospitalization. Hence, outcome measures used for assessment of cardiac critical team performance have to be disentangled from contribution of other care teams encountered by a patient during care episode.

Perioperative care is perhaps the most illustrative example of the challenges involved in team quality assessment. For example, postoperative sepsis after a particular operative procedure depends on proper postoperative antibacterial prophylaxis, administration of good nutrition, and meticulous infection prevention practices and wound care by the CICU team. However, despite any efforts made by the CICU to protect patients from nosocomial infection, this metric is profoundly impacted by the preoperative state (deconditioned malnourished patient, unknown colonization with multidrug-resistant organisms), intraoperative anesthesia practices (time and choice of perioperative antibiotics, intraoperative re-dosing), and complicating surgical morbidities (residual cardiac defects, delayed sternal closure, bleeding, unplanned reoperations). All of the above will represent quality of care provided by other provider teams. Thoughtful approaches to outcome measurement and risk adjustment are necessary to understand the unique impact that the pediatric cardiac critical care team performance imparts on surgical patient outcomes.

Presenting existing data on overall program performance (e.g., hospital mortality after cardiovascular surgery) alongside CICU performance (e.g., CICU "attributable" mortality) may provide deeper insights to hospitals on where strengths and weaknesses lie in their overall perioperative care process.

Outcomes of medical (nonsurgical) CICU encounters may better reflect quality of care provided by the CICU team. Establishing outcome benchmarks for commonly used quality metrics in general pediatric critical care (e.g., catheter-associated bloodstream infections, unplanned extubations, reintubations, frequency of cardiac arrest, and iatrogenic pneumothorax) is necessary to understand the difference in performance of cardiac critical care teams. Determining how to appropriately risk-adjust outcomes specifically for surgical and medical patients in the CICU presents a challenge, but this approach also holds promise to provide useful, granular information to CICU providers.

12.2 Key Components of Cardiac Critical Care Database

The ideal cardiac critical care database would manage the challenges described previously around heterogeneity of patients, separating CICU care from other domains, and providing the data for developing risk-adjusted quality metrics. All of the above would ultimately allow it to also serve as an excellent research data repository to answer important critical care quality questions. In addition, these databases should be based on three key principles:

1. Standard nomenclature
2. Mechanisms to facilitate linkage between registries and reduce data entry burden

3. Reliability of data collection/data integrity confirmed by periodic data audits

12.2.1 Common Nomenclature

Accurate measurement of clinical outcomes in congenital cardiac care depends on a common nomenclature and standardized data collection. The International Society for Nomenclature of Paediatric and Congenital Heart Disease (ISNPCHD) [http://www.ipccc.net/] and the Multi-Societal Database Committee for Pediatric and Congenital Heart Disease (MSDC) developed a consensus-based, comprehensive nomenclature for the diagnosis, procedures, and complications associated with the treatment of patients with pediatric and congenital cardiac disease [3, 4]. This nomenclature has been adopted by majority of clinical databases:

- The Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database
- The European Association for Cardio-Thoracic Surgery (EACTS) Congenital Heart Surgery Database
- The IMPACT Interventional Cardiology Registry™ (**IM**proving **P**ediatric and **A**dult **C**ongenital **T**reatment) of the National Cardiovascular Data Registry® of The American College of Cardiology Foundation® and The Society for Cardiovascular Angiography and Interventions (SCAI)
- The Joint Congenital Cardiac Anesthesia Society – Society of Thoracic Surgeons Congenital Cardiac Anesthesia Database
- The Virtual PICU System (VPS)
- The Pediatric Cardiac Critical Care Consortium (PC^4)

A common nomenclature allows comparison of reported outcomes from different databases and registries, and more importantly facilitates data sharing and integration across these sources.

12.2.2 Linking Databases

As is true in the clinical care of patients with pediatric and congenital cardiac disease, outcomes assessment benefits from multi-disciplinary collaboration. Linking subspecialty databases (e.g., surgery, critical care, anesthesia, and cardiology) can facilitate sharing of longitudinal data across temporal, geographical, and subspecialty boundaries [4–6]. Clinical and administrative databases have been successfully linked using indirect identifiers [7], and similar techniques could be used to link clinical databases. Innovative new software platforms can also facilitate direct sharing of data variables between registries, and will promote more effective approaches to indirect linkage. Careful thought must be given during the design phase when new registries are developed in order to ensure the most efficient and seamless harmonization across registries.

12.2.3 Data Verification

Accurate and complete data is the expectation of providers and families, payers, and government. In the era of public reporting and transparency, it is a pressing need for a body governing a particular database to establish structured ongoing data verification process. The reports of efforts to verify data in the congenital surgical databases of the United Kingdom, Europe, and the United States have been published [8–10]. Gaies et al. reported the methodology and results of the initial audit of the Pediatric Cardiac Critical Care Consortium (PC^4) clinical registry. In-person, on-site audits consisted of source data verification and blinded chart abstraction, comparing findings by the auditors with those entered in the database. Quantitative evaluation of completeness, accuracy, and timeliness of case submission were reported. They concluded that the aggregate overall accuracy was 99.1% and there was no evidence for selective case omission.

These audits also serve as a collaborative peer-to-peer learning for the data entry team. Each database should set standards for timeliness, completeness, and accuracy with participants achieving these standards maintaining privileges of data use. Remediation is necessary for those programs that fail to meet the standards [11].

12.3 Risk Adjustment in Critical Care Outcomes and Quality Assessment

Risk adjustment, broadly defined, is a methodologic approach to measure outcomes while accounting for unique baseline patient characteristics that impact those outcomes and are unrelated to the quality of care provided by the hospital or provider team [12]. In order for CICUs to understand their performance, adjusted quality metrics must reflect the unique patients they care for, and the illness severity of those patients at the time they assume care of the patient. Multi-institutional clinical registries provide an excellent source of data for generating risk adjustment models, and for applying those models to calculate adjusted outcome measures that can be reported back to hospitals.

Risk adjustment after congenital heart surgery remains the most thorough and successful effort to date within the field of congenital cardiac care. The Society of Thoracic Surgeons Congenital Heart Surgery Mortality Risk Model represents the current gold standard in surgical mortality risk adjustment [13]. This empirically derived model accounts for patient characteristics and operative complexity prior to surgery. However, examination of two hypothetical patients undergoing the same operation highlights why additional tools are needed to assess CICU quality.

Consider two patients with no comorbidities or preoperative complications undergoing Norwood operation for Hypoplastic Left Heart Syndrome. The first patient undergoes an uncomplicated operation and returns to the CICU with open chest, on inotropic support and mechanical ventilation. The second patient has difficulty coming off cardiopulmonary bypass because of hypoxemia and suffers cardiac arrest upon transfer from the OR table to the hospital bed. He undergoes emergent chest exploration and placement on extracorporeal membrane oxygenation (ECMO). He is then transported to the Cath lab where the Blalock-Taussig shunt is found to be partially occluded prompting return to the cardiac OR where his shunt is revised. When the patient eventually arrives to the CICU after a prolonged operation and several bypass runs, he is on ECMO with moderate amount of bleeding. Clearly, the challenges to the CICU team differ significantly in these two patients, and operative mortality is much more likely in the second case than the first independent of the quality of care provided by the CICU team. Using the existing STS risk adjustment model, these patients would have identical predicted risk of mortality, and it reflects none of the complexity faced by the second CICU patient. Measuring performance in the CICU must include markers of physiologic derangement and illness severity at the time of care transfer to the CICU team in order to understand how CICU care impacts eventual patient outcome. Thus, complementary risk adjustment approaches to disentangle quality of CICU care must be developed.

Existing risk adjustment models used in general pediatric critical care outcomes assessment have proven insufficient for understanding the quality of pediatric CICU care, particularly in the setting of postoperative care [14]. Databases specifically designed to capture cardiac critical care outcomes have been used to develop new risk adjustment methods that may solve this difficult problem of isolating CICU team performance. The first such attempt was performed using the VPS database cardiac module. Jeffries et al. [15] developed the Pediatric Index of Cardiac Surgical Intensive Care Mortality from a cohort of 16,574 cardiac surgery patients, and it predicted postoperative mortality in the ICU with an area under the curve of 0.87 and good calibration. However, important questions remained regarding this approach. The model included some postoperative variables that were collected up to 12 hours after admission from the OR. Some of these predictor variables, such as use of extracorporeal membrane oxygenation within 12 hours of surgery, may be related more to CICU performance rather than baseline severity of illness upon arrival to the CICU and thus may lead to erroneous conclusions about quality. Further, this model is applied at the time of CICU admission, not when the patient returns from the OR. Thus, in cases where patients are admitted preoperatively (e.g., neonates with ductal-dependent systemic or pulmonary blood flow), illness severity is not assessed in the early postoperative period, and analysis of CICU postoperative care quality may be inaccurate.

To address remaining knowledge gaps and improve on existing methods, investigators from PC^4 developed a new risk adjustment model to assess postoperative care quality in the CICU, again using mortality as the quality metric. The important new features of this model include:

1. It is always applied at the time postoperative care begins in the CICU, providing a consistent assessment of patient illness severity at that time point.
2. Illness severity measures are collected only within the first two postoperative hours, reducing the likelihood that variables like postoperative vasoactive support or ECMO utilization reflect the quality of CICU care.

From a sample that included 8543 postoperative encounters across 23 dedicated CICUs, they found the significant risk factors that affected mortality included: age at surgery preterm neonate (OR = 4.62; 95% CI, 2.2–9.8), term neonate (OR = 2.5; 95% CI, 1.3–4.6), any chromosomal abnormality (OR = 1.58; 95% CI, 1.1–2.3), more than two previous cardiac surgeries (OR = 3.05; 95% CI, 1.7–5.5), any Society of Thoracic Surgeons preoperative risk factor (OR = 2.13; 95% CI, 1.5–3), preoperative mechanical ventilation (OR = 2.49; 95% CI, 1.8–3.5), STS-European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality Category 4 and 5 (OR = 1.5; 95% CI, 1.3–1.8), mechanical ventilation at 2 hours after the procedure in the cardiac ICU (OR = 4.57; 95% CI, 1.6–13), maximum vasoactive inotropic score during the first 2 hours after the procedure (OR = 1.02; 95% CI, 1.01–1.03), and use of extracorporeal membrane oxygenation during the first postoperative hour (OR = 15.88; 95% CI, 9.8–25.8).

The model demonstrated good discrimination (C statistic = 0.92) and calibration. The researchers concluded that the risk adjustment method was effective for comparative analyses of cardiac ICU quality of care [16]. The model is being used to provide real-time information to PC^4 hospitals on adjusted CICU ("CICU attributable") surgical mortality for benchmarking and quality improvement purposes.

The approaches described above can be applied more widely to investigate CICU quality metrics that expand beyond mortality. The risk adjustment models within PC^4 have been developed for postoperative cardiac arrest, duration of mechanical ventilation, postoperative complications, postoperative use of mechanical circulatory support, and CICU/hospital length of stay accounting for illness severity at the time of CICU admission in postoperative encounters. It remains unclear whether new CICU-specific risk adjustment models are necessary and will outperform existing methods [17–19] in use for general pediatric critical care in the measurement of outcomes for nonsurgical (medical) encounters. Several efforts are underway within PC^4 to develop risk adjustment models for medical patients. Case mix adjusted mortality for CICU encounters without Index CV operation and cardiac arrest in the same patients' population are currently being explored.

12.4 Cardiac Critical Care Databases

A recent effort summarized the current scope of clinical registry projects in congenital cardiac and pediatric critical care [20, 21]. Three databases – the Paediatric Intensive Care Audit Network (PICANet, United Kingdom), VPS, and PC^4 – focus solely on critically ill patients, while many others include some data related to critical care (e.g., congenital surgical and pediatric cardiology databases). Other national and regional critical care databases – for example, the Australia and New Zealand Pediatric Intensive Care (ANZPIC) Registry – will include some cardiac-specific data on outcomes and practice. Of these, the PC^4 clinical registry is the only database exclusively dedicated to the cardiac critical care population.

12.4.1 Virtual PICU Systems (VPS,LLC) Database

The VPS clinical database has been operated since 1997. The founders developed a repository to collect demographic, diagnostic, and severity of illness adjusted outcome data from member units on all patients. The database has supported patient care, quality improvement, and numerous research initiatives. This platform provided a valuable resource of information to investigate how pediatric critical care is practiced across the United States and abroad. The database now includes several hundreds of thousands of cases from 120 pediatric and pediatric cardiac ICUs from 100 participating hospitals, including those outside of North America. One particularly useful aspect of VPS is that it contains severity of illness scores including Pediatric Risk of Mortality (PRISM) III, Pediatric Index of Mortality (PIM) 2, Pediatric Logistic Organ Dysfunction (PELOD), and several cardiac intensive care unit complexity scores (see above) [21].

A separate cardiac module within the VPS database was created to provide more information on patients with critical cardiovascular disease. The VPS adopted the International Pediatric and Congenital Cardiac Code [http://www.ipccc.net/] nomenclature for cardiac diagnoses, cardiac surgical procedures, and cardiac surgical complications. This cardiac module has been used to explore several outcomes related to cardiac critical care [22–24], and to develop risk adjustment methods [15] for outcome reporting (see above).

12.4.2 Pediatric Cardiac Critical Care Consortium (PC^4) Clinical Registry

In 2012, twelve children's hospitals formed the Pediatric Cardiac Critical Care Consortium (PC^4; pc4quality.org) as a quality improvement collaborative for children with critical cardiovascular disease [25]. A detailed, CICU-specific clinical registry was developed to be the data infrastructure for quality assessment and clinical research that would power improvement initiatives through the collaborative learning (see below). All CICU encounters from participating hospitals have been entered since 2013, and at the time of this writing, more than 49,000 CICU encounters and close to 29,000 surgical index cases exist in the database. Since 2013 the number of hospitals submitting data to PC^4 has risen from 6 to now include over 40 from North America (Fig. 12.1).

The PC^4 clinical registry populates a real-time, web-based analytics and reporting platform that participants use to view comparative reports on quality metrics and resource utilization (Figs. 12.2 and 12.3). This registry shares common variables with the Society of Thoracic Surgeons Congenital Heart Surgery Database and the IMPACT Registry; most participating centers use a software solution that ensures identical data on patient characteristics, anatomic, and procedural variables across all of the three registries. The data in the PC^4 registry are rigorously audited and this process has revealed excellent data integrity as described previously [11]. PC^4 investigators have published numerous reports from the clinical registry demonstrating variation in outcomes across hospitals, elucidating the epidemiology of cardiac critical care outcomes and practice, and have developed new risk adjustment methods to assess CICU quality [26–34].

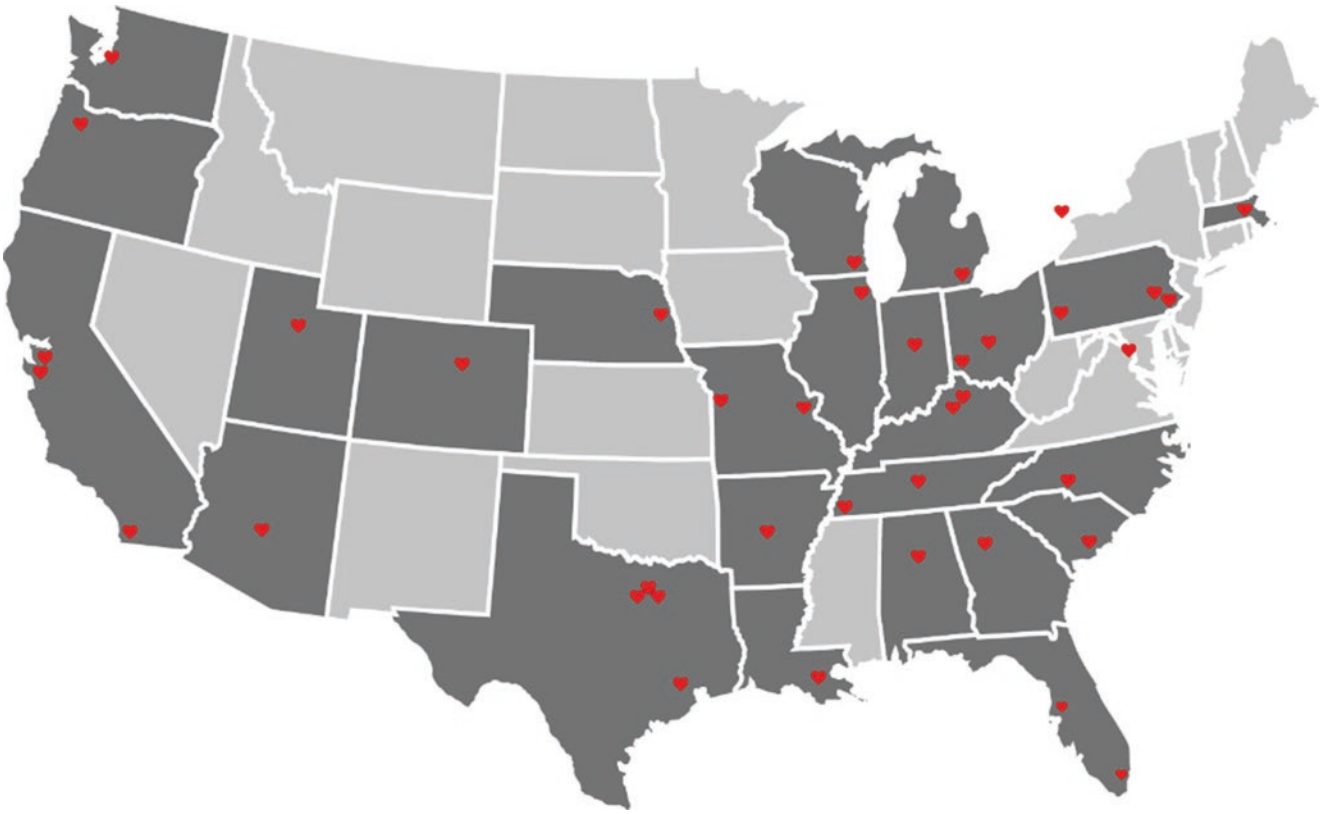

Fig. 12.1 PC[4] participating centers (July 2018)

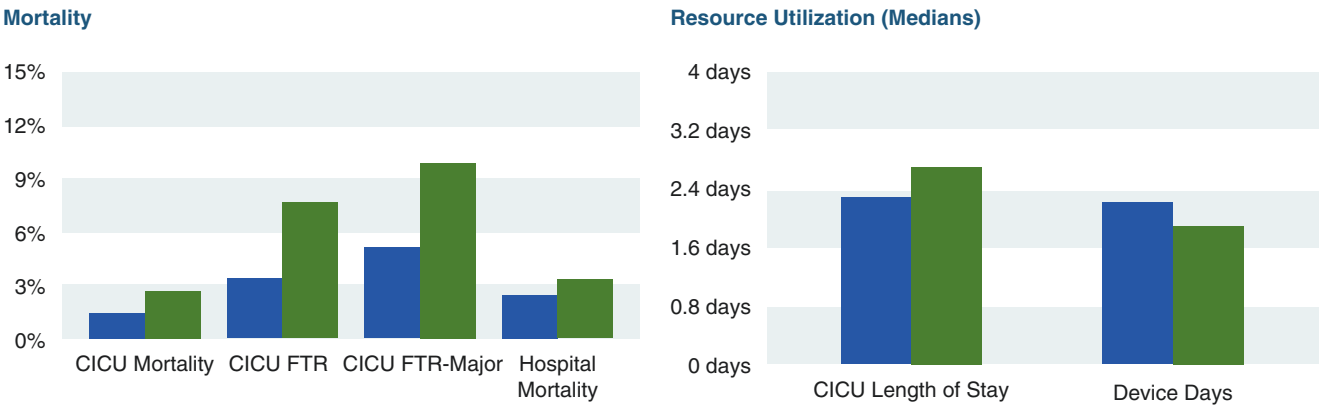

Fig. 12.2 Unadjusted quality metrics and resource utilization. (Downloaded by Y. Domnina from PC4quality.org July 6, 2018)

12.5 Future Direction: Collaborative Learning

Clinical registries and databases should not merely exist as data repositories; instead, they have to be actively used as key instruments to promote better care for the patients with critical cardiac disease. Participation in database projects alone is not sufficient to facilitate quality improvement. A growing body of literature demonstrates that simply submitting data to a clinical database does not result in improved clinical or resource utilization outcomes [35, 36]. Regional or national collaborations are more effective in improving the quality of healthcare.

One of the first successful collaborative quality initiatives was pioneered by the Northern New England Cardiovascular Disease Study Group [37]. It established

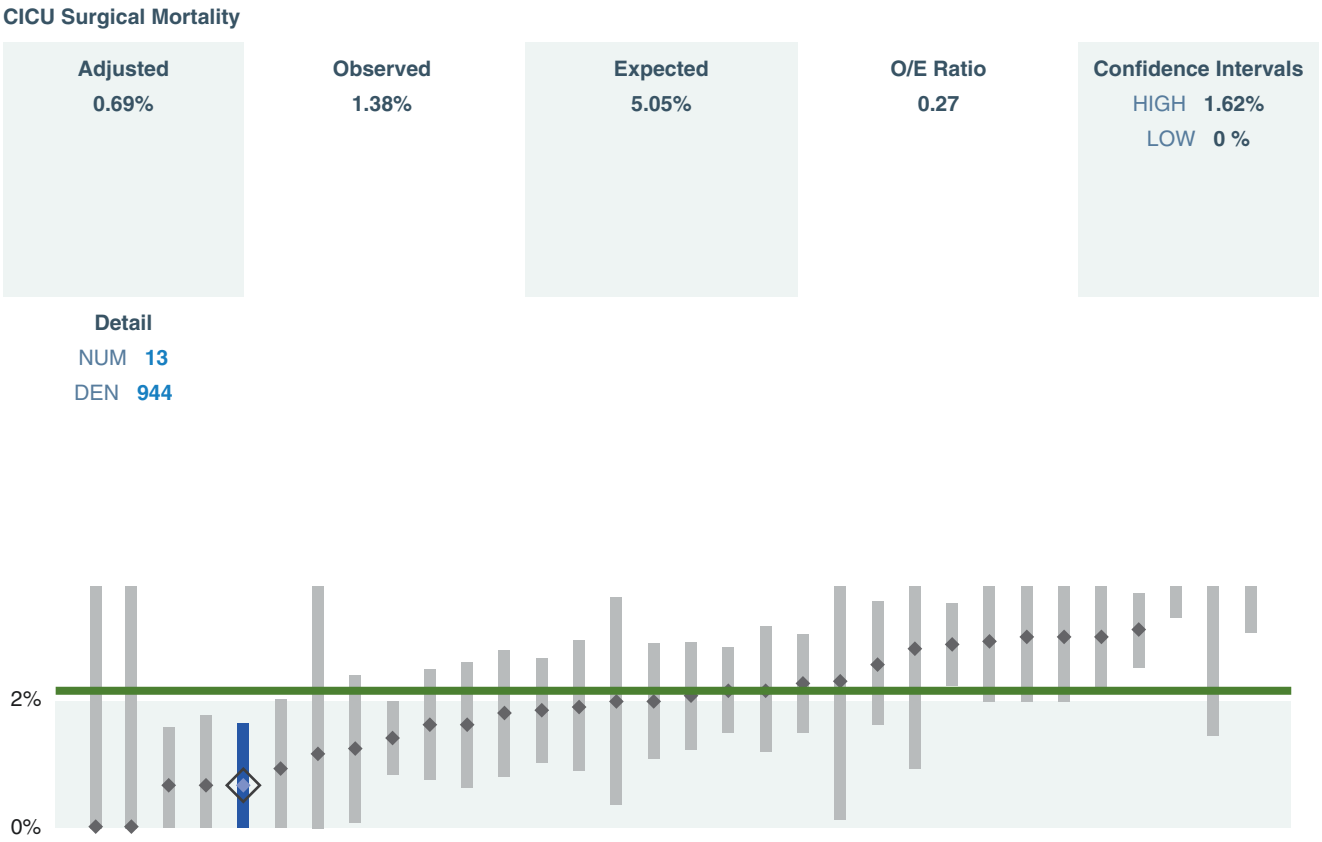

Fig. 12.3 Example of real-time, adjusted benchmark reports for cardiac critical care units in PC4. Adjusted CICU surgical mortality is shown in the figure. (Downloaded by Y. Domnina from pc4quality.org July 6, 2018)

the necessary components of successful collaborative improvement program:

1. Clinical registry containing detailed information about patients' risk status, processes of care, and outcomes
2. Regular and consistent flow of information on the performance of participants from the registry coordinating center
3. Regular review and interpretation of the data focusing on areas of variation in practice or outcomes
4. Identification, dissemination, and implementation of best practices across the region

Subsequently researchers from the Michigan Value Project highlighted the outcome benefits gained from participation in quality improvement collaboratives over participation in a national registry [38]. Investigators showed greater improvement in rates of complications and mortality for adult patients undergoing cardiovascular interventions, and general, vascular, and bariatric surgical procedures at hospitals that belonged to statewide quality collaborative programs for these specialties in Michigan compared to hospitals that submitted data to the National Surgical Quality Improvement Program (NSQIP) but were not part of any quality collaborative. This analysis highlights the gap between simply measuring and reporting outcomes versus an active infrastructure to promote quality improvement through collaboration.

New collaborative learning approaches to congenital cardiac care have begun to permeate the field. The National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) demonstrated success in achieving better weight gain and lower mortality during the interstage period for children undergoing stage 1 palliation for HLHS and related diagnoses [39, 40]. The new Pediatric Acute Care Cardiology Collaborative (PAC3) was just unveiled at the 12th international Pediatric Cardiac Intensive Care Society meeting. The emphasis of PAC3 is on improving outcomes of pediatric cardiology patients within all cardiac hospital-based inpatient non-intensive care units. At the cornerstone of this collaborative is partnership and seamless integration of data collection, management, and storage with PC^4. This inter-collaborative partnership is strategically positioned to better understand the way care is provided in the hospital setting across a patient's continuum of care, and offers

new opportunities to determine best practices for improving clinical outcomes, value of care, and patient/family experience.

PC[4] has been developed and organized to promote collaborative learning among its participants. In addition to providing the infrastructure for ad hoc local quality improvement efforts, PC[4] has generated data suggesting opportunities for more far-reaching, multi-institutional collaborative learning projects. At the time of this writing, a collaborative-wide cardiac arrest prevention (CAP) intervention has been implemented based on data showing wide variation in adjusted CICU rates of cardiac arrest across PC[4] participating institutions.

12.6 Conclusion

Unique challenges exist in defining and assessing quality in the CICU, but several recent efforts prove that success is achievable. Thoughtful analytic approaches to isolate and identify quality of CICU care are underway. Various risk adjustment methods are undergoing implementation and evaluation to provide appropriately adjusted outcome data and develop quality metrics for ongoing measurement of critical care performance. These data reveal high-performing CICUs, and armed with a principal of transparent sharing of data on outcomes and practice the pediatric cardiac critical care community can help improve the lives of children and adults with critical cardiovascular disease by learning collaboratively or from one another.

Finally, each collaborative must look for ways to reduce costs to maximize institutional "return on investment" (ROI). Limiting the personnel costs associated with data collection is probably the greatest lever for minimizing a hospital's investment, and capturing the data directly from the electronic health record is a means to this end. In doing so, hospitals and collaboratives will have to ensure that they can maintain the same level of data integrity that makes the information valuable in the first place.

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Part II

Specific Cardiac Lesions

Chapter 13
Patent Ductus Arteriosus

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Abstract This chapter provides a general overview of the characteristics, diagnosis, and management of the persistence of ductus arteriosus patency in different group ages.

13.1 Introduction

The ductus arteriosus is a normal and vital fetal structure that arises from the left sixth aortic arch. It connects the main pulmonary artery to the descending thoracic aorta just distal and opposite to the origin of the left subclavian artery (Fig. 13.1). The pulmonary end usually tapers and is narrower than the aortic end.

The histology of the ductus arteriosus differs from that of arteries in that the media is deficient in elastic fibers and is instead composed of poorly arranged smooth muscle cells in a spiral configuration. This smooth muscle is especially sensitive to prostaglandin-mediated relaxation and oxygen-induced constriction.

During fetal life, approximately 60% of the right ventricular outflow is shunted across the ductus arteriosus and away from the high-resistance pulmonary vascular bed. Circulating prostaglandins produced by the placenta actively keep the ductus patent during fetal life. After birth, with the removal of the placenta and with active breathing that causes an increase in the arterial oxygen tension which inhibits prostaglandin synthetase, there is an abrupt decrease in prostaglandin levels that leads to ductal constriction [1]. Contraction of the medial muscle causes shortening of the ductus and its functional closure. Lately, folding of the endothelium and proliferation of sub-intimal layers cause permanent closure, usually during the first several weeks of life [2].

Steven P. Goldberg is a Former Attending Cardiac Surgeon who is deceased at the time of publication of this chapter.

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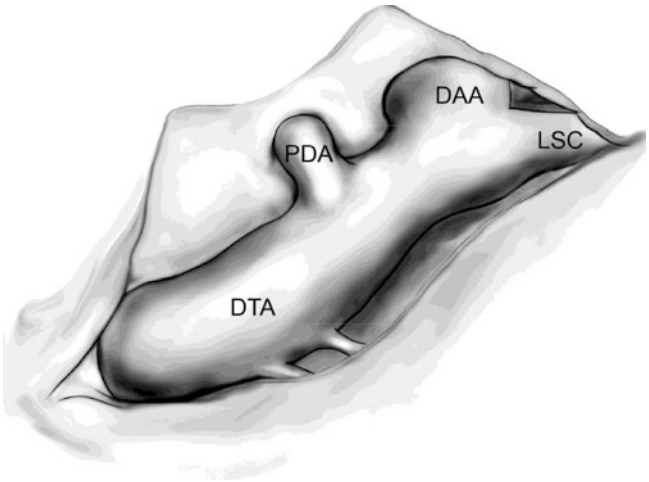


Fig. 13.1 Ductus arteriosus anatomy as seen through a left thoracotomy. (DAA distal aortic arch, LSC left subclavian artery, PDA patent ductus arteriosus, DTA descending thoracic aorta)

13.2 Epidemiology and Natural History

Patent or persistent ductus arteriosus (PDA) accounts for 5–10% of all congenital heart defects. The overall incidence in preterm infants is 20–30%, with the incidence rising sharply with earlier gestational age and lower birth weight (>32 weeks: 20%; <28 weeks: 60%). In preterm infants, immature ductal tissue is less sensitive to oxygen-mediated constriction and more sensitive to prostaglandin vasodilation [3].

In preterm infants, a PDA can contribute to morbidity secondary to decreased systemic flow due to the diastolic steal induced by the left-to-right shunt: renal failure, intracranial hemorrhage, necrotizing enterocolitis, abnormal cerebral blood flow, respiratory distress syndrome, and chronic lung disease.

When left untreated, a large PDA can lead to irreversible pulmonary hypertension with the development in the mid to long term of a right-to-left shunt and Eisenmenger's syndrome. Suprasystemic pulmonary artery pressure can develop as early as 6 months of life.

Functional closure of the ductus arteriosus usually occurs within the first 48 hours of life in most newborns of more than 36 weeks of gestation, with complete anatomic closure within 6 weeks [4–7]:

24 hours	42%
40 hours	78%
48 hours	90%
96 hours	100%

However, closure may occur later in life. It has been estimated that the percentage of PDA closing after 1 year of age is 0.6% per year [8].

Prior to the antibiotic era, the average age of death in patients with a PDA who survived infancy was 36 years, with infective endocarditis being the most common cause of demise.

13.3 Pathophysiology

PDA may be the source of a significant left-to-right shunt between the aorta and the pulmonary artery. Depending on the degree of shunting and the ratio of systemic and pulmonary resistances, this increased shunt may cause with various degrees of cardiac failure and pulmonary arterial hypertension. Moreover, the diastolic steal imposed on the systemic circulation, as depicted herein, may cause significant and even life-threatening co-morbidities (Fig. 13.2). Also, the excessive blood flow into the lungs as the pulmonary vascular resistances naturally decrease over the first few weeks of life results in significant alterations of the lung compliance which, added to cardiac failure, may explain the ventilator dependency that characterizes neonates with hemodynamically significant ductus arteriosus.

The hemodynamic impact of the PDA depends mainly on the following factors:

(a) The size and length of the PDA (flow is directly proportional to the diameter, inversely proportional to the length)
(b) The ratio between systemic resistance (SVR) and pulmonary resistances (PVR)
(c) The blood viscosity (low viscosity increases the severity of the shunt)

When PAH is severe and suprasystemic, there may be an inversion of both the intracardiac shunt (right-to-left shunt through the foramen ovale) and the extracardiac shunt (right-to-left shunt through the ductus arteriosus). Once treated and when pulmonary resistances drop below systemic levels, both shunts might become left-to-right, this being an appeal to caution in patients with poor left ventricular function (Figs. 13.3 and 13.4).

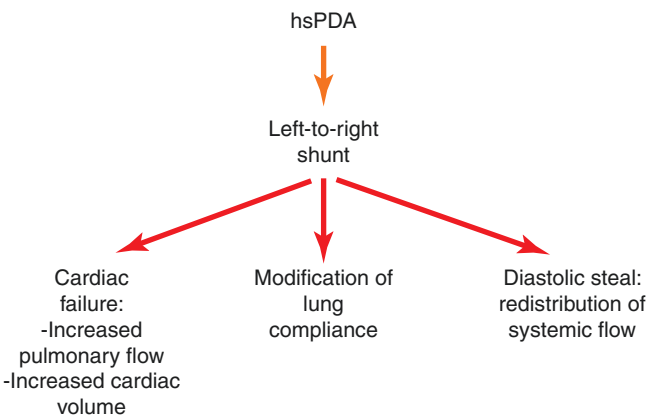


Fig. 13.2 Pathophysiology of the PDA

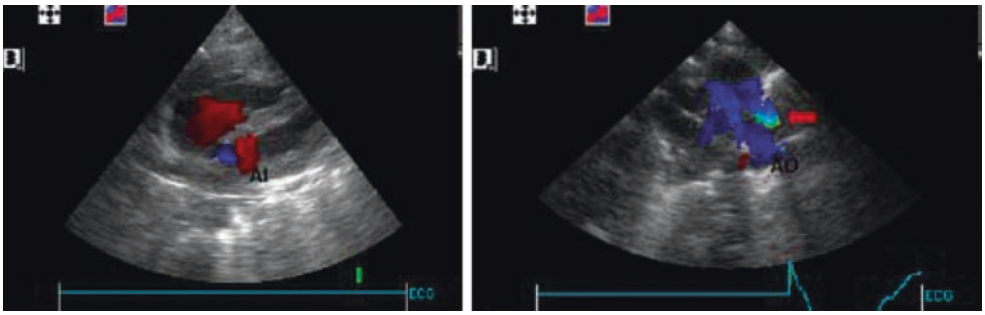


Fig. 13.3 Severe PAH with right-to-left shunt through the foramen ovale and the ductus arteriosus (prior to treatment)

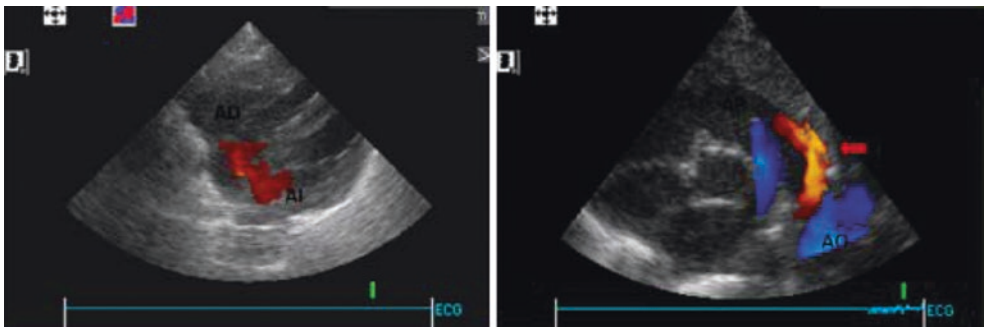


Fig. 13.4 Once treated, pulmonary hypertension becomes infrasystemic and there is an inversion of the shunt from right-to-left to left-to-right, across both the foramen ovale and the ductus arteriosus

13.4 Diagnosis

13.4.1 Clinical

A PDA may be symptomatic in 55–70% of premature babies with less than 1000 g or 28 weeks [9, 10]. Hemodynamically significant ductus arteriosus (hsPDA) concerns 60% of premature babies less than1 week old [11].

Symptoms and physical findings depend on the size and length of the ductus as well as the degree of shunt, the ratio between systemic and pulmonary resistances, blood viscosity (Pouseuille's law), and associated cardiac or extracardiac defects.

Premature babies should be screened for hsPDA in the presence of persistent dependence of the mechanical ventilation, feeding intolerance or any complication as described above.

Clinically, the main signs (Table 13.1) to be explored are cardiac murmurs, the presence of a significant systolic–diastolic gradient, precordial hyperactivity, and the anomalous peripheral pulses. Signs of cardiac failure are usually very unspecific in this patient population. The murmur of the PDA may be systolic, but with increasing size of the shunt, it becomes louder, more prolonged, and finally continuous, usually heard in the second and third intercostal space. Pulses are bounding and reflect the degree of diastolic steal.

Table 13.1 Clinical symptoms and signs of hsPDA

Suggestive symptoms and signs	Unspecific symptoms and signs
Tachycardia	Spells of bradycardia
Hyperdynamic precordium	Recurrent apnea
Bounding pulses	Spells of cyanosis
Continuous cardiac murmur	Hemodynamic instability
Increased systolic–diastolic gradient	Respiratory instability and mechanical ventilation dependency
Cardiothoracic Index >0.65	Metabolic acidosis
Pre-post ductal saturation differential	Diagnosis of NEC, intracranial hemorrhage, kidney failure
	Signs of diastolic steal on the cerebral or mesenteric Doppler

Clinical PDA scores (Table 13.2) [12] may be useful in order to assess the hemodynamic impact of the PDA.

13.4.2 ECG

The electrocardiogram may be normal in small PDAs, but with increasing size of the shunt, the electrocardiogram may show moderate to severe left ventricular hypertrophy, as well as left atrial enlargement.

Table 13.2 PDA score: a total of more than 3 points suggests the presence of an hsPDA

Data/score	0	1	2
Heart rate	<150	150–170	>170
Precordium	Normal	Dynamic on palpation	Dynamic on inspection
Murmur	Absent	Systolic	Continuous
Pulses	Normal	Increased upper limbs	Increased lower limbs
CTI	<0.60	0.60–0.75	>0.75

Modified from Yeh et al. [12]
CTI cardiothoracic index

13.4.3 Chest X-Ray

Chest X-ray findings are variable and depend on the size of the ductus and the amount of left-to-right shunting. Patients with a small ductus may have a normal radiography. Classical signs of a hsPDA are mild to moderate cardiomegaly, prominent pulmonary vascularization, the presence of a dilated left atrium, and of a horizontalized left main bronchi. Patients with significant PAH in the setting of a PDA may display a prominent pulmonary vascularity or clear lungs depending on the pulmonary vascular resistances and the degree and direction of shunting.

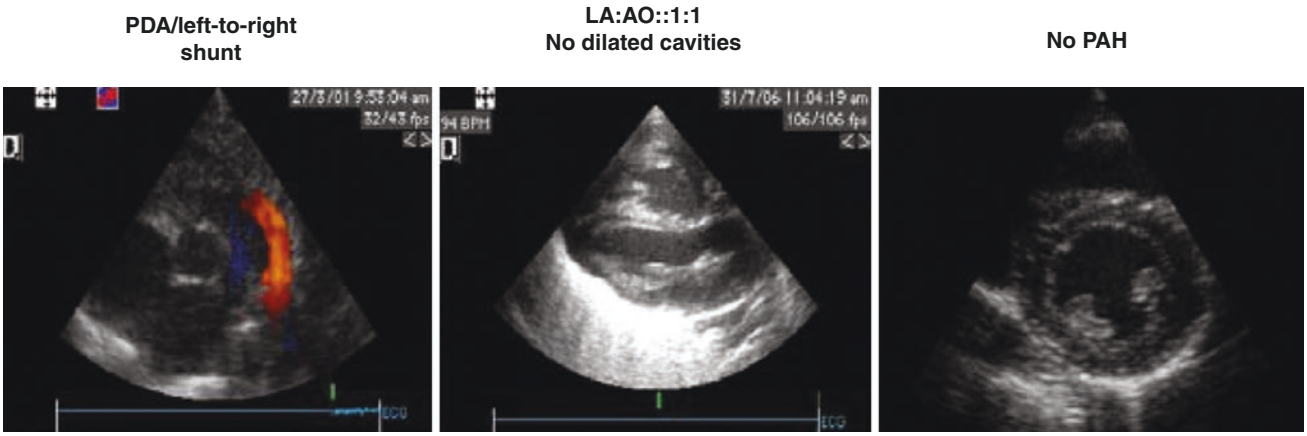
13.4.4 Echocardiography

Echocardiography with Doppler flow studies remains the gold standard for diagnosis of PDA. It allows the diagnosis of the ductal patency as well as the assessment of associated intracardiac defects, ventricular function, the degree and type of shunt (Qp/Qs; left-to-right or right-to-left), flow characteristics across the foramen ovale, and presence and severity of pulmonary arterial hypertension (PAH). As PAH increases, echocardiography will identify the progression of the ductal shunt from left-to-right, to bidirectional, to right-to-left (if pulmonary pressure is suprasystemic), and finally a reversal of flow (becoming right-to-left) across the foramen will be observed.

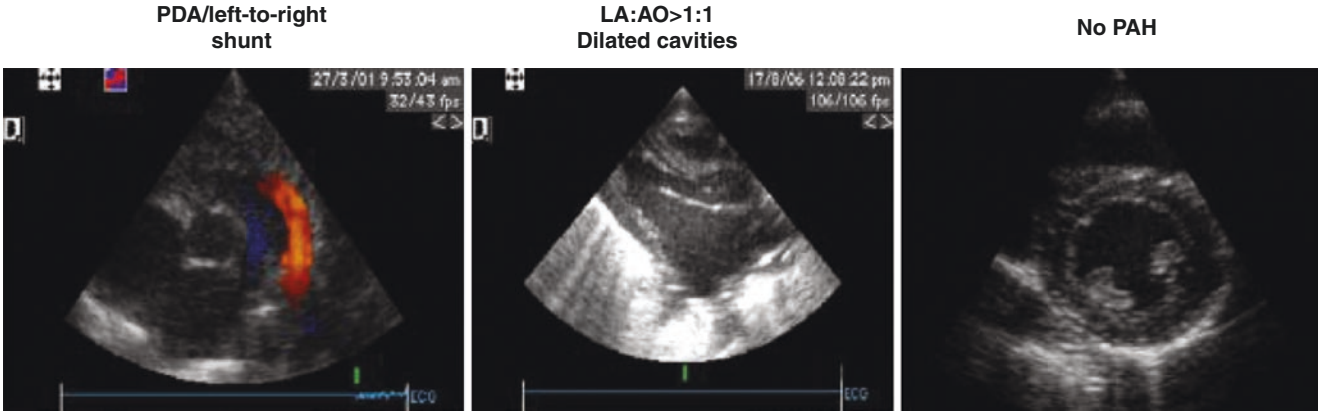
Importantly, the echocardiographic evaluation needs to be exhaustive and completely explore the cardiovascular anatomy; of note, in the setting of a large ductus arteriosus, particular caution needs to be taken to rule out an associated – even if subtle – coarctation of the aorta. Echocardiography is also fundamental in the appraisal of therapeutic efficiency.

Five pathophysiological scenarios may be documented by echocardiography:

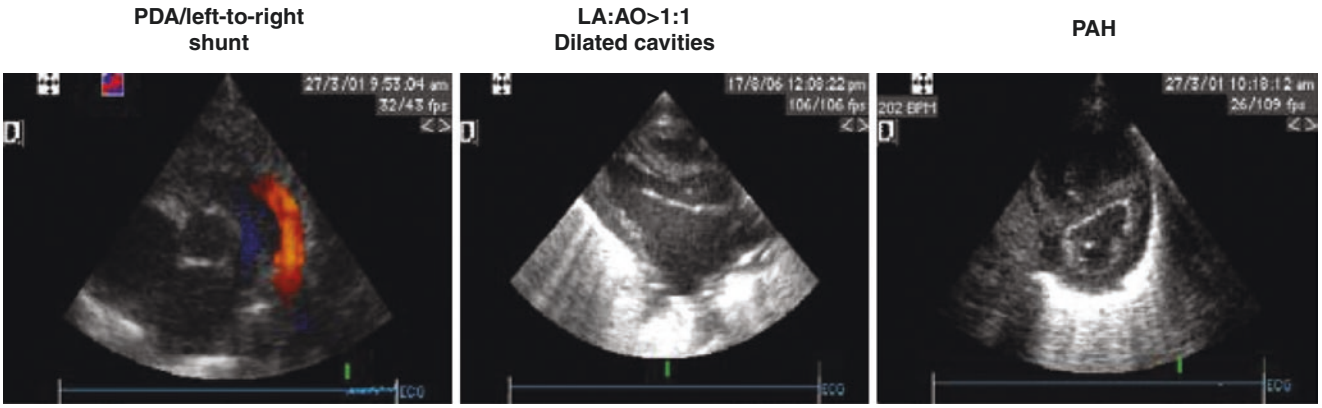
1. Left-to-right shunt through a restrictive ductus arteriosus, thus with normal Qp/Qs and nondilated left heart cavities and normal pulmonary pressures (normal PVR):



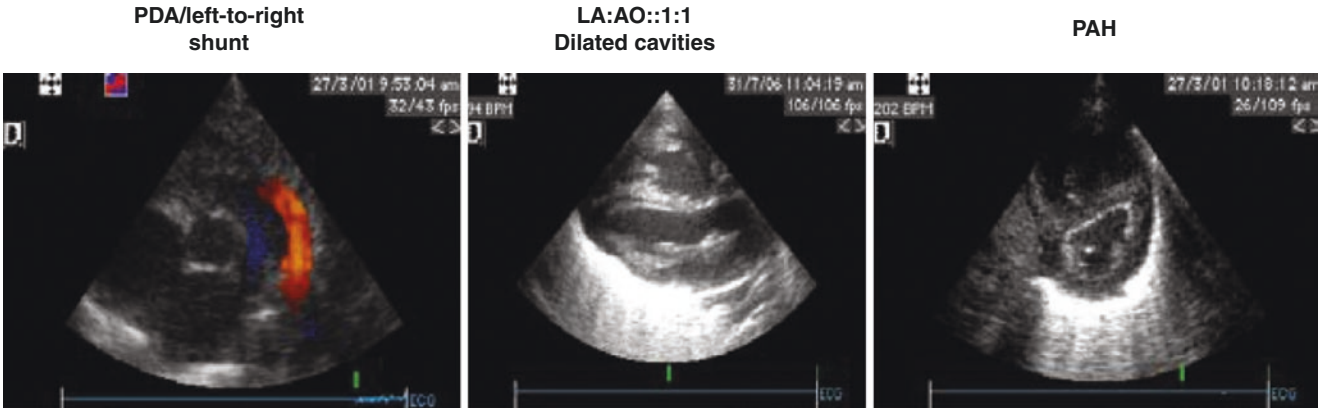
2. Left-to-right shunt through a nonrestrictive ductus arteriosus, with high Qp/Qs and subsequent dilatation of the left cardiac cavities, but still with normal pulmonary pressures (normal PVR):



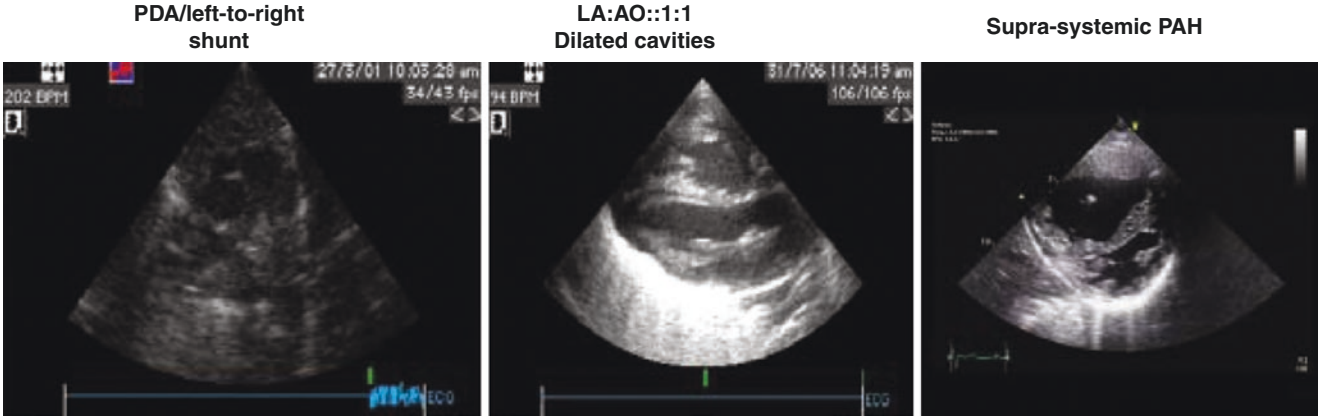
3. Left-to-right shunt through a nonrestrictive ductus arteriosus, with high Qp/Qs and subsequent dilatation of the left cardiac cavities, and with pulmonary arterial hypertension (normal PVR) and possibly dilated right heart cavities:



4. Left-to-right shunt through a nonrestrictive ductus arteriosus, nonsignificant Qp/Qs, and nondilated left heart cavities, and yet with pulmonary arterial hypertension (due to high PVR) and dilated right heart cavities:



5. Right-to-left shunt through a nonrestrictive ductus arteriosus, low Qp/Qs, and nondilated left heart cavities, and suprasystemic pulmonary arterial hypertension (high PVR) and dilated right heart cavities that may compress the left ventricle.



13.4.5 Cardiac Catheterization

Diagnostic cardiac catheterization is seldom required for isolated PDA in the young infant. In grown-up untreated individuals with significant pulmonary hypertension, a cardiac catheterization should be performed prior to ductal closure.

Interventional catheterization is a common and safe practice for PDA closure, also possible although relatively limited in small weight premature neonates [13, 14]. Currently, most persistent ductus in toddlers, infants, and children may be closed with very low associated morbidity by percutaneous techniques including coils and devices.

13.5 Medical Management

There are few contraindications to treat the PDA with hemodynamic significance. The primary cause of concern relates to pulmonary hypertension secondary to elevated pulmonary vascular resistances or to excessive pulmonary blood flow, and obviously the suspicion on any potential ductal physiology, including cardiac malformations with right or left obstruction.

13.5.1 Preterm and Term Neonates

When and how to treat PDA in neonates is still a controversial matter. Main principles of the medical treatment include:

(a) The use of NSADs or paracetamol
(b) Fluid restriction
(c) Maintenance of a high viscosity if hsPDA
(d) Probably the use of loop-diuretics
(e) Phototherapy

Figure 13.5 depicts a possible algorithm to start medical treatment in neonates with a hemodynamically significant ductus arteriosus. Interestingly, a large recent study of data related to infants <30 weeks from 280 neonatal units in the USA documented significant decreases in the diagnosis and the treatment of the PDA, with no evidence of increased morbidities [15].

The most commonly used NSAIDs are indomethacin and ibuprofen. Indomethacin was introduced in 1976 as a method of PDA closure in preterm infants. It has since become the standard of management in preterm infants with a significant ductus. Multiple protocols have been proposed. A dose of 0.1 to 0.2 mg/kg is given intravenously for three doses, 12 to 24 hours apart, before the infant is considered for surgical closure. A scheme of 0.1 mg/kg every 24 hours for 6 days may be used in stable premature babies. Ibuprofen may be used at high (20-10-10 mg/kg/dose) or low (10-5-5 mg/kg/dose) doses and no difference has been documented between these dosing regimens neither in terms of efficiency nor in the occurrence of adverse effects [16–19]. No significant therapeutic difference has been reported between the two drugs, but data suggest that intravenous administration is more effective than oral administration [19, 20–23]. Some case reports suggest that paracetamol may be an alternative to the above drugs, but additional studies are needed [24, 25]. The long-term effects of these therapies are unknown. Whatever protocol is chosen, caregivers should keep in mind that there are no medications without side effects. Some authors have described that the use of medical treatment with NSAIDs is useless in up to 64% of treated premature babies [26]. Early treatment of hsPDA reduces symptoms, need for surgical ligation, and

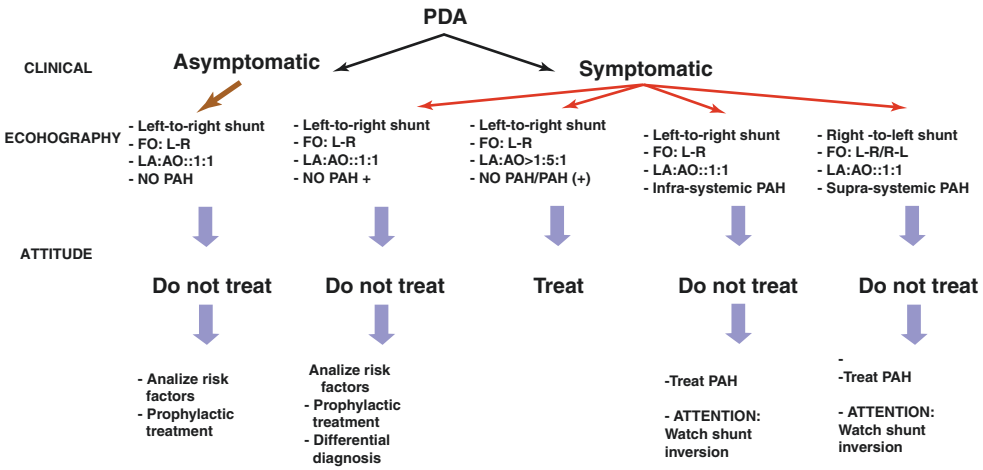


Fig. 13.5 Algorithm for the treatment of hemodynamically significant PDA of the neonate. PDA persistent ductus arteriosus, PAH pulmonary arterial hypertension, FO foramen ovale, LA left atrium, AO aorta, L-R left-to-right shunt, R-L right-to-left shunt

duration of ventilator support and hospitalization in premature neonates [20–22]. Treatment seems to be more efficient on the first day of life and efficacy is inversely proportional to age. Late use of NSAIDs might be inefficient.

Prophylactic use on Indomethacin is also controversial. In premature newborns <28 weeks, prophylaxis between 6 and 15 hours of life may decrease the incidence of intracranial and pulmonary hemorrhage and the need for surgical ligation [27, 28]. Still, there is no evidence-based data demonstrating significant differences in mortality and complications. Further randomized, double-blind, placebo-controlled studies are required to elucidate the potential benefits of this practice.

Contraindications to the use of NSAIDs include:

(a) Active hemorrhage
(b) Suspicion of NEC
(c) Diuresis<0.6 ml/kg/hour
(d) Creatinine >2 mg/dl
(e) Platelets <50,000/mm^3
(f) Coagulopathy
(g) Sepsis
(h) Hyperbilirubinemia
(i) Ductal-dependent congenital cardiac malformation
(j) Renal or intestinal congenital abnormality (relative)

NSAIDs are not free of potential adverse effects and caregivers need to identify patients with added risk factors in whom these drugs may need to be considered with further thoughtfulness. Some of such side effects are as follows.

(a) Decreased gastrointestinal perfusion
(b) Decreased renal blood flow
(c) Interference with platelet function with the potential for bleeding
(d) Possible reduction of renal blood flow
(e) Hypertension on intravenous administration

From a safety and quality standpoint, a number of recommendations should be followed prior and during NSAIDs administration:

(a) Check coagulation profile prior to treatment
(b) Control diuresis before and throughout the treatment
(c) Check platelet count before and throughout the treatment
(d) Check renal function before and throughout the treatment
(e) Fastening for 48 hours
(f) Echocardiography before and after the treatment

13.5.2 Toddlers and Children

In patients beyond the neonatal period, medical treatment is not recommended since inefficient. If therapy is indicated, interventional or surgical alternatives are warranted.

13.6 Interventional and Surgical Management

Closure of large and hemodynamically significant PDA is the standard of care to avoid the risk of pulmonary hypertension and cardiac failure; nonetheless, recommendations to manage the very small and hemodynamically insignificant PDA to prevent the rare infective endocarditis, particularly if "silent" and incidentally diagnosed, are less clear. Although many practitioners recommend closure of the latter, mostly when clinically audible, data is currently equivocal [29].

13.6.1 Interventional Catheterization

As described earlier in this chapter, most PDA are closed by interventional catheterization. Closure of PDA by interventional catheterization essentially relies on the use of coils and various other specific devices. A chapter on cardiac catheterization with further details can be found elsewhere in this book.

13.6.2 Surgery

Surgical treatment of the PDA is indicated in the following circumstances:

(a) Therapeutic failure of the NSAIDs in the neonate
(b) Complications of the NSAIDs in the neonate
(c) Contraindication to the NSAIDs in the neonate
(d) Patient size and weight
(e) Size or shape of the PDA contraindicating interventional closure

Surgery may be performed by thoracoscopy [30–36] or by mini-thoracotomy. The traditional surgical approach includes ligation, ligation and division, or the use of hemoclips (Fig. 13.6); the chosen method depends on the size of the PDA and on surgeon's or institutional preferences. Contraindications for surgery may be the inability of the patient to tolerate anesthesia or a thoracotomy as well as severe systemic disease like septicemia.

13.7 Postoperative Management

13.7.1 Monitoring

Monitoring of these patients is simple and includes continuous ECG, cardiac and respiratory rate, oxygen saturation, and eventually NIRS. Central and arterial lines are seldom required unless patients are unstable or have supplementary risks or associated defects.

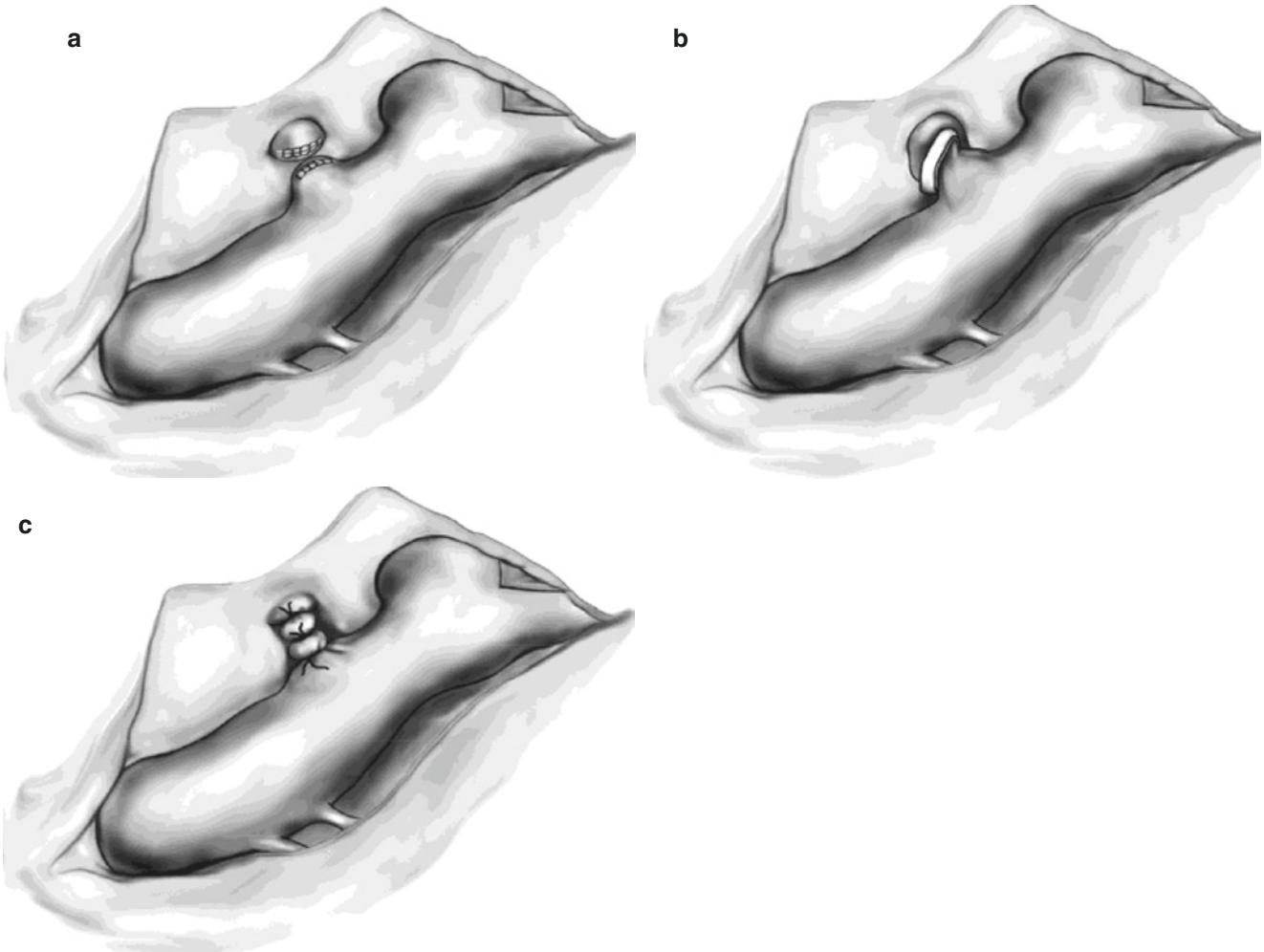


Fig. 13.6 Surgical options for repair of a PDA. Via a left posterolateral thoracotomy, or with thoracoscopy, the PDA is visualized and carefully dissected. Surgical options include (**a**) ligation and division, (**b**) hemoclip occlusion, or (**c**) ligation

13.7.2 Fluid Management

PDA closure is a close heart intervention and therefore fluids are to be administered at the physiological rate, except in patients with severe cardiac failure of volume overload in whom fluid restriction may be indicated and customized to the patient's physiology.

13.7.3 Sedation and Analgesia

Thoracotomies are particularly painful and close attention is needed with regards to analgesia. Sedation and analgesia should be provided in order to keep patients comfortable and free of pain and yet with spontaneous breathing allowing early extubation. The use of nonopioid medications decreases the required doses of opioids (morphine or fentanyl) that are usually administered with low dose of benzodiazepines for the amnestic effect. In patients above 5 years of age, concomitant use of NSAIDs, patient-controlled analgesia opioid administration, or epidural analgesia may be considered.

13.7.4 Respiratory Management

After PDA closure, airway management varies with the clinical circumstances. Premature neonates may require a delayed extubation owing to their co-morbidities and possibly lack of respiratory drive or maturity. In older patients, extubation may take place in the operating room or else during the first few postoperative hours in the intensive care unit. Most patients are managed under a fast-track algorithm. In the unlikely occurrence of immediate failure of extubation, suspicion of phrenic or recurrent laryngeal nerve insult should be raised.

13.7.5 Inotropic and Vasodilator Management

After surgical closure of the PDA, patients exceptionally need inotropic and vasodilator support. If required, dopamine would be the elective option.

13.7.6 Anticipated Potential and Rare Complications

PDA closure by surgical techniques may be associated with:

(a) Bleeding
(b) Horner's syndrome
(c) Diaphragmatic paresis and palsy (phrenic nerve lesion)
(d) Vocal chordae palsy (laryngeal-recurrent nerve lesion)
(e) Chylothorax
(f) Residual shunt
(g) Re-permeabilization
(h) Ligation of the aorta/left pulmonary artery
(i) Aortic coarctation

Interventional catheterizations for PDA closure, on the other hand, may be at risk for the following:

(a) Bleeding
(b) Blood vessel injury
(c) Arrhythmias
(d) Vascular occlusion
(e) Device migration
(f) Residual shunt
(g) Hemolysis

13.8 Outcomes

Patent ductus arteriosus treatment in older patients carries very low risks and the long-term outcomes are favorable. In neonates and mostly in those with very low weight or extreme prematurity, medical and surgical treatments have been variably associated with neonatal morbidities and neurodevelopmental impairment. Meta-analysis, although affected by potential bias due to important pre-interventional confounders and co-morbidities, seem to suggest that when compared to medical treatment, surgical ligation is associated with increases in neurodevelopmental impairment, chronic lung disease, and severe retinopathy of the premature, but with a reduction in mortality [37]. In general, literature shows that over the last few years, there is a trend to approach PDA with a more conservative and less interventional stance [15, 38].

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Chapter 14
Atrial Septal Defects

Eduardo M. da Cruz, Steven P. Goldberg, Lisa B. Howley-Willis, and Deborah Kozik

Abstract Atrial septal defects (ASD) represent a varied spectrum of deficiencies in the interatrial septum, ranging from common forms existing in as many as 1 in 1500 births (even higher if considering a pathologically patent foramen ovale under the same umbrella) to relatively uncommon ones, like the vestibular type ASD (Backer and Mavroudis. *Pediatric Cardiac Surgery*. 3rd ed. Philadelphia: Mosby, 283–297, 2003; Sharratt et al. *Cardiol Young* 13:184–190, 2003). The ASD holds a unique position in the story of congenital heart defects, as it was the subject of the very first open cardiac operation in history, as well as being the vanguard of the modern revolution in catheter-based correction of intracardiac defects. This chapter reviews the diagnosis and management of these entities.

14.1 Introduction

Atrial septal defects (ASD) represent a varied spectrum of deficiencies in the interatrial septum, ranging from common forms existing in as many as 1 in 1500 births (even higher if considering a pathologically patent foramen ovale under the same umbrella) to relatively uncommon ones, like the vestibular type ASD [1, 2]. The ASD holds a unique position in the story of congenital heart defects, as it was the subject of the very first open cardiac operation in history, as well as being the vanguard of the modern revolution in catheter-based correction of intracardiac defects.

Atrial septal defects may be diagnosed as isolated anomalies or associated with other cardiac defects or with syndromes (i.e., Lutembacher syndrome when associated with mitral stenosis), sometimes linked to familiar traits (i.e., the Holt-Oram syndrome).

14.2 Embryology

The complete atrial septum actually represents the culmination of a complex interplay between formation and resorption of various parts of two individual septa. Beginning around the fourth week of gestation, the *septum primum* begins to descend from the roof of the primitive common atrium, dividing it into two on its way to meet the endocardial cushions arising from below, which partition the ventricles (Fig. 14.1a). The *ostium primum* is the gap that remains between the inferior rim of the septum primum and the endocardial cushions. As this gap closes, in order to continue to allow interatrial mixing, the superior portion of

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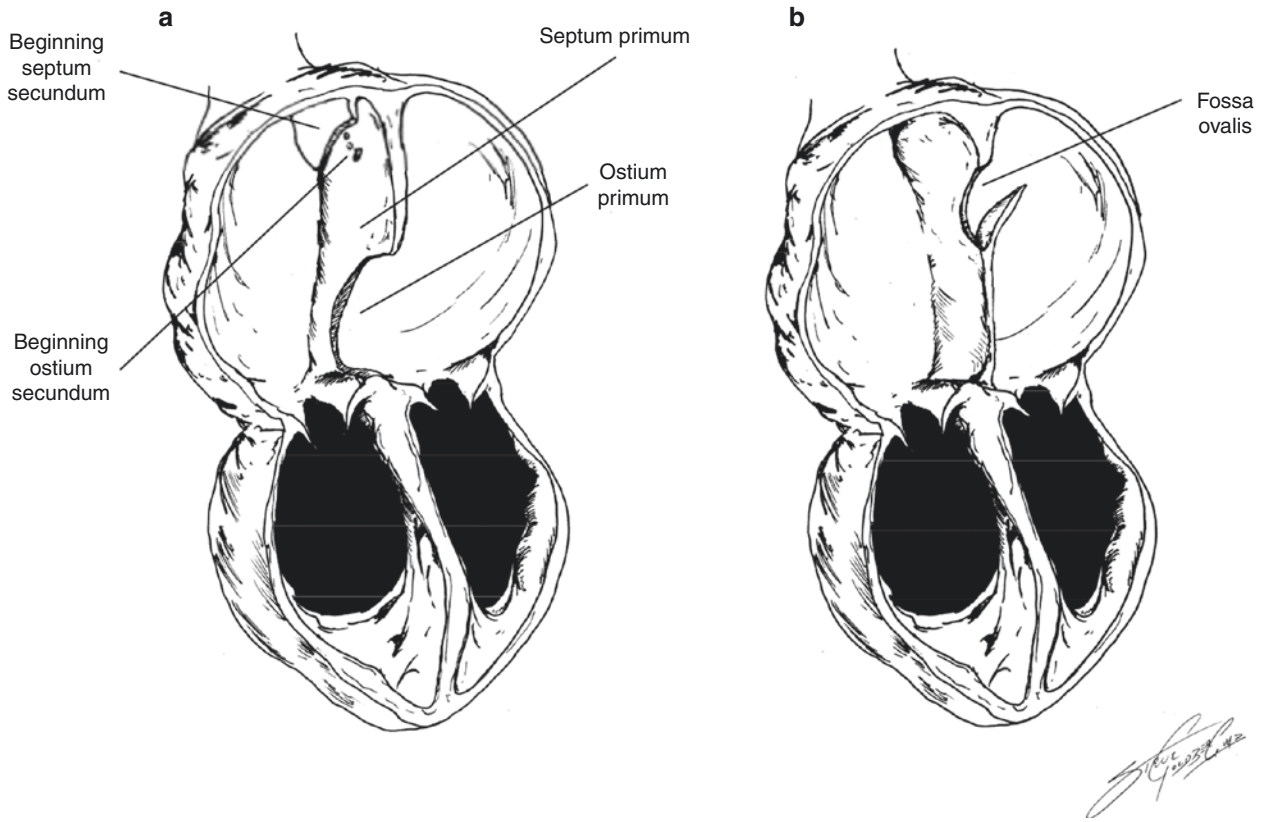

Fig. 14.1 (**a**) The septum primum partitions the common atrium. As the septum secundum forms, the ostium secundum begins as a vacuolization of the septum primum. (**b**) Fusion of both septa, except for the flap-valve mechanism of the fossa ovalis

the septum primum begins to resorb, leaving behind the *ostium secundum*. Contemporaneously with this, by the sixth week of gestation, the *septum secundum* likewise descends, curtain-like, from the atrial roof, on the "right atrial" side, finally closing off the remaining ostium primum. As it does this, however, it courses around the ostium secundum, leaving behind the flap-valve mechanism of the *fossa ovalis* (Fig. 14.1b). Save for this offset valve-like apparatus, the mature septum is a fusion of the two parallel primitive septa [3]. The common forms of an atrial septal defect, then, depend on failures at different points in this stepwise process.

14.3 Anatomy

The most common morphological subtype of ASD (80%) is the *ostium secundum defect* (Fig. 14.2a), which sits relatively centrally within the atrial septum, and can form as either a failure of septum secundum tissue to cover the ostium secundum, or as a result of excessive resorption of septum primum tissue, leaving too large a gap.

Ten percent of ASD are an *ostium primum defect* (Fig. 14.2b), representing a closure failure of the ostium primum at the base of the septum. This defect, with its nearly ubiquitously associated cleft in the mitral valve, constitutes the *partial* form of *atrioventricular septal defects*, as the absence of a ventricular septal defect and the existence of anatomically separate right and left atrioventricular valves distinguish it from the *complete atrioventicular septal defect (CAVSD)*, which is discussed elsewhere in the book.

An additional nearly 10 percent fall under *sinus venosus defects* (Fig. 14.2c), which lie high in the superior-posterior aspect of the atrium, and as such are almost invariably associated with some form of *partial anomalous pulmonary venous connection* (PAPVC). In the commonest configuration, one or more right upper lobe pulmonary veins enter the right atrium (RA), either at the junction of the superior vena cava (SVC) with the RA, or more cephalad in the SVC itself.

The rarest ASD forms are the *unroofed coronary sinus*, in which the wall separating the left atrium from the posteriorly coursing coronary sinus is obliterated, and the markedly desaturated venous effluent from the coronary sinus empties directly into the left atrium, making its way to the right atrium by way of the septal orifice of the coronary sinus itself [4, 5] and the *vestibular ASD*, seldom described in literature [2, 6, 7].

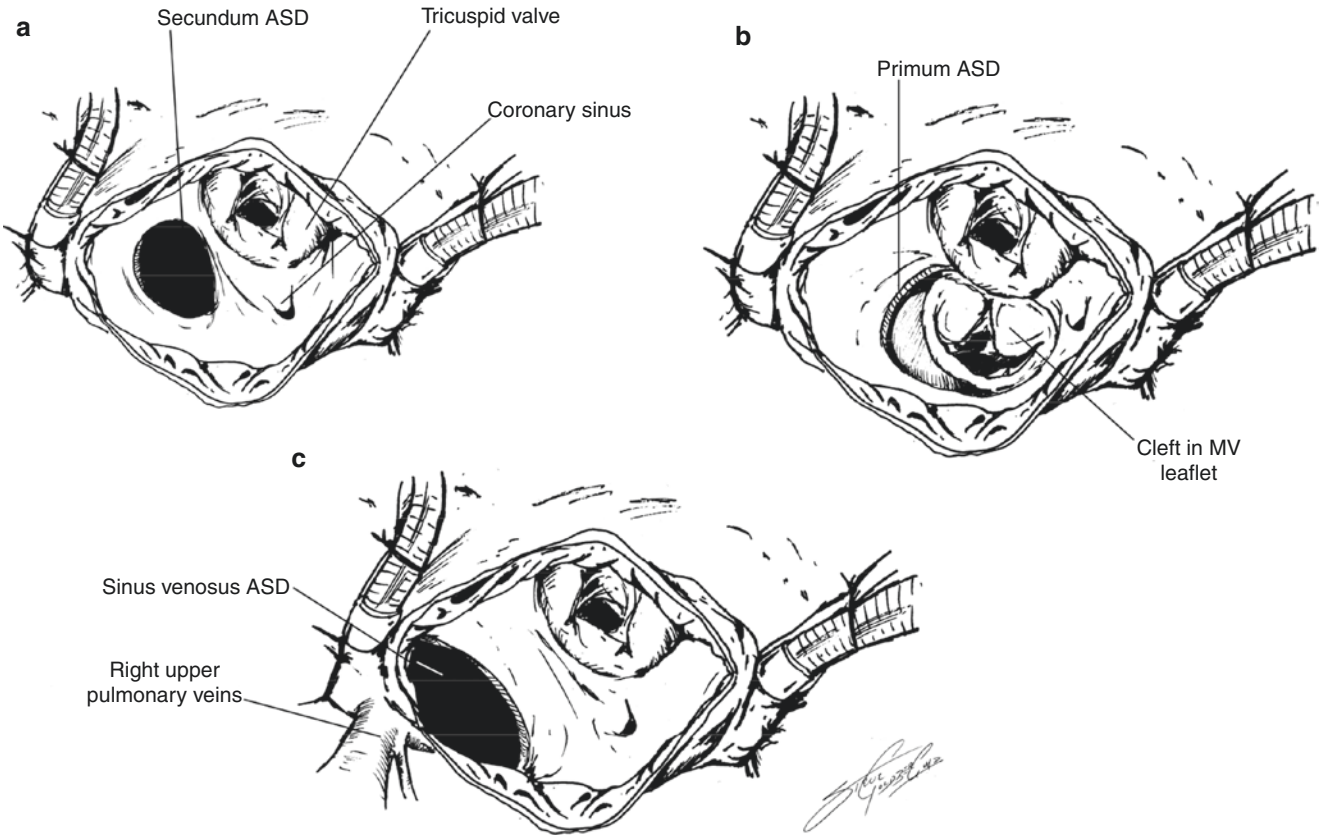

Fig. 14.2 The three major types of atrial septal defect (ASD). All views are in surgical orientation, viewed through a right atriotomy. Venous cannulas are shown in the superior and inferior vena cavae: (**a**) Secundum ASD; (**b**) Primum ASD (showing cleft in mitral valve leaflet); (**c**) Sinus Venosus ASD (showing anomalous drainage of right upper lobe pulmonary veins)

14.4 Pathophysiology

The main pathophysiological consequence of ASD is the presence of an intracardiac shunt. This shunt flow is overwhelmingly left-to-right owing to the differential pressures and compliance in the two sides of the heart, yielding excessive pulmonary blood flow and an elevated Q_p:Q_s ratio. The magnitude of the shunt is only accentuated with the usual post-neonatal fall in pulmonary vascular resistances (PVR). The right ventricle (RV) is volume overloaded, and becomes both dilated and hypertrophic. The enlargement of the RV bulges the ventricular septum leftward, impinging upon the left ventricular cavity, and eventually although rarely impairing the left heart function. Additionally, the RV hypertrophy increases the wall stress and diastolic pressure, impeding filling of the subendocardial coronary vasculature in diastole. In the long term, right atrial distension is a substrate for dysrrhythmias such as atrial fibrillation and flutter. The excessive pulmonary blood flow, over time, does lead to pulmonary vascular disease and an elevated PVR if the ASD is not corrected in adulthood, but to a lesser degree than in unrestrictive ventricular septal defects [1, 5, 8].

When associated with mitral cleft or other forms of endocardial cushion defects, there may also coexist crossed shunts (i.e., left ventricle-to-right atrial shunt) and various degrees of mitral regurgitation leading to postcapillary pulmonary hypertension.

14.5 Diagnosis

14.5.1 Clinical

Clinically, children presenting with an ASD may be asymptomatic or discretely symptomatic on exertion, with easy breathlessness, tachypnea, and sinus tachycardia.

Clinical examination will reveal a fixed split second sound, made evident on sustained inspiration and explained by the volume overload of the pulmonary circulation delaying closure of the pulmonary valve. Auscultation will also document a functional pulmonary systolic murmur due to the excessive Q_p:Q_s, and possibly a diastolic rumble across the tricuspid valve mimicking that of tricuspid stenosis.

14.5.2 ECG

Electrocardiographic features of an ASD are essentially those of right atrial enlargement and RV hypertrophy and right deviation of the electrical axis (+100 degrees). A first-degree atrioventricular block and an rSR' pattern may also be identified. The background rhythm is usually sinus. In the presence of endocardial cushion defects, the QRS axis will vary between −30 and −120 degrees.

14.5.3 Chest X-Ray

Chest roentgenography demonstrates cardiomegaly, and possibly plethoric pulmonary hilar vessels, right atrial enlargement and right ventricular dilatation.

14.5.4 Echocardiography

The essential mainstay of diagnostic evaluation is the echocardiography (Figs. 14.3, 14.4, 14.5, 14.6, and 14.7). Two-dimensional imaging is excellent at:

(a) Delineating the anatomic features of ASD, the exact diameter and shape, as well as the characteristics of the surrounding septum, aortic roof, coronary sinus, mitral valve, and pulmonary veins (fundamental for the assessment during the percutaneous closure)
(b) Following the course of pulmonary venous drainage
(c) Determining the degree of diastolic overload, degree of right-sided dilatation, and the presence of a paradoxical

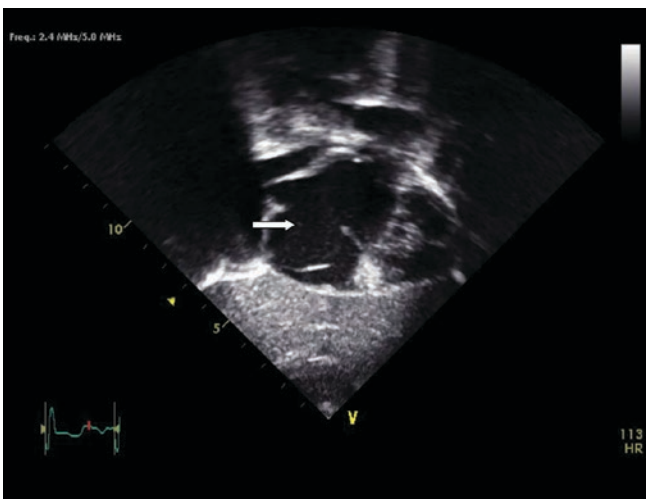

Fig. 14.3 Transthoracic echocardiography showing a large ostium secundum type ASD

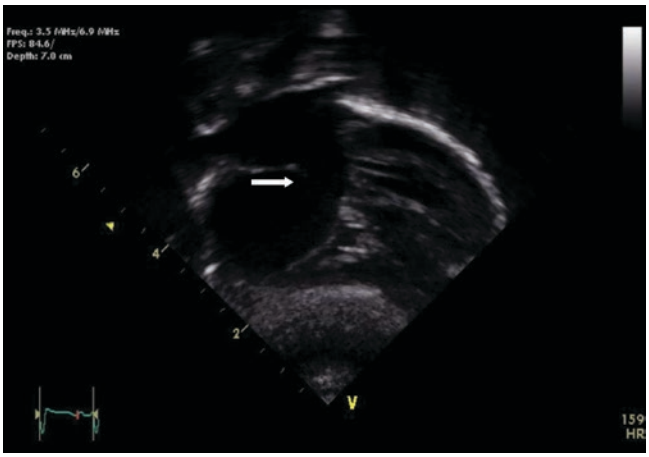

Fig. 14.4 Transthoracic echocardiography showing a large ostium primum type ASD

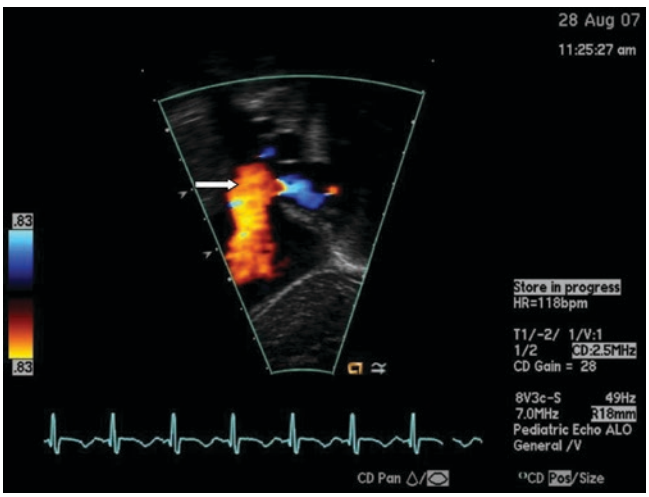

Fig. 14.5 Transthoracic echocardiography showing a large sinus venosus type ASD

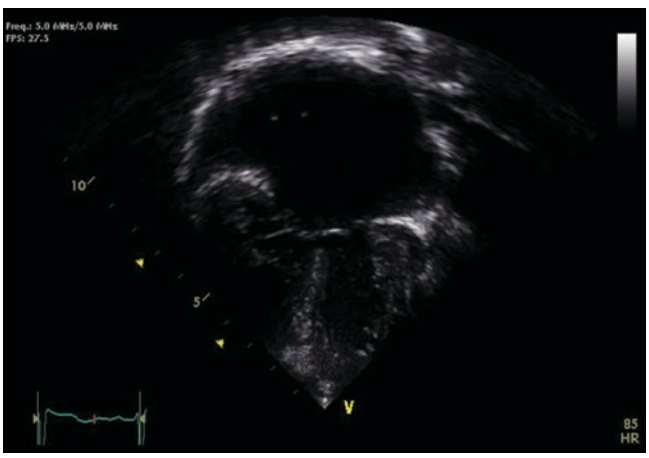

Fig. 14.6 Transthoracic echocardiography showing a single atrium

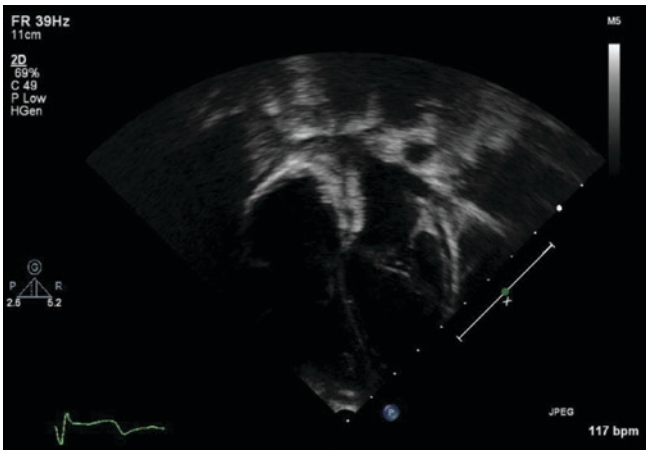

Fig. 14.7 Transesophageal echocardiography documenting the adequate position of an Amplatzer® device after delivery. Note that pulmonary veins, the mitral valve, and the coronary sinus are unobstructed by the device

motion of the interventricular septum that is usually present

(d) Evaluating for associated defects

Color-flow Doppler interrogation is indispensable in quantifying the magnitude of the shunt, as well as examining the degree of mitral incompetence in ostium primum defects or other anomalies with cleft anterior mitral leaflets.

Transesophageal echocardiography is useful to assess the defect in the perioperative setting and to follow the percutaneous closure of atrial septal defects and may be essential to visualize the anatomy in large-sized individuals in whom the transthoracic imaging is technically limited.

3-D echocardiography may also offer a number of useful anatomic information instrumental in taking therapeutic decisions and in following percutaneous or surgical closure of the defect. For the same purpose, intravascular echocardiography may also be useful in grown-up patients.

14.5.5 Cardiac Catheterization

With the quality of echocardiographic imaging in the modern era, there is limited role for cardiac catheterization in the routine diagnostic evaluation of an ASD. Indications for catheterization currently are:

(a) Complementary in the diagnosis of ASD with suspected pulmonary hypertension or reactivity

(b) Evaluation of other associated defects

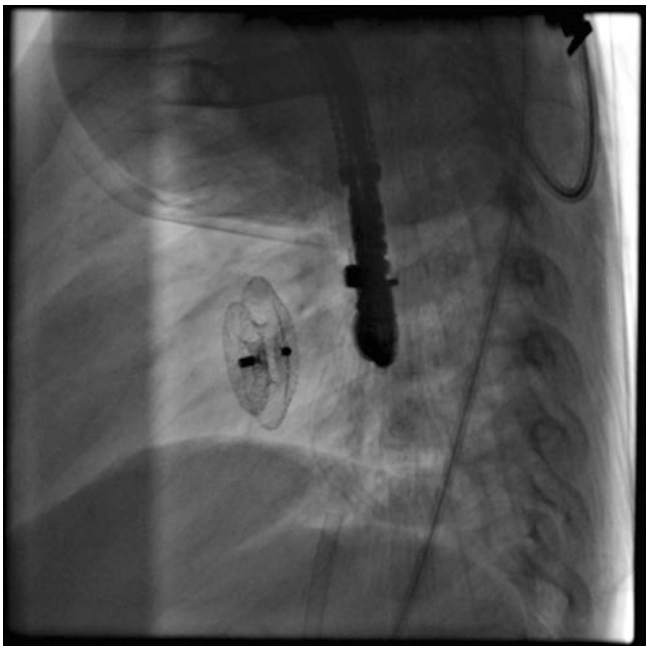

Fig. 14.8 Percutaneous ostium secundum ASD closure: Amplatzer device in situ after delivery

(c) Trans-catheter or percutaneous closure of the ASD itself (Fig. 14.8) [1, 5, 8].

14.5.6 Others

CT scans and cMRI do not add significantly to findings of echocardiography.

14.6 Indications for ASD Closure

ASD that are smaller than 4 mm have been known to undergo spontaneous closure, whereas those larger than 8 mm are far less likely to close on their own [9]. Generally accepted upon indications for intervention are uncomplicated defects with a Q_p:Q_s of 1.5:1 or greater, or echocardiographic evidence of right heart overload.

Most children are repaired by 1–5 years of age, ideally before they begin school. Earlier repair definitely correlates with improved long-term survival, compared to those corrected in adulthood.

Contraindications to closure are few, but irreversible pulmonary hypertension, defined as a PVR of 8–12 Wood units/m^2 that does not decrease to at least 7 with pulmonary vasodilatory maneuvers (e.g., 100% oxygen, inhaled nitric oxide), is the principal one, as the right heart would lose its mechanism to decompress elevated pulmonary pressures [8].

Closure may be achieved by *percutaneous or transcatheter procedures* or by *open heart surgery*. Ostium secundum ASD are the main anatomic forms eligible for percutaneous closure. Ostium primum and sinus venosus ASD or forms with significant associated cardiac defects require a mandatory surgical approach.

14.7 Percutaneous Closure

There has been a paradigm shift in recent years in the management of uncomplicated secundum ASD, with a greater number of children able to have their defects closed in the catheterization laboratory with an increasing array of available occlusion devices. One of the more commonly used devices is the Amplatzer (AGA Medical, Golden Valley, Minnesota), which consists of two disks (the larger of the two rests on the left atrial (LA) side to hold it in place with higher LA pressure) connected by a central stalk that bridges the defect (Fig. 14.9). Success with devices such as these ranges from 80 to 95%, but there is a size limit to industry-made devices, and there must be a sufficient rim of atrial tissue on which to land the disks [10]. Case reports appear periodically of dislodgement and embolization of occluder devices, to either side of the circulation [10, 11]. As mentioned above, because of the anatomical features associated with ostium primum and sinus venosus defects, transcatheter closure is not used for these defects.

14.8 Surgical Management

Atrial septal defects were the first intracardiac conditions to be addressed surgically. Correction of ASD in the pre-cardiopulmonary bypass era was challenging, and included creative solutions by way of a mostly closed atrium. In 1952, Floyd Lewis and Mansour Taufic at the University of Minnesota used surface hypothermia and inflow occlusion to rapidly (5.5 minutes) suture close an ASD in a young girl, the first time anyone operated inside a human heart [12]. With the advent of cardiopulmonary bypass in 1955 by John Kirklin, the modern era of closure of all manner of ASD had finally arrived [13].

Currently, of those secundum defects that are referred for surgical rather than percutaneous closure, many can be closed primarily by suturing the rims of the defect together. There is usually enough laxity in the tissues to allow for secure closure without tension. The other common technique is patch closure with a segment of autologous pericardium that is harvested promptly after opening the chest (Fig. 14.10). Care is taken in excising the pericardial patch to avoid injury to either phrenic nerve. The operation is conducted on full cardiopulmonary bypass, usually cooling to only mild hypothermia (28–32 °C), with cardioplegic arrest of the heart. There is usually enough distance between the inferior rim of the defect and the atrioventricular node as to make iatrogenic heart block an exceedingly rare occurrence. One important potential complication is inadvertent incorporation of the Eustachian valve of the inferior vena cava (IVC) into the inferior lip of the patch (an area that can be difficult to see due to traction from the IVC cannula), which diverts systemic venous blood from the IVC into the left atrium, causing marked desaturation. Prompt recognition of this is vital, and the only treatment is a return to cardiopulmonary bypass and revision of the patch.

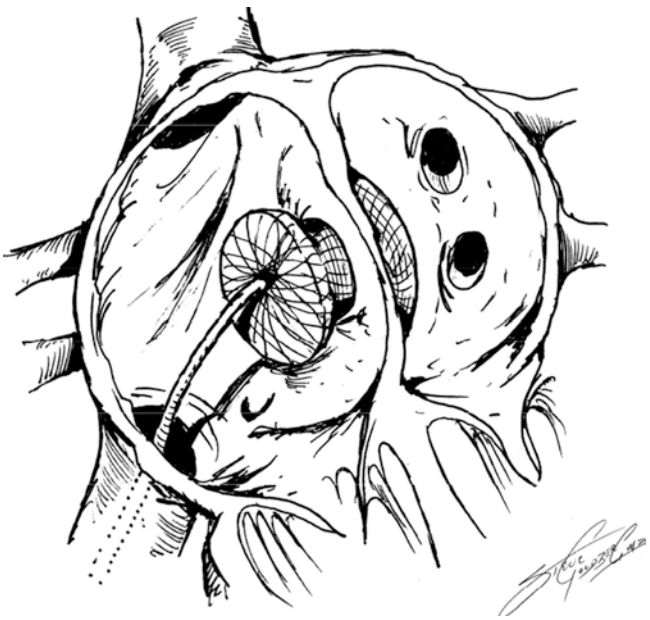

Fig. 14.9 Amplatzer occluder device closure of a secundum ASD

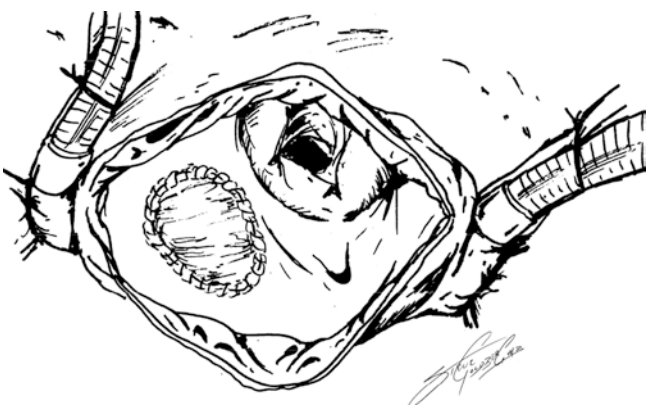

Fig. 14.10 Pericardial patch closure of a secundum ASD

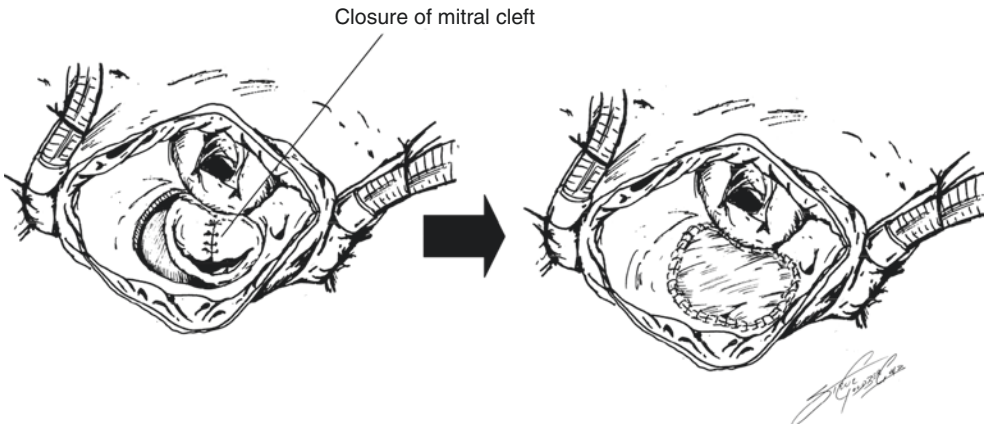

Fig. 14.11 Closure of mitral valve cleft, followed by pericardial patch closure of a primum ASD

Repair of ostium primum ASD mandates a patch, as the size and location of these defects are not amenable to primary closure. The cleft in the mitral valve is sutured closed to restore competency to the valve, prior to closing the atrial septum (Fig. 14.11). Pericardium is favored in these cases over prosthetic material, as a regurgitant jet from the mitral valve striking artificial material has a higher risk of serious hemolysis. The atrioventricular node in ostium primum defects is displaced inferiorly and posteriorly (as the triangle of Koch no longer exists), and great care is taken when carrying the suture line around the region of the coronary sinus. As complete heart block is a legitimate concern, some surgeons favor carrying the patch way laterally around the coronary sinus, which would then put it inside the left atrium. The resultant right-to-left shunt is usually well tolerated.

Sinus venosus defects require a patch as well, in order to re-direct, or "baffle" the anomalous pulmonary veins back into the left atrium. If the entry of the veins is relatively close to the SVC-RA junction, the patch can be carried superiorly into the lumen of the SVC (Fig. 14.12), capturing the anomalous veins within the pericardial baffle, and allowing the SVC to drain normally into the RA. Two anatomical considerations mandate a change in strategy however: (a) potential luminal compromise of SVC drainage by a protruding patch, and (b) entry of the anomalous veins high in the SVC. One alternate plan is to use a second patch to augment the SVC; the other is to perform a *Warden procedure* (Fig. 14.13) [14]. The SVC is divided above the level of entry of the anomalous pulmonary veins. The ASD is then patched to include the native orifice of the SVC, which now is simply the point of entry of the pulmonary veins into the LA. The cephalad SVC, still responsible for systemic venous drainage, is then re-anastomosed to the RA appendage, restoring normal return to the right atrium.

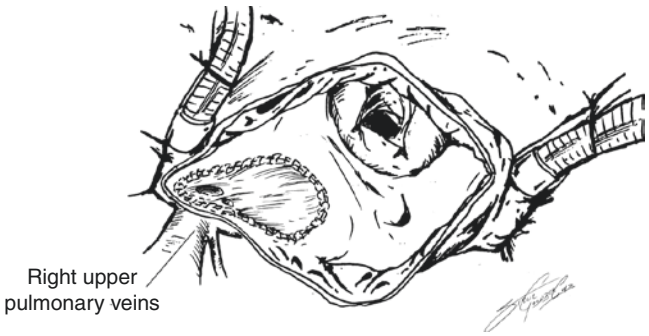

Fig. 14.12 Patch closure of a sinus venosus ASD, re-directing the pulmonary veins to the left atrium

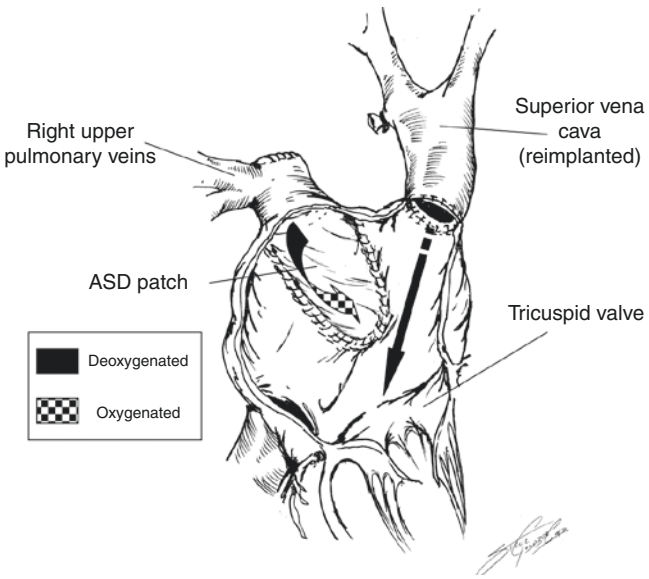

Fig. 14.13 The Warden procedure: the ASD is patched, baffling the anomalous pulmonary veins to the left, while the divided SVC is reimplanted in the right atrial appendage

14.9 Postoperative Care

After percutaneous ASD closure, patients seldom require ICU admission. Their post-interventional management consists essentially of pain control and anticoagulation with intravenous heparin until resuming enteral feeding and initiating oral antiplatelet therapy. Patients in their postoperative period of surgical ASD closure are admitted to the CICU, usually for a short length-of-stay and even if operated under a fast-track protocol.

14.9.1 Monitoring

Monitoring is customarily by continuous ECG, cardiac and respiratory rate and oxygen saturation, an arterial line, a central venous line, and occasionally a pulmonary artery line or a Swan-Ganz catheter if there are concerns about elevated pulmonary pressures.

14.9.2 Fluid Management

Postoperative fluid management is the same as for any case involving cardiopulmonary bypass – one-half of the age – and weight-appropriate amount of maintenance fluids because of the obligatory total body volume overload from the pump oxygenator. So, immediately upon return from the operating room, it is recommended to set a goal of total fluid administration at 30–50% of maintenance requirements calculated by weight, to be increased to 75% on day 1 and to 100% on day 2.

In older children, ASD closure may be performed with hemodilution techniques. These patients remain relatively anemic and a careful control of fluid intake is required in order to avoid the need for transfusion of blood products.

14.9.3 Sedation and Analgesia

After an ASD closure, the objective is to maintain patients comfortable, free of pain and anxiety, and yet with spontaneous breathing and efficient cough. Non-opioid pain control should be promptly started and associated with either NSAIDs as soon as surgical bleeding has been ruled out. The use of low-dose opioids (morphine or fentanyl) associated with benzodiazepines has proved useful during the first 48 hours of postoperative course and as required. In patients beyond 5 years of age, patient-controlled analgesia opioid infusions are very useful. Epidural analgesia is also an interesting option to be considered in this group of patients.

14.9.4 Inotropic and Vasodilator Management

Inotropic support is seldom required. Whenever necessary, a low dose of dopamine (2–5 μg/kg/minute) and/or milrinone (0.5–0.75 μg/kg/minute) is the most commonly used.

14.9.5 Respiratory Management

Most children undergoing repair of uncomplicated ASD can often be extubated in the operating room or shortly after arrival to the intensive care unit. For this purpose, it is essential to use sedation protocols that allow spontaneous breathing.

Chest tube drainage is observed closely. The mediastinum is drained postoperatively, but the presence or absence of tubes in the pleural cavities is dependent upon whether either pleural space was entered at the time of surgery (e.g., during sternotomy, pericardial patch harvest, etc.). There are no set standards for what amount of chest drainage necessitates a return to the operating room, but a generally agreed upon guideline for acceptable drainage is <1 ml/kg/hour.

14.9.6 Others

Temporary epicardial pacing wires are often not necessary in routine secundum or sinus venosus ASD, but are often left if there were intraoperative arrhythmias encountered when coming off cardiopulmonary bypass. Because of the suture lines for a primum ASD that course along the vicinity of the conduction bundle, pacing wires are usually included in those cases.

Routine anticoagulation is not necessary in children, but adults (particularly over 40) are more susceptible to atrial arrhythmias and thromboembolic events and should be fully anticoagulated with warfarin for approximately 3 months.

14.10 Anticipated Complications

Postoperative complications are exceptional after an ASD closure. Some arrhythmias like sinus node dysfunction, junctional ectopic tachycardia, or complete AV block may occur after sinus venosus repair or in the context of more complex endocardial cushion defects. Systemic or pulmonary venous obstructions, also more likely to happen after repair of sinus venosus type ASD, may require interventional catheterization procedures or reoperation to be rectified. Grown-up patients with borderline pulmonary pressures and

resistances may also require support for pulmonary hypertension and ventricular systolic or diastolic dysfunction. Hypoxemia should motivate the search of undiagnosed systemic venous returns onto the left atrium.

Another potential worth mentioning complication is the Post-Pericardiotomy Syndrome (PPS) that curiously occurs in a significant number of cases, throughout the first postoperative month. Patients may have discrete symptoms like asthenia, fever, and chest pain and may develop a pericardial rub. They may also accumulate fluid in the pericardial sac and progress toward a cardiac tamponade physiology. Treatment is based on analgesia and NSAIDs. In refractory cases, steroids may be considered. Pericardiocentesis is required in case of tamponade or in cases refractory to medical treatment.

14.11 Outcomes

In the current era, surgical mortality is 1% or less. In infants and children, long-term survival is essentially no different from the general population [8]. Following atrial septal defect repair, subsequent long-term follow-up is indicated if there are other cardiac lesions, preoperative or postoperative atrial arrhythmias, pulmonary artery hypertension, or if the ASD was repaired during adulthood. Patients who have had the ASD repaired during childhood and who have uncomplicated early postoperative courses generally are free of late complications and activity restrictions. In terms of competitive sports, the 2015 scientific statement of the American Heart Association and American College of Cardiology (AHA/ACC) [15] provides the following recommendations:

1. Patients with untreated ASD and normal pulmonary pressure can participate in all competitive sports.
2. Patients with untreated ASD and pulmonary hypertension may participate in low-intensity (class IA) sports.
3. Patients with untreated ASD and associated pulmonary vascular obstructive disease (PVOD) with cyanosis and large right-to-left shunt should be restricted from participation in all competitive sports.
4. Patients with repaired ASD can participate in all competitive sports three to six months after closure if they have normal pulmonary pressure and ventricular function, and no arrhythmias.

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Chapter 15
Ventricular Septal Defects

Wonshill Koh, Evonne Morell, Melita Viegas, Diego Moguillansky, Traci M. Kazmerski, and Ricardo A. Munoz

Abstract Ventricular septal defects (VSDs) are the most common form of congenital heart disease (20–25% of congenital heart disease) and consist of defects in any portion of the ventricular septum. Spontaneous closure may occur in early adulthood during the first 10–15 years of life. The size and cross-sectional area of the VSD, in the initial echocardiogram, are good predictive factors to assess the likelihood of requiring surgical repair in the future. is also important, with most small muscular and perimembranous defects having a higher likelihood of spontaneous closure during the first 2 years of life. A larger VSD is often associated with other intracardiac anomalies including but not limited to coarctation of aorta, tetralogy of Fallot (TOF), truncus arteriosus, and transposition of great arteries. It is commonly associated with chromosome aneuploidies including trisomy 13, trisomy 18, and trisomy 21.

15.1 Background

Ventricular septal defects (VSDs), defects in the ventricular septum, are the most common form of congenital heart disease (20–25% of congenital heart disease) [1, 2]. Spontaneous closure may occur in early adulthood during the first 10–15 years of life [1–3]. A spontaneous decrease in the defect size may occur as well over the years. The size and cross-sectional area of the VSD, in the initial echocardiogram, are good predictive factors to assess the likelihood of requiring surgical repair in the future. Restrictive VSDs, smaller than 5–6 mm, are very likely to close or become hemodynamically insignificant [4]. The location of the defect

15.2 Anatomy

Since the first description by Henri Roger in 1879, several classifications have been published to describe VSDs [1]. The two major systems used to describe VSDs are classifications by Van Praagh, and Soto and Anderson [5–7]. Per Soto and Anderson, there are three separate components of the ventricular septum: an inlet septum, an apical trabecular septum, and an outlet/infundibular septum. A VSD is characterized perimembranous, muscular, or doubly committed juxtarterial, based on its relation to these structures (Fig. 15.1). Per Van Praagh, there are four major components of the interventricular septum, inlet (atrioventricular canal), muscular, septal band, or proximal conal

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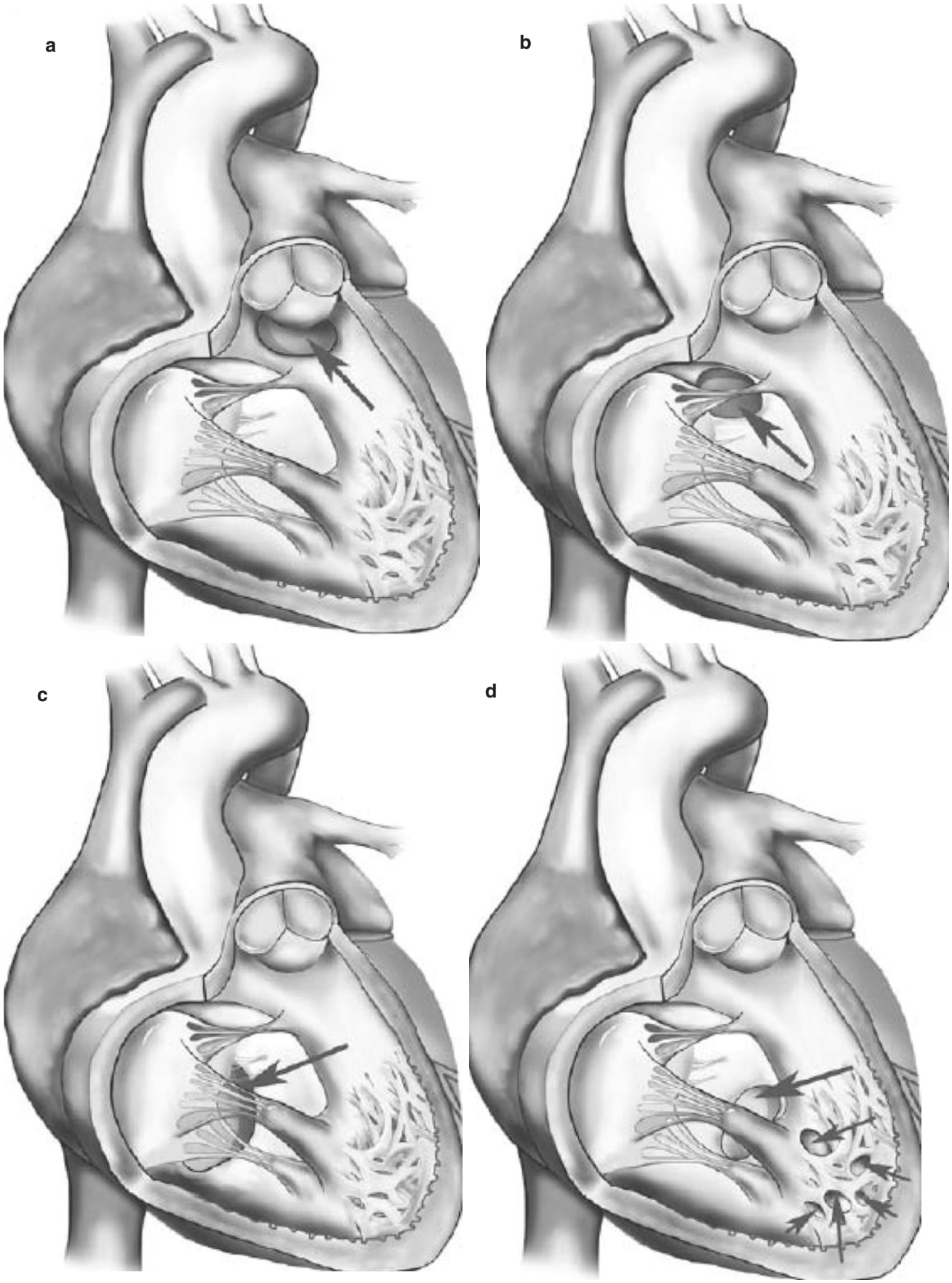

Fig. 15.1 Types of ventricular septal defects: (**a**) conoseptal/doubly committed juxtarterial, (**b**) conoventricular/perimembranous defect, (**c**) inlet, and (**d**) muscular

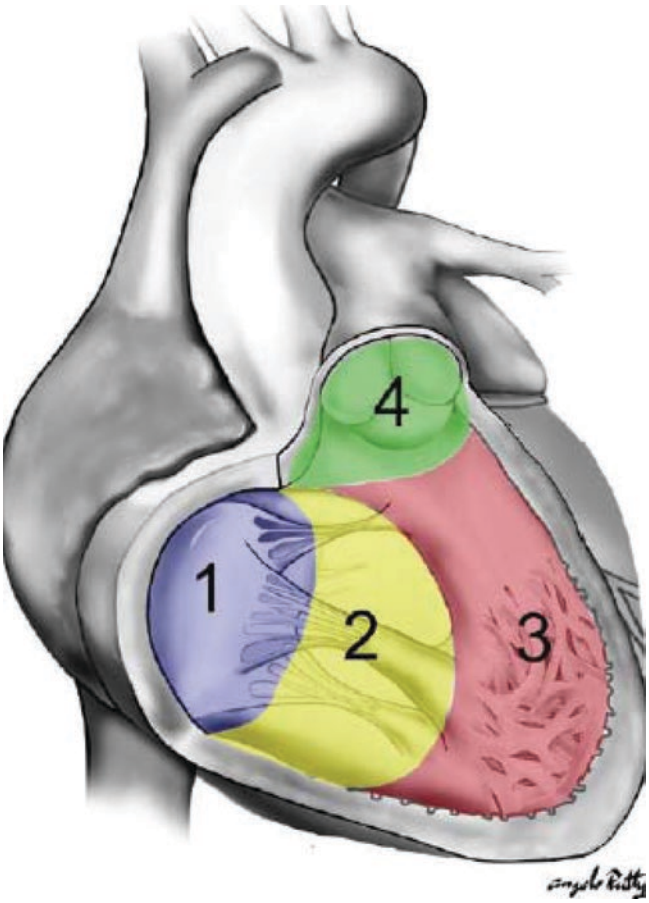

Fig. 15.2 Components of the interventricular septum: (**1**) inlet, (**2**) muscular, (**3**) septal band, and (**4**) parietal band

septum, and parietal band or distal conal septum (Fig. 15.2), and defects can be characterized in relation to these structures (Fig. 15.1). In atrioventricular canal type, the defect is located in the atrioventricular canal portion where the area of septum is formed by endocardial cushion tissue. It can be associated with abnormalities of the atrioventricular valves. Muscular VSDs are the second most common defect, accounting for 10–20% of VSDs. They consist of several subtypes—apical, central, marginal, and "swiss cheese" when multiple defects are present. With membranous VSD, the conal and ventricular sinus septa are normal, and the deficiency is anatomically restricted to the membranous septum. Conoventricular defects are located between the conal and muscular septum and are due to either hypoplastic conal septum or malalignment. A VSD due to hypoplastic conal septum is the most common VSD. They are often associated with abnormalities of the aortic valve and prolapse of aortic leaflet. They are located superior to the division of the septal band and adjacent to the junction of the septal and anterior leaflets of the tricuspid valve. The Bundle of His passes near the VSD at the posterior and inferior vertices of the defect. With malaligned conoventricular VSD, an anterior deviation of the septum causes a right ventricular outflow tract obstruction (TOF), while a posterior deviation causes a left ventricular outflow tract obstruction (VSD associated with coarctation of the aorta and/or hypoplastic or interrupted aortic arch). Conal septal defects account for approximately 5% of defects. It overlies the conal septum and is located below the pulmonary valve. It is also referred to as supracristal, subarterial, conal, infundibular, or subpulmonary defect.

There is a strong association with VSDs and double-chambered right ventricle (DCRV) [8, 9]. The presence or history of VSD has been noted in 70–90% of the DCRV cases. This rare entity results from hypertrophy of muscle bands leading to formation of a proximal high-pressure chamber and a distal low-pressure chamber within the cavity of the right ventricle.

15.3 Pathophysiology

Clinical presentation of VSDs depends on the size of the VSD, pulmonary vascular resistance (PVR), and systemic vascular resistance (SVR). The left-to-right shunt through the VSD is also influenced by the presence of other intracardiac defects such as atrial septal defect, patent ductus arteriosus, right and left ventricular outflow tract obstruction, and arch obstruction.

The size of VSD can be compared to the aortic valve and classified as small (less than 1/3 of the aortic valve annulus), moderate (more than 1/3 and less than ½ of the size of the aortic valve annulus), and large (more than ½ of the size of the aortic valve annulus). With small defects, the left-to-right shunt across the VSD is restrictive. When the defect is moderate sized, there is left heart volume load from the left-to-right shunt, but the PVR is normal or minimally elevated. When the defect is large, the flow is unrestrictive, and the left-to-right shunt will increase over time as the PVR normalizes, following the immediate neonatal period. This results in pulmonary overcirculation and a significant volume overload to the left side of the heart. If the large defect remains uncorrected, long-standing left-to-right shunt will result in pulmonary vascular obstructive disease. This will result in elevation of the PVR, and the shunt will eventually reverse, leading to cyanosis and Eisenmenger's disease.

Depending on the size of the VSD and the amount of shunting, the pulmonary artery pressure can vary from normal to systemic levels. It is important to understand that high pulmonary artery pressure does not necessarily mean high PVR.

Muscular and perimembranous defects, especially if they are small and restrictive, close spontaneously in 80% of patients. Canal type, conoseptal, and malalignment VSDs do not close spontaneously. Conoseptal/doubly committed juxtarterial and conoventricular type/perimembranous VSDs can be often associated with prolapse of one of the aortic valve cusps (the right coronary or noncoronary cusp) across the VSD. Even though this event tends to decrease the left-to-right shunt, prolapse also causes damage to the aortic valve with the development of progressive aortic regurgitation (AR). The incidence of aortic valve prolapse has been shown to be as high as 73% in patients with conoseptal VSDs and 14% in patients with perimembranous VSDs [10].

15.4 Diagnosis

15.4.1 Clinical Presentation

The clinical presentation of a VSD is determined by the size of the defect and resistance of pulmonary and systemic vascular beds.

In neonates and infants with a small VSD, a murmur is usually noted either in the newborn nursery or during a routine examination in the first few weeks of life. The murmur is holosystolic and often high pitched with a thrill (reflecting a high left-to-right gradient across the defect). In conal or perimembranous VSDs, the murmur may be most audible over the upper left sternal area with normal first and second heart sounds. If there is minimal left-to-right shunting with the Qp:Qs less than 1.5:1, patients remain asymptomatic with normal growth and development.

Infants with moderate to large defects present with symptoms of heart failure as the PVR drops at 2–6 weeks of age. These symptoms include difficulty in feeding, poor weight gain, diaphoresis, recurrent pulmonary infections, hepatomegaly, and respiratory distress due to pulmonary overcirculation. The physical examination yields a harsh pansystolic murmur best heard in the mid-sternal border that radiates throughout the entire precordium. The precordium may be hyperactive with a thrill and/or prominent RV impulse. The intensity of the pulmonic component of S2 may be normal or increased, reflecting elevated RV and pulmonary artery pressures.

15.4.2 ECG

While small VSDs do not have any abnormalities on the ECG, biventricular hypertrophy is usually seen with moderate to large VSDs.

15.4.3 Chest Radiography

Cardiomegaly (due to LA and LV dilatation) and increased pulmonary vascular markings are seen on the CXR with moderate to large defects.

15.4.4 Echocardiography

Transthoracic echocardiography (TTE) is the mainstay for the diagnosis of VSDs. Two-dimensional echocardiography combined with color and spectral Doppler, utilizing multiple imaging windows, can be used to delineate the following: to determine the size and location of the defect; relations to tricuspid, aortic, and pulmonary valves; associated right or left outflow obstruction; associated aortic valve prolapse and aortic regurgitation; evidence for volume overload (left atrium and ventricle dilation); shunt direction; estimated right ventricular and pulmonary artery pressures; and ventricular function. Intraoperative transesophageal echocardiography (TEE) can offer clarification of certain anatomic and physiological details, as well as evaluation of repair and early identification of residual defects. Three-dimensional echocardiography is becoming readily available and can offer accurate morphology of defects and other complex-associated cardiac anatomies [11, 12].

15.4.5 Cardiac Catheterization

In modern era, patients with VSDs rarely undergo cardiac catheterization as the echocardiogram is the mainstay of diagnosis for VSD [1, 11, 13–16]. The size and location of the primary defect, additional VSDs, and other associated lesions can be accurately assessed using echocardiogram. Cardiac catheterization is indicated for those with suspected or actual pulmonary vascular disease to assess PVR and test reactivity of PVR to pulmonary vasodilators. Angiography can provide additional information on the number of defects as well as size/amount of shunting of defect.

Transcatheter VSD closure can be considered in certain patients as a surgical alternative [17, 18]. It has been mostly used for muscular VSDs where the locations are hard for complete surgical closure, but successful transcutaneous device closure of perimembranous VSDs has been reported as well [17–21].

15.5 Preoperative Management

The preoperative management of VSDs depends on clinical symptoms which are related to the size and location.

Small defects are usually asymptomatic and have a high likelihood of closing spontaneously. They do not usually require medical or surgical therapy.

Moderate to large defects are frequently associated with symptoms of congestive heart failure (CHF) and often require medical therapy. ACE inhibitors for afterload reduction and diuretics are often used. The use of digoxin has become somewhat controversial, but it is also still frequently used. Due to the increased caloric requirements secondary to CHF, nutritional supplementation with formulas with high caloric concentration or fortified breast milk is usually required.

If the patient is admitted to the intensive care unit, due to severe pulmonary edema, oxygen should be administered carefully as it acts as a selective pulmonary vasodilator, which may potentially increase the Qp/Qs, and worsens clinical symptoms. Diuretic therapy should be administered intrave-

nously and intravenous inotropic agents including milrinone for afterload reduction may be needed. Careful monitoring to prevent the development of electrolyte imbalances, particularly in children on digoxin and diuretics, is required.

Serial echocardiograms are often performed to evaluate ventricular function, development of pulmonary hypertension, monitor the defect size, and watch for potential complications such as aortic valve prolapse or AR.

Patients in whom the defect size does not appear to decrease or who continue to have symptoms of heart failure despite medical therapy should be considered for surgery. Symptomatic infants despite maximum medical therapy should be referred for surgical repair as soon as possible, especially given the excellent surgical results in young infants [22, 23].

A small number of patients present after having developed severe pulmonary obstructive disease and are not surgical candidates. Supplemental oxygen and partial exchange transfusions in cases of severe cyanosis, as well as prevention of iron deficiency with iron supplements, can be helpful. A subset of these patients can be considered for lung or heart–lung transplantation. Treatment of pulmonary hypertension is indicated in patients who show response to oxygen and nitric oxide and a small number of these patients can then become candidates for surgical repair, usually with a fenestrated VSD patch or small atrial communication.

15.6 Surgical Management

15.6.1 Indications for Surgical Intervention

Commonly accepted indications for surgical closure of a ventricular septal defect in infants include congestive heart failure refractory to medical therapy and large shunts that are unlikely to close. In older patients, surgical indications include Qp:Qs > 2:1, volume overload of the left side of the heart/decreased ventricular function, progressive aortic regurgitation, and/or prior history of endocarditis.

15.6.2 Surgical Technique

Surgical patch closure of the VSD has largely become the technique of choice in most centers; it requires cardiopulmonary bypass, cardioplegic arrest, and is usually performed with mild hypothermia. The majority of conoventricular, inlet, and muscular defects can be repaired with a transatrial approach (Fig. 15.3). Conoseptal defects can be closed through the pulmonary valve and/or a transverse infundibulotomy. Apical defects frequently require closure via a right (or left) apical ventriculotomy or via a transventricular hybrid approach. The surgical closure of VSDs can be performed with a very low mortality rate (<2%) and minimal sequelae. Injury to the conduction system causing irreversible complete heart block occurs in approximately 2% of patients.

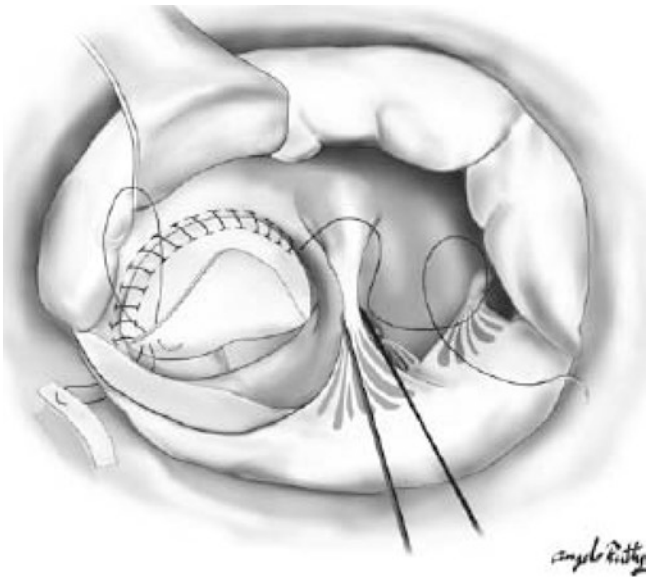

Fig. 15.3 VSD closure. Via a right atriotomy, the tricuspid valve leaflets are retracted exposing the VSD. The perimembranous VSD is closed with a prosthetic patch using a running suture technique

Given the close proximity of the VSD to several key structures, careful attention must be paid to exposure, retraction, and suture placement. When approaching any VSD, the approximation of the defect to the conduction system is very important. The sinoatrial node is located at the junction of the SVC to the right atrium. When making the right atriotomy, it is important to avoid extending the incision too superiorly to avoid the sinoatrial node as well as division of the crista terminalis which contribute to its blood supply.

Once the right atrium is open, the tricuspid valve should be carefully retracted. Visualization of the VSD can be difficult due to excess tricuspid valve tissue or crossing bands. It is often necessary to take down the septal leaflet of the tricuspid valve in order to fully appreciate the defect. Once the margins are delineated, sutures are placed on the right side of the ventricular septum. Careful attention must be paid at the superior and inferior margins of the VSD. The aortic valve is located at the superior margin of the VSD. Deep suture placement in this region leads to tethering of the aortic valve leaflet and resultant aortic insufficiency. At the posterior margin, the Bundle of His pierces the central fibrous body and tricuspid annulus before entering the ventricular septum. In order to avoid damage to the conduction system, sutures must be placed 3–5 mm away from the inferior rim of the VSD. The AV node is located within the triangle of Koch, created by the septal leaflet of the tricuspid valve, coronary sinus, and Tendon of Todaro. Superficial suture placement along the septal leaflet of the tricuspid valve will

avoid this region. It is also important to remember that in the case of inlet defects, the conduction system is displaced posterior-inferiorly. Adhering to these landmarks will lead to successful preservation of the conduction system.

When accessing the VSD via the great vessels, the same concepts apply. Via the aortic valve, the conduction system is located under the noncoronary leaflet to the mid-portion of the right coronary leaflet. Careful avoidance of this area is very important. Additionally, it is particularly important not to damage the valve leaflets with retraction or suture placement. Via the pulmonary valve, it is also important to avoid damage or tethering of the pulmonary valve during suture placement. In the case of particular conoseptal VSDs, the conduction system is remote.

If it is necessary to access the VSD via a right or left ventriculotomy, avoidance of the coronary arteries is extremely important. Limited incisions are necessary to avoid the risk of long-term ventricular dysfunction and/or arrhythmias.

Certain apical defects are best approached using a hybrid approach for closure. This can be performed via a right atriotomy or periventricular approach. It may be performed with or without cardiopulmonary bypass, depending on the location of the defect. Fully appreciating the location of the VSD will decrease the risk of heart block, residual shunt, valve damage, and embolization post-procedure.

Pulmonary artery banding (Fig. 15.4), as part of a two-stage repair, has been relegated to patients who are critically ill, have multiple VSDs, or present with associated anomalies.

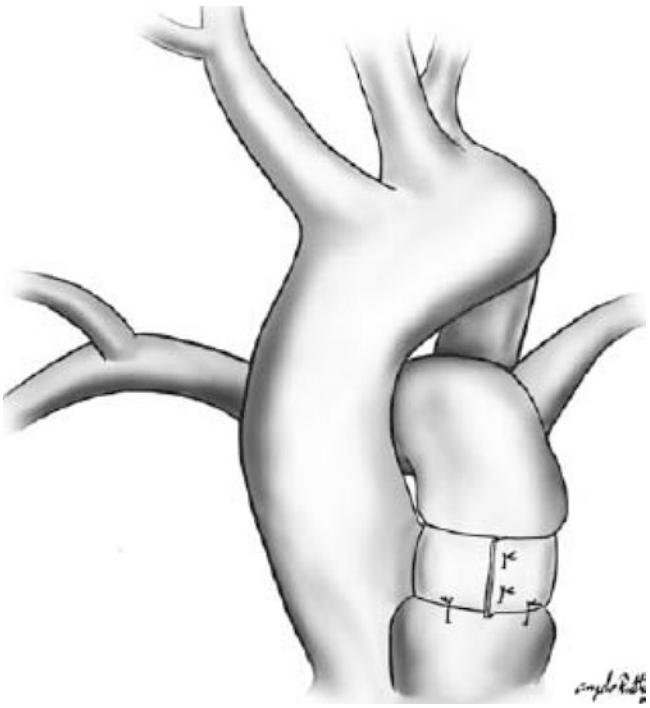

Fig. 15.4 Pulmonary artery band. Via a left thoracotomy or a median sternotomy, the "band" is placed around the main pulmonary artery restricting the pulmonary flow

15.7 Postoperative Management

15.7.1 Monitoring

Invasive monitoring including central venous and arterial lines is the standard of care. Atrial and ventricular epicardial wires are also routinely used, and can be extremely helpful in the diagnosis and treatment of postoperative arrhythmias and conduction abnormalities.

15.7.2 Cardiovascular Management

Postoperative assessment of ventricular function will determine the selection of the inotropic agent and the duration of therapy. At Children's Hospital of Pittsburgh, milrinone is usually started in the operating room and is maintained for the first 12–24 hr and then discontinued. Administration of milrinone in neonates and infants with low cardiac output after surgery lowers filling pressures, systemic and pulmonary arterial pressures, and vascular resistances, improves cardiac index, and increases heart rate without significantly altering myocardial oxygen consumption [24].

Transient or permanent complete heart block and junctional ectopic tachycardia may be seen in the immediate postoperative period. In the event of complete heart block postoperatively, patients are A-V sequentially paced (DDD mode) or V paced (VVI mode) and pacemaker wires should be periodically tested to determine threshold and sensitivities. If the patient remains in complete heart block after 7–10 days, permanent pacemaker placement should be planned.

Postoperative complications and sequelae of VSD repair are uncommon but include RV or LV dysfunction, cardiac arrhythmias, residual VSDs, and/or pericardial effusions. The use of intraoperative transesophageal echocardiography has become routine in most centers and enables early recognition and immediate postoperative care of some of these surgical complications [2, 25]. Most residual VSDs do not usually warrant reoperation. The presence of RV or LV dysfunction is rare and can be associated with poor myocardial protection during the surgery. If a ventriculotomy was performed, it may also cause RV or LV dysfunction as well as the late development of ventricular arrhythmias.

15.7.3 Respiratory Management

Most patients are frequently admitted extubated but younger infants or those with evidence of pulmonary hypertension will remain intubated. The ventilatory management of the child at risk of pulmonary hypertension is more challenging.

Cardiac catheterization data should be utilized to determine the most appropriate therapy; the combination of oxygen and inhaled nitric oxide is greatly beneficial.

15.7.4 Fluid Management

Negative fluid management is advisable during the initial 12–24 hrs following surgery, and it is important particularly in patients who are intubated or have an open chest, to facilitate sternal closure. Diuretics are routinely started 6–12 hrs after surgery.

15.7.5 Sedation and Analgesia

Pain, sedation, and anxiolysis are successfully achieved with narcotics, dexmedetomidine, and benzodiazepines. Morphine and fentanyl are the most commonly used opioids. Nonopioid therapy may be achieved with dexmedetomidine or acetaminophen. Deep sedation, analgesia, and paralysis should be employed in the patients with hemodynamically significant pulmonary hypertension.

15.8 Long-Term Outcomes

Patients with isolated VSDs overall have excellent long-term outcomes [1, 22, 23]. Patients with small defects usually have an excellent prognosis, as the majority of these defects spontaneously close in the first 2 years of life and, even if they do not, have minimal hemodynamic implications [4, 16, 26]. A small risk of endocarditis or aortic valve prolapse may exist. Patients with moderate to large defects are often symptomatic and usually require congestive heart failure therapy and repair. Most of these patients undergo surgery within 1–2 years of life with very low morbidity and mortality and experience excellent long-term results.

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Chapter 16
Complete Atrioventricular Septal Defects

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Abstract This chapter will briefly review the diagnosis and management of the complete atrioventricular defect characterized by the failure of development of the atrial and ventricular septum and a single orifice AV valve. For the complete atrioventricular septal defect, the results are a balanced pair of ventricles and atria that are essentially equal in size and dimensions.

16.1 Introduction

Complete atrioventricular septal defect (CAVSD) refers to a complex malformation of the atrial and ventricular septum and is defined by abnormal embryological development of the endocardial cushions in the atrioventricular canal resulting in maldevelopment of the atrial-ventricular valves [1].

CAVSD represents around 3% of congenital cardiac defects, and it is a frequent anomaly in the context of autosomic trisomic anomalies, particularly in patients with Down syndrome (trisomy 21) and Edward's syndrome (trisomy 18). Fifty percent of atrioventricular septal defects are diagnosed in patients with Down syndrome, and 30% of these patients have a CAVSD [2].

Steven P. Goldberg is a former attending cardiac surgeon who is deceased at the time of publication of this chapter.

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The pathophysiology of this defect and the course from diagnosis through repair, extending into the postoperative period, may be predicated upon the degree of atrial and ventricular level shunting and atrioventricular valvar dysfunction.

The term *atrioventricular defect* encompasses a wide spectrum of anatomic variants, and there is an overabundance of terms for this congenital cardiac malformation, like complete atrioventricular defect, atrioventricular canal defect, and endocardial cushion defect. There have also been many sub-classifications within this anomaly: in general, defects are described as partial, incomplete or intermediate, complete, and common atrium. Partial AVSDs, with no ventricular component, may behave physiologically as a primum atrial septal defect.

An unbalanced atrioventricular septal defect, depending on the degree of ventricular discrepancy, may be considered as a physiologic variant of a single ventricle.

This chapter will deal with the complete atrioventricular defect which we understand as characterized by the failure of development of the atrial and ventricular septum and a single orifice AV valve. For the CAVSD the results are a balanced pair of ventricles and atria that are essentially equal in size and dimensions.

16.2 Anatomy

Complete atrioventricular septal defects are characterized by the failure of the central portions of the anterior and posterior cushions to fuse. This results in the underdevelopment of the tricuspid and mitral valves or more accurately the right and the left atrioventricular (AV) valves [2–5]. The anatomic expression of this deficit is quite variable. However, in most patients with CAVSD, the endocardial cushion defect is positioned so that there is relatively equal opening into the right and left ventricles. When this is not the case and there is a left or right ventricular dominance with regard to flow through the orifice, the result is a functional single ventricle physiology.

The main components of the CAVSD are as follows (Fig. 16.1):

1. A *ventricular septal defect*: in the inlet area, that is unrestrictive in the case of the CAVSD or restrictive in the case of an intermediate or incomplete atrioventricular septal defect.
2. An *atrial septal defect*: most commonly an ostium primum type atrial defect or a common atrium, almost always associated with a mitral cleft; an ostium secundum atrial septal defect may also be associated.

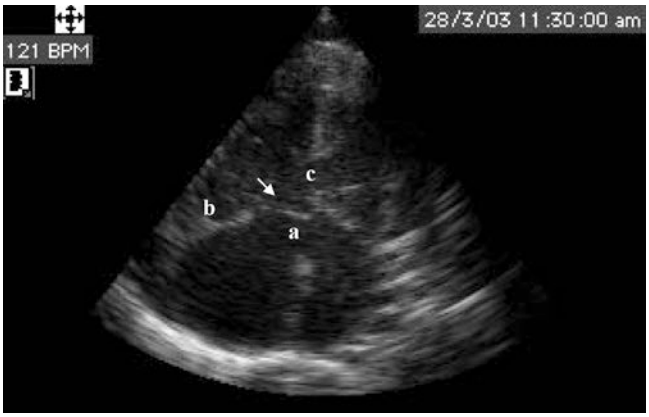

Fig. 16.1 Echocardiographic four-chamber view showing the main components of the complete atrioventricular canal: ostium primum atrial septal defect (**a**), single atrioventricular valve (**b**), and ventricular septal defect (**c**) with a mitral cleft (arrow)

3. *Anomalous atrioventricular valves*: the atrioventricular annulus is shared by both ventricles, and there are usually five components with different degrees of dysplasia, a left-sided "mitral" cleft, and an abnormal subvalvular apparatus with different types of insertions. This anatomic feature was classified by Rastelli (Fig. 16.2). In 4 to 10% of cases, there may be an accessory mitral orifice.
4. Various degrees of *left ventricular outflow tract obstruction*: often described as a "swan-neck" obstruction.

The CAVSD may be associated with other cardiac or extra-cardiac malformations:

1. Other associated cardiac defects:
   - Persistent ductus arteriosus
   - Conotruncal anomalies (tetralogy of Fallot, double outlet right ventricle, truncus arteriosus)
   - Aortic coarctation
   - Left superior vena cava (LSVC)
   - Heterotaxy
2. Associated extra-cardiac defects:
   - Renal
   - Osteoarticular
   - Intestinal
   - Other malformations related to specific chromosomal anomalies

Some malformative associations contraindicate a surgical total repair and confine the indications to palliation and eventually to a univentricular-type repair:

1. Multiple ventricular septal defects
2. Unbalanced ventricular cavities
3. Extra-cardiac contraindications

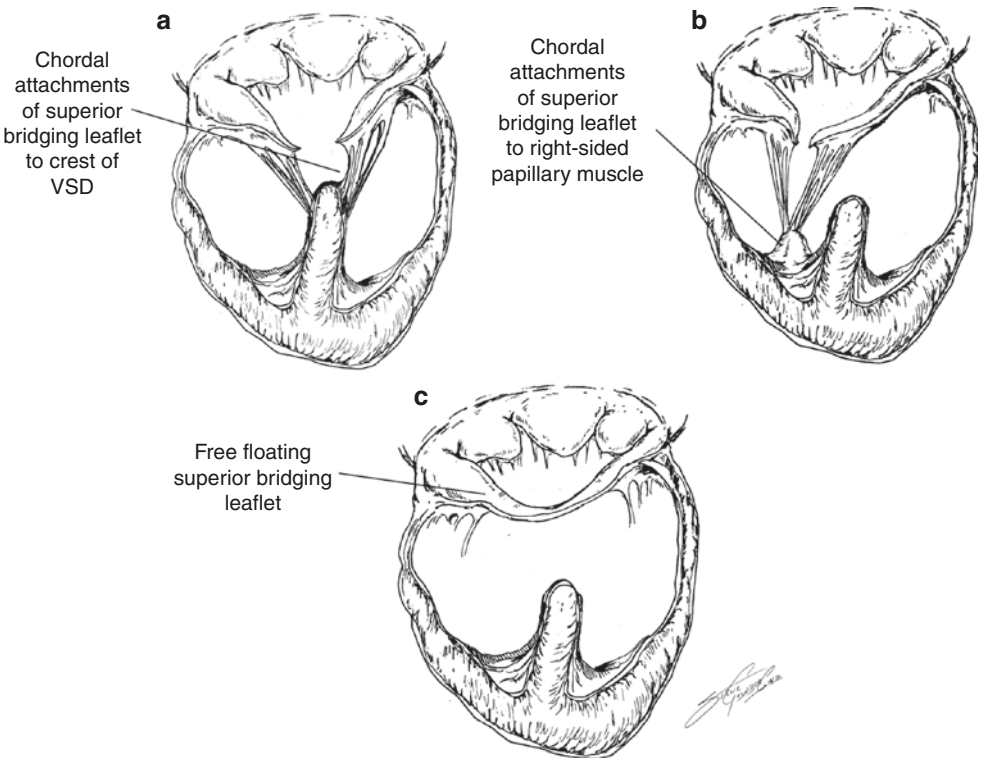

Fig. 16.2 Rastelli's classification of CAVSD

16.3 Pathophysiology

The newborn with CAVSD can be expected to develop signs and symptoms of congestive heart failure within 4–8 weeks of life as the pulmonary vascular resistances (PVR) fall [6, 7]. In cases of persistently elevated PVR as commonly seen in infants with CAVSD and Trisomy 21, congestive heart failure may develop more slowly; however, these infants may be more profoundly cyanotic and thus declare themselves to be suffering from congenital heart disease immediately after birth.

The main pathophysiological characteristics of the CAVSD may be schematized as follows:

1. Shunts:
   (a) Left-to-right at the ventricular level
   (b) Left-to-right at the atrial level
   (c) "Crossed" LV-RA and/or RV-LA shunts
   (d) Right-to-left in the setting of Eisenmenger's complex
2. Valvular regurgitation:
   (a) Mitral regurgitation: central and/or by a mitral cleft
   (b) Tricuspid regurgitation

Consequently, patients display symptoms and signs of severe left-to-right shunt with high Qp/Qs, unless pulmonary resistances are high. If, as in the majority of patients, the VSD is unrestrictive, there will be an iso-systemic, precapillary pulmonary hypertension that can be worsened by a postcapillary component when the AV valve regurgitation is significant. Patients with Down syndrome may have an exquisite pulmonary vascular reactivity adding a capillary factor to the pulmonary hypertension. This, in combination with the pre- and postcapillary components can promote fixed pulmonary resistances which can progress toward an Eisenmenger's complex early in life, if left untreated. Hence, the current practice is to preemptively repair this cardiac malformation around 3–4 months of age.

16.4 Clinical Presentation

Since the CAVSD is a mixing lesion, most infants are symptomatic soon after birth and may exhibit some degree of cyanosis until the pulmonary vascular resistances decrease. As pulmonary vascular resistances fall, the effects of a large left-to-right shunt become more apparent. Nevertheless, the clinical presentation of a CAVSD may be determined by the characteristics of the anatomic defect [7]. Usually the atrial septal defect is quite large, whereas the ventricular septal defect can be of variable size. Patients with a large atrial level component and small ventricular component may present identical to an ostium primum

defect with a large left-to-right atrial level shunt and a predominant right-sided diastolic volume overload in the absence of overt cardiac failure. In the case of a large ventricular defect with a large left-to-right shunt at the ventricular level, the presentation is likely that of left-sided or global congestive heart failure. Signs such as cardiomegaly, pulmonary over-circulation, and pulmonary edema and evidence of end-organ dysfunction may be present in patients who have symptoms of moderate to severe failure to thrive, breathlessness upon feeding, tachypnea, and tachycardia. Over time, this can progress to evolving pulmonary hypertension right-sided heart failure with elevated central venous pressures, hepatic congestion, and peripheral edema. Many of these patients are prone to recurrent airway intercurrent infections. As a matter of fact, viral infections like RSV or Influenza may be poorly tolerated.

It is worth noting that given the high association of this lesion with trisomy 21, all infants with the genetic syndrome should arouse a high index of suspicion for congenital heart disease and summarily be screened for such with a thorough clinical examination, electrocardiogram, radiography, and echocardiography.

16.5 Radiology

The chest X-ray remains an important tool in the assessment of patients with CAVSD. The classical radiological findings are consistent with the severe left-to-right shunt: moderate to severe cardiomegaly and increased pulmonary vascularization. In patients with severe pulmonary hypertension, the vascular markings may become normal, and there may even be hypoperfusion in the case of Eisenmenger's.

16.6 Electrocardiography

The electrocardiogram (ECG) of the neonate or infant with CAVSD may demonstrate:

1. QRS complex with a superior leftward axis (between −30 and − 90 degrees)
2. A QRS complex that demonstrates an rSR' pattern in the right precordial leads that is indicative of right ventricular conduction delay
3. Evidence of atrial enlargement or ventricular hypertrophy depending upon the physiologic and anatomic correlates: degree of intra-cardiac shunt, AV regurgitation, or outflow obstruction [8]

16.7 Echocardiography

Echocardiography (Fig. 16.3) is the cornerstone technique for diagnosis as it provides a complete understanding and evaluation of the CAVSD [9]. The main anatomic and physiological features to be assessed are:

1. The clear definition of the main lesions as described above
2. The degree of AV valve regurgitation
3. The ventricular balance and global function
4. The degree of shunting
5. The degree of pulmonary hypertension
6. A careful assessment of other associated cardiac malformations. Rarely is it necessary to employ any other imaging modalities prior to surgical intervention, unless there is an indication for interventional catheterization.

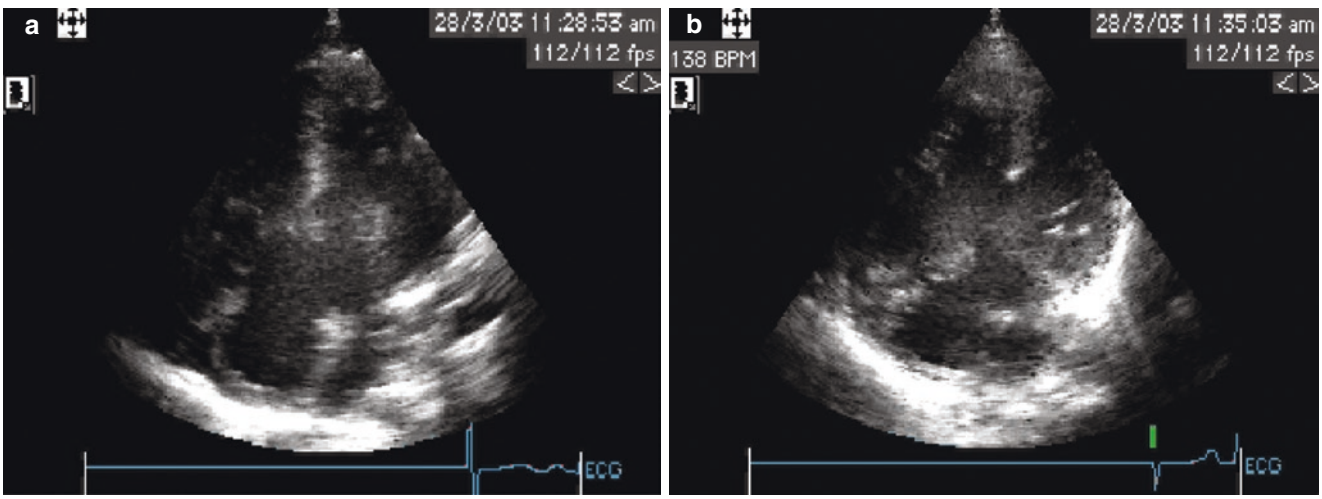

Fig. 16.3 Echocardiographic four-chamber views showing a CAVSD with an open (**a**) and a closed AV valve (**b**). When opened, this valve allows massive left-to-right shunts at the ventricular and the atrial level, as well as crossed shunts (left ventricular to right atrial and/or right ventricular to left atrium)

16.8 Cardiac Catheterization

Cardiac catheterization is rarely required in the pre-surgical evaluation of CAVSD, particularly if surgical correction is performed in the early infancy in which case it will likely not yield much to the diagnosis. It should be assumed that there is likely to be elevated but not fixed pulmonary artery pressures and this can be managed expectantly in the postoperative period.

Nevertheless, in patients who display a doubtful pathophysiological status, or in the setting of a late diagnosis of CAVSD, cardiac catheterization is beneficial to perform functional tests to appraise pulmonary vascular resistances and responsiveness to therapy (i.e., oxygen, nitric oxide, prostacyclin, calcium inhibitors).

16.9 Preoperative ICU Management

The diagnosis of CAVSD is usually made by fetal echocardiography or soon after birth in the neonatal period. It is therefore uncommon for the infant with a CAVSD to present undiagnosed in severe congestive heart failure. However, the lability of neonatal and infant PVR can affect the severity of congestive heart failure and it is possible that an infant can become rapidly ill to the point of requiring critical care. A more common scenario would be the infant who requires hospitalization prior to surgical correction for failure to thrive and poor weight gain. Pre-surgery, these infants are also at a greater risk for respiratory failure due to pneumonias, both viral and bacterial. This justifies preventive protocols that include the administration of palivizumab and the Influenza vaccine during the endemic periods.

The most common symptoms upon presentation for surgical correction are congestive heart failure based upon the degree of left-to-right shunting. At conditions of elevated altitude and/or in the presence of an elevation of the pulmonary artery pressures, these patients may need to be placed, seemingly paradoxically, on oxygen, with the recognition that under normal conditions, this would increase the left-to-right shunt and possible exacerbate symptoms of congestive heart failure.

Surgical correction is the definitive treatment for this lesion and should be offered early in life (Fig. 16.4); thus if a child presents in extremis due to either severe congestive heart failure or elevated pulmonary artery pressures, every effort should be undertaken to ensure that he or she is an acceptable candidate and can progress to the operating room. Diuretics and afterload reduction are the mainstay of congestive heart failure treatment for these infants and children. Evaluation of end-organ function prior to cardiopulmonary bypass may be needed if these patients do present critically ill.

Preoperative management may depend upon the degree of congestive heart failure as well as the degree of atrioventricular valve insufficiency. In the setting of severe right- or left-sided atrioventricular valve regurgitation, right- or left-sided heart failure symptoms may be quite apparent. In very symptomatic patients, early mechanical ventilation and the use of inotropic and vasodilators associated with loop-diuretics may be instrumental in optimizing the patient's conditions prior to the surgical intervention.

More often than not, the preoperative management of the infant with CAVSD is in the hands of the outpatient cardiologist and general pediatrician and care centers around managing congestive heart failure and perhaps the underlying pathologies related to chromosomal abnormalities specifically trisomy 21. Classical management includes the use of diuretics, oral vasodilators, and often digoxin, although the usefulness of this latter is controversial. Avoiding anemia is also a crucial factor in the medical management of these patients.

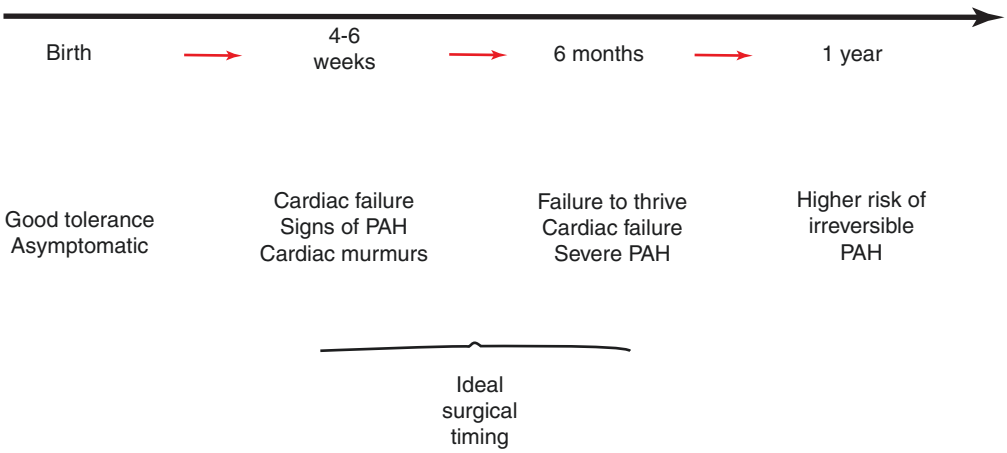

Fig. 16.4 Clinical course of CAVSD

Failure to thrive may encompass many etiologies, including genetic abnormalities and it is important to remember that moving ahead with surgical correction may improve some, but by no means all of the symptoms of failure to thrive.

16.10 Surgical Management

There are three main objectives in the surgical management of patients with a CAVSD, and they consist of the elimination of the intra-cardiac shunting by closing the ASD and the VSD, the creation of two AV valves from the common valve, and the repair of the left-sided cleft [10–12]. Three surgical repairs are commonly utilized for this lesion, the one-patch technique (Fig. 16.5), the two-patch technique (Fig. 16.6), and the Australian technique (Fig. 16.7). They are all performed via a median sternotomy incision, with cardiopulmonary bypass and the administration of cardioplegia.

Right or left ventricular hypoplasia is frequently seen in patients with unbalanced atrioventricular valve anatomy, often requiring a single ventricle repair. Occasionally, surgical palliation (pulmonary artery banding) is indicated as the

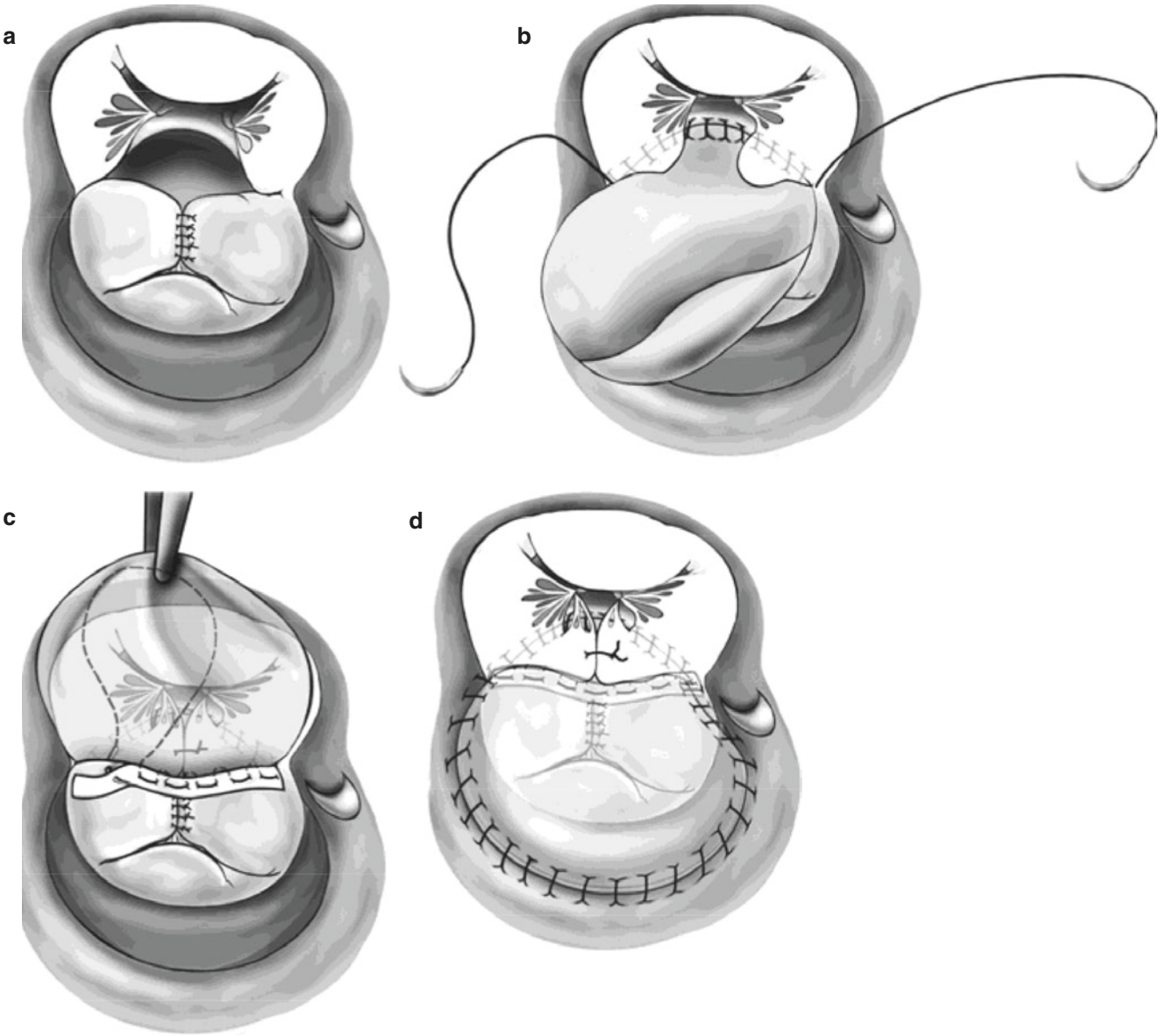

Fig. 16.5 One-patch technique. (**a**) First, the cleft in the left-sided atrioventricular valve is closed with interrupted sutures. (**b**) The VSD is closed with the patch; the sutures are placed on the right side of the crest of the ventricular septum to avoid injuring the conduction system. (**c**) The medial edge of both valves is sutured to the VSD patch; a strip of autologous pericardium is used along the left AV valve sutureline for reinforcement. (**d**) The atrial segment of the patch is used to close the interatrial communication, leaving the coronary sinus draining into the right atrium

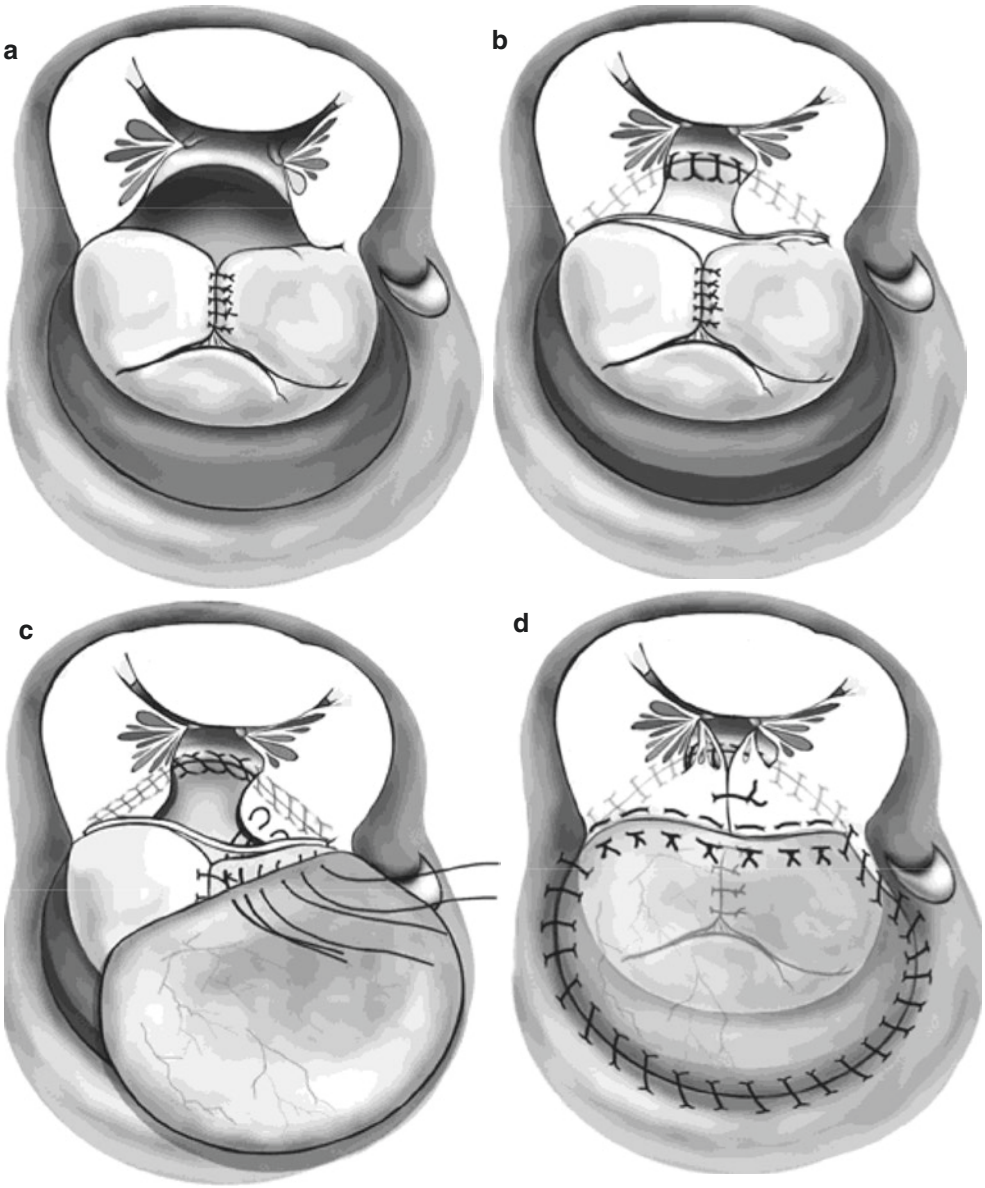

Fig. 16.6 The two-patch technique. (**a**) The cleft of the left-sided atrioventricular valve is closed with interrupted sutures. (**b**) The VSD patch is sutured on the right side of the crest of the ventricular septum to avoid injuring the conduction system. (**c**) The medial edge of both atrioventricular valves is sutured to the VSD patch; the same sutures are used to secure the medial aspect of the ASD patch. (**d**) The ASD patch suture line is completed

initial form of surgical therapy for the management of high-risk patients, including those with significant prematurity and/or multiple other congenital anomalies.

16.11 Postoperative Management

16.11.1 Monitoring

Postoperative management of the patient with CAVSD may be assisted by the placement of a pulmonary artery catheter (Swan-Ganz or transthoracic catheter) or left atrial line allowing to monitor pulmonary artery or left-sided pressures, in addition to arterial and venous lines. It should be expected that a good number of these children will experience some elevation of their pulmonary artery pressures due to preoperative elevated pulmonary vascular reactivity perhaps exacerbated by exposure to the inflammatory insult of cardiopulmonary bypass.

Other standard monitored signs are the usual heart and respiratory rate and peripheral oxygen saturation. Near-Infra-Red Spectroscopy is also a very useful technology to assess regional perfusion in these patients, as a surrogate of mixed venous saturations. Other markers that ought to be followed on a regular basis are blood lactate levels and the sVO_2.

Some important premises are to be considered when managing the postoperative course of a CAVSD:

1. Even after a good surgical repair, AV valves remain abnormal. It is therefore essential to "protect" the AV valvular plasty, by avoiding volume overload and systolic

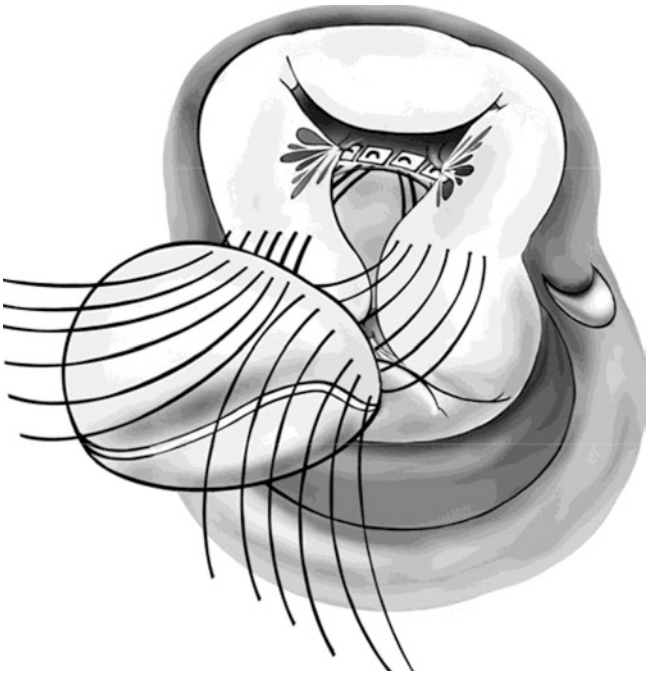

Fig. 16.7 Australian technique. This technique requires multiple pledgeted sutures to be placed along the right side of the crest of the ventricular septum and passed through the common atrioventricular valve and then the atrial septal defect patch. Once all the sutures are tied, the atrioventricular tissue is brought down to the level of the crest of the ventricular septum, obliterating the ventricular septal defect. The cleft is repaired in the usual fashion

hypertension that would reflect the interventricular pressure during systole.
2. Patients, mostly those with Down syndrome, are predisposed to and at risk for pulmonary arterial hypertensive (PAH) crisis.

The postoperative strategy for the child with CAVSD should include and target the following specific aspects of support:

(a) Anticipation of and prevention and aggressive treatment of PAH crisis
(b) Attempt to maintain low filling pressures (preload)
(c) Providing appropriate inotropic support and systemic vasodilation
(d) Vigilance for arrhythmias and heart block
(e) Prevention and treatment of specific problems and anticipated complications as specified below

General intensive care measures that are also crucial in the management of these patients are:

(a) Careful assessment of extra-cardiac abnormalities
(b) Maintenance of physiological body temperature
(c) Maintenance of anabolic status (aggressive enteral and parenteral nutrition)
(d) *Ad minimum* handling
(e) Providing gastric protection
(f) Treatment with anticoagulation/antifibrinolytic agents

16.11.2 Mechanical Ventilation

After surgical correction, rapid extubation may be possible. However, the underlying preoperative physiology may dictate attention to particular potential complications in the postoperative period. Albeit these complications can be anticipated and treated, they also may delay extubation and progression of care.

Ventilation around the expected functional residual capacity (FRC) can prove difficult; however, in many cases, this translates into providing adequate support to prevent atelectasis and limit overdistention and the maintenance of a normal or even alkalotic arterial pH via hyperventilation. Care must be also taken to avoid barotrauma and volutrauma as these can cause alveolar damage and further increase pro-inflammatory cytokines and further agitate an already reactive pulmonary vascular bed.

General considerations regarding mechanical ventilation:

1. PEEP:
   - With normal lungs PEEP should remain around 5 cm H_2O.
   - In case of interstitial edema or hypoxemia, cautious increments as required.
   - With such adjustments, cardiopulmonary interactions must be considered.
2. pH:
   - pH exerts a strong influence on pulmonary vascular resistances.
   - It is recommended to target a relative alkalosis, with a pH between 7.45 and 7.55, this being particularly useful in the setting of elevated PVR.
   - Some groups discuss the use of ventilation vs. HCO_3^- or THAM infusions to ensure such alkalosis with less barotrauma.
3. Hyperventilation may be useful during the acute PAH crisis.
4. Permissive hypercapnia is a useful tool as a pulmonary reactivity test, prior to weaning ventilation.
5. HFOV may be considered in patients with significant parenchymal involvement or requiring high ventilatory parameters in conventional ventilation.

16.11.3 Fluid Management

Immediately upon return from the operating room, it is recommended to set a goal of total fluid administration at 30–50% of maintenance requirements calculated by weight. Volume administration and resuscitation depends of course upon the clinical situation, and it is not uncommon that the child status post-CAVSD repair requires hemodynamic support in the form of intravascular volume. However, it is important to remember the specifics of surgical repair and that in the immediate postoperative period, the reconstructed right- and left-sided AV valves may be vulnerable to injury and even disruption if volume is given too aggressively.

16.11.4 Sedation and Analgesia

The strategy for sedation and analgesia in the postoperative CAVSD repair depends in part upon the pre-morbid and co-morbid state of the child in the intensive care unit. Stable hemodynamics, low ventilator requirements, the absence of serious arrhythmias, minimal postoperative bleeding, and low pulmonary artery or left atrial pressures may dictate early and rapid extubation, and therefore intermittent administration of analgesics and sedatives until the child is deemed ready for this. In this case, the shorter-acting opioids such as fentanyl and shorter-acting sedatives such as midazolam may be preferred, all the more that it has been shown that fentanyl is more efficient and better tolerated in patients with pulmonary hypertension, when compared with morphine.

If however the postoperative CAVSD exhibits hemodynamic instability, abnormal lung mechanics, malignant arrhythmias such as JET, or elevated PA or left atrial pressures, it may be prudent and in fact necessary to keep the child sedated, eventually on muscle relaxants and mechanically ventilated until the time that these issues improve and/or resolve. In this case, a continuous infusion of analgesia and a sedative is recommended.

The child with trisomy 21 and CAVSD may present with particular obstacles for an effective sedation strategy. As mentioned earlier, these are the children who carry the biggest risk of PAH. They are also known to suffer from decreased muscle tone, redundant pharyngeal tissue, and airway obstruction. They are often difficult to effectively sedate and require rapidly escalating doses of sedatives and analgesics. It is our experience with these children that we often adopt a strategy of a "gentle and deep extubation" in the intensive care unit. In these circumstances, avoiding peri-extubation agitation that can exacerbate PVR lability or airway compromise, or both, is desired. Sedation may be provided with Propofol [13] or dexmetomidine: as either drug may allow for spontaneous breathing during endotracheal tube removal and both share the pharmacologic properties of rapid onset and rapid metabolism with short half-lives.

16.11.5 Inotropic and Vasodilator Support

Inotropic and vasoactive support for the CAVSD in the postoperative period is not so different from many of the other congenital lesions. Afterload reduction is the mainstay of treatment to facilitate post-surgical left-sided AV valve competency and to optimize cardiac output [14, 15]. This is achieved with milrinone and, if necessary, agents such as sodium nitroprusside, nitroglycerin, or esmolol. In the setting of low cardiac output, vasopressor support with dopamine and low-dose epinephrine is paramount.

Attention must be paid to the pro-arrhythmic properties of these vasopressors and the potential for postoperative junctional ectopic tachycardia or JET. However, depending upon the complexity of the repair, the myocardium may require such support. It is our approach to be generous in the support of the struggling postoperative myocardium with vasoactive agents and attempt to limit the aggressive administration of fluids that can result in valvar and left atrial distention.

16.12 Postoperative Complications

The *main anticipated postoperative complications* related to this malformation are as follows:

1. Valvar regurgitation and stenosis
2. Elevated pulmonary artery pressure
3. Arrhythmias and conductive disorders
4. Low cardiac output syndrome (LCOS)
5. Residual intra-cardiac shunt

16.12.1 Valvar Regurgitation and Stenosis

It is important to remember that even after a successful repair of a CAVSD, the atrioventricular valves are not normal, nor will they ever be normal. This reality may guide postoperative management and determine strategy insofar as aggressive volume administration must be avoided in order to prevent distention of the left atrium and elevation of left

atrial pressure and contribute toward valvar regurgitation and elevation of left atrial pressures.

Severe left AV valve regurgitation is likely to be poorly tolerated even in the immediate postoperative period as this can lead to annular dilation and consequently worsening valvar regurgitation. Echocardiography both transesophageal and transthoracic can determine the degree of valvar dysfunction. In some cases, prompt return to the operating room is the only solution.

Similarly, the provider should be cognizant of potential left-sided valvar regurgitation or stenosis as recognized by the development of a diastolic (valvar regurgitation) or systolic (valvar stenosis) murmur, sudden increase of the left atrial and pulmonary pressures, and decrease of systemic pressures, concomitant with progressive metabolic acidosis. These can be detected on physical exam by the astute provider as well as with echocardiography. Left-sided AV valve disease is less tolerated than right-sided AV valve disease.

16.12.2 Elevated Pulmonary Artery Pressure

A specific chapter on acute pulmonary hypertension may be consulted elsewhere in this book.

The degree of pulmonary hypertension may be predicted based upon the preoperative condition. Again, a child with CAVSD and trisomy 21 is usually a different postoperative patient than a child with normal chromosomes. The Down syndrome child may have a predilection to pulmonary vascular reactivity. Causes of elevated pulmonary artery pressures must be distinguished between obstructive anatomic lesions such as left-sided valvar obstruction or insufficiency (postcapillary), residual lesions such as a VSD (precapillary), pulmonary vascular reactivity (capillary), or a combination of these. If the pre- and postcapillary causes are ruled out by exam and echocardiography, then the intensivist is left with treating intrinsic elevated pulmonary artery pressure that may have been exacerbated by exposure of the pulmonary vasculature to the pro-inflammatory effects of cardiopulmonary bypass.

In fact, pulmonary hypertension should be anticipated as a likely postoperative entity and steps should be in place that can effectively mitigate this. Factors that contribute to the occurrence and severity of pulmonary hypertension are age of repair, underlying chromosomal abnormality, and even length of time the lungs have been exposed to cardiopulmonary bypass. Potentially malignant and life-threatening PAH crises are those that become iso- or supra-systemic or those that are associated with LCOS, hypoxia, arrhythmia, or acidosis.

Prevention of PAH should be the main goal of the intensivist caring for these patients. Many factors, discussed above, may be considered as predisposing or triggering PAH, and prevention starts in the preoperative period.

16.12.2.1 General Measures to Prevent PAH in the Perioperative Period

(a) Adequate surgical indications and "timing"
(b) Minimizing perioperative risks:

1. CPBP conditions
2. Surgical technique
3. Myocardial protection
4. Ultrafiltration
5. Systemic steroids
6. Controlled reoxygenation
7. Leucocyte depletion

(c) Thoughtful ventilation strategy
(d) Early use of iNO in labile patients
(e) Ensuring metabolic and acid-basic balance
(f) Avoid/anticipate/treat:

1. Fever
2. Hypothermia
3. Anemia
4. Acidosis
5. Dehydration
6. Volume overload
7. Hypoxia
8. Hypercapnia
9. Sepsis
10. Agitation
11. Pain

In some cases, in patients with borderline indications for surgery because of high pulmonary resistances, the use of preoperative pulmonary vasodilators (i.e., iNO, sildenafil, endothelin-blockers) should be seriously considered. This practice, so far, is not based on evidence-based data.

16.12.2.2 Management of PAH Crisis

Approach to patients with postoperative acute PAH should be individualized since all therapies carry risks. In some circumstances, moderate and well-tolerated PAH should be treated conservatively rather than aggressively.

*An important premise in such patients is that it is crucial to rule out residual lesions that might explain such severe PAH crisis (*i.e.*, mitral valve incompetence, residual or recurrent ventricular shunt, left ventricular dysfunction).*

Ventilation should be provided as described above. It is important to ensure adequate arterial oxygen content, provide sedation and analgesia, limit noxious stimuli for the immediate postoperative period, and avoid acidosis. Not uncommonly, despite enacting all these measures, it is necessary to initiate pulmonary vasodilator therapy with inhaled nitric oxide.

Patients without pain and relaxed are better controlled in these circumstances. The association of opioids (fentanyl),

hypnotics (benzodiazepines), and muscle relaxants as required is recommended in labile patients with recurrent PAH crisis.

Intravenous vasodilator drugs are not selective to the pulmonary vascular bed and are inconsistently efficient. Nevertheless, lusitropic drugs, such as Milrinone, may need to be increased. Nitroprusside and nitroglycerine have some pulmonary vasodilator effect but with a significant and disproportioned systemic vasodilator effect.

Inhaled NO is the cornerstone of therapy [14, 15]. Patients requiring iNO, who show evidence of NO-dependent pulmonary vascular resistances, should promptly be started on sildenafil to facilitate the eventual weaning of the latest.

Patients with "malignant" or refractory PAH crisis may benefit from:

(a) The creation of a calibrated atrial or ventricular septal defect (on the patch) that will function as a decompressing mechanism
(b) Extracorporeal life support (ECLS) for 48–72 hours while the inflammatory "storm" is controlled or self-limited

16.12.3 Arrhythmias

Arrhythmias following surgical repair of CAVSD defect are not uncommon [16]. Much of the surgical repair of the AV valves in particular occurs in the region of the AV node, thus AV synchrony may be disrupted and require temporary pacing. Atrial and ventricular pacing wires are therefore mandatory.

Junctional ectopic tachycardia (JET) is a rare but potentially dangerous occurrence. This is a tachycardia originated at the AV node, with rates usually below 200 bpm and associated with periods of atrioventricular asynchrony in which the ventricular rate is higher than the atrial rate. JET may be poorly tolerated even for a short while and multiple treatments may be instituted simultaneously. Treatment of JET has been extensively described elsewhere; however, mild to moderate body surface cooling in the range of 33–36 °C is often the first course of action. This might necessitate using paralytics to prevent shivering. The main objective of therapy is to reduce the ventricular rate and to re-establish the atrioventricular synchrony. Amiodarone is currently the first-line pharmacotherapy. We recommend a bolus dose of 5 mg/kg over 1 hour, and this can be repeated up to 15 mg/kg total IV load. A continuous amiodarone infusion is often required and the usual dose ranges between 5 and 15 μg/kg/minute. It is also very important to reduce vasoactive drugs as much as possible since this is an autonomic-driven tachycardia (please consult the chapter on arrhythmias for further details). Although JET can be a catastrophic postoperative complication requiring in the most extreme circumstance mechanical circulatory support, it is often quite transient and resolves within the first 24 hours.

16.12.4 Low Cardiac Output Syndrome

As in most congenital heart lesions that undergo surgical repair, low cardiac output syndrome is often a ubiquitous term applied to impaired cardiac function and systemic output, vasopressor and inotrope dependence, and evidence of end-organ hypoperfusion. For the infant with CAVSD, there are specific considerations that may make a patient with this lesion particularly vulnerable to LCOS. As stated earlier, the neo left and right AV valves will never be normal, and the surgery of CAVSD can involve extensive repair and manipulation of the atrioventricular valves and in fact requires the creation of two competent valves from one common valve. Thus, in the postoperative period, if the patient is in a low cardiac output state, investigation must be undertaken to ensure that the AV valves are functional. This is best accomplished by echocardiography; however, if the patient is unstable in spite of an optimized medical therapy with inotropic drugs, systemic vasodilators, and diuretics, then reoperation should be carried out.

As a matter of fact, echocardiographic assessment of these patients is mandatory to rule out, other than valvar regurgitation or stenosis, ventricular dysfunction, persistent intra-cardiac shunts, or pulmonary hypertensive crisis.

The length of aortic cross-clamp time can contribute to postoperative diastolic dysfunction as can the adequacy of myocardial protection particularly with right ventricular hypertrophy.

Steps to limit AV valve regurgitation should be instituted; thus avoidance of rapid large volume infusions could cause sudden atrial distention and worsening valvar regurgitation. In our experience, afterload reduction with milrinone can also provide inotropic support without a significant risk of tachycardia. Milrinone is also one of the few available medications that may provide lusitropy in the setting of postoperative diastolic dysfunction [17, 18].

Anticipation of LCOS and follow-up of the adopted medical strategies require the use of serial assessment of arterial blood gases, blood lactate levels, sVO_2 if possible, but also cerebral and splanchnic NIRS. In patients with a Swan-Ganz catheter, information regarding cardiac output and index is instrumental in steering the therapy.

Patients with persistent LCOS might be candidates for extracorporeal support, sooner than later. As described previously, milrinone is the mainstay postoperative inotrope. The use of levosimendan was previously held as an effective and complementary medication for presumed lusitropic effects; however, so far there is not enough data providing evidence

of its efficacy in the pediatric population with AVSD. Finally, in some cases with conductive disorders, interventricular resynchronization might significantly optimize cardiac output.

16.13 Long-Term Outcomes

Perioperative mortality in the current era has been described between 3% and 5%. However, residual lesions such as left or right AV valve regurgitation have been described in as many as 50% of operated patients. Two recent reviews of surgical outcomes after primary repair of CAVSD have depicted left AV valve (LAVV) pathology and dysfunction as the most common indication for reoperation and the principal long-term morbidity [16, 19].

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Chapter 17
Aortopulmonary Window

Wonshill Koh, Evonne Morell, Diego Moguillansky, Ricardo A. Munoz, and Victor O. Morell

Abstract Aortopulmonary (AP) window is a rare cardiac anomaly accounting for 0.1–0.2% of all cases of congenital heart disease. It represents a communication between the ascending aorta and the main pulmonary artery in the presence of two separate semi-lunar valves. While it can occur as an isolated lesion, it is frequently associated with other cardiac defects, including type A interruption of the aortic arch, aortic origin of the right pulmonary artery, Tetralogy of Fallot, anomalous origin of the coronary arteries from the pulmonary artery, transposition of the great arteries, or tricuspid atresia. Pathophysiology of AP window is similar to that of other left-to-right shunt lesions, such as ventricular septal defect (VSD) or patent ductus arteriosus (PDA). AP windows do not close spontaneously, nor do they show decrease in size over time. Therefore, early recognition is important to allow for surgical closure before the development of pulmonary vascular obstructive disease, especially when the defect size is large.

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17.1 Anatomy and Pathophysiology

Aortopulmonary (AP) window is a rare cardiac anomaly representing a communication between the ascending aorta and the main pulmonary artery in the presence of two separate semi-lunar valves. It occurs when the two opposing conotruncal cushions fail to fuse, inhibiting the division of the truncus arteriosus into separate aorta and pulmonary artery. Accounting for 0.1 to 0.2% of all congenital heart diseases, AP windows can occur as an isolated lesion but more often are associated with other cardiac defects, including aortic origin of the right pulmonary artery, type A interruption of the aortic arch, Tetralogy of Fallot, anomalous origin of the coronary arteries from the pulmonary artery, transposition of the great arteries, or tricuspid atresia [1–6].

Since it was first described in 1830, several classifications of AP window have been described. Most commonly used is the one by Mori and colleagues, where AP window is classified into three different types based on the location: type I (proximal), type II (distal), and type III (total) (Fig. 17.1) [7]. Although it can vary in size, the defect is usually large and AP windows do not close spontaneously or decrease in size over time and growth [1, 2, 4, 8]. Therefore, unrepaired AP windows lead to significant left-to-right shunt over time with subsequent volume overload in the left side of the heart and dilation similar to large VSD or PDA. Without corrective surgery, patients will eventually develop irreversible pulmonary vascular obstructive disease.

17.2 Diagnosis

17.2.1 Clinical Presentation

Patients with AP window present with symptoms consistent with left-to-right shunts. These include signs of congestive

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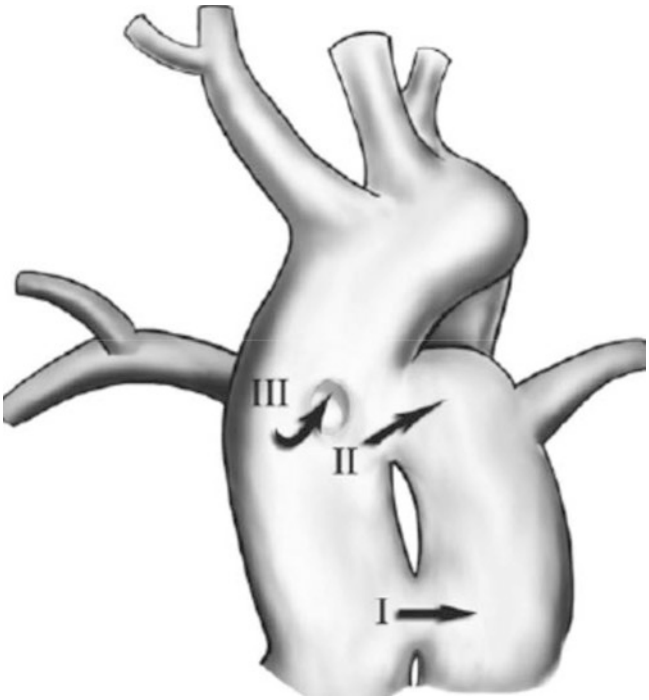

Fig. 17.1 Classification of aortopulmonary (AP) window

heart failure secondary to left atrium and ventricle volume overload. Clinical symptoms include failure to thrive, tachypnea, diaphoresis, and recurrent respiratory infections as the pulmonary vascular resistance normalizes 2–6 weeks following birth. The second heart sound can be narrowly split and accentuated in the presence of pulmonary hypertension. There might be loud systolic ejection murmur at the left upper sternal border and bounding pulse. Cyanosis is usually not present until later in the life when a bidirectional shunt occurs secondary to pulmonary vascular obstructive disease. Patients with small defect are usually asymptomatic, and a diagnosis is made when a murmur is heard. When associated malformations are present, the clinical presentation can change to reflect the combined hemodynamic features. For example, when associated with an interrupted aortic arch or coarctation of aorta, patients can present in cardiogenic shock after PDA closure, making the clinical diagnosis of AP window more challenging [2, 4, 7].

17.2.2 ECG

The ECG is usually without any specific characteristics. It can demonstrate right ventricular hypertrophy or biventricular hypertrophy with long-standing defects [7].

17.2.3 Chest Radiography

There is usually cardiomegaly with prominent pulmonary vascular markings secondary to left-to-right shunt. Pulmonary edema can be seen [4, 7].

17.2.4 Echocardiography

The diagnosis can be made by echocardiography, either prenatally or postnatally. Echocardiography can accurately demonstrate the AP window defect (Fig. 17.2), as well as most associated cardiac anomalies, in the majority of the patients [4, 9, 10]. The left atrium, left ventricle, and pulmonary arteries are dilated in the presence of a large left-to-right shunt. The semilunar valves are usually normal, unless associated defects are present. The defect in the AP septum can be visualized by 2D imaging, and color Doppler will demonstrate the abnormal, continuous forward flow in the pulmonary arteries. The forward direction of the flow in the pulmonary arteries helps differentiate AP window from a PDA (retrograde in the distal pulmonary arteries). When tricuspid regurgitation is present, echocardiography is also helpful to assess right ventricular (RV) and pulmonary artery (PA) pressure [4, 9, 11].

17.2.5 Cardiac Catheterization

There is usually no need for cardiac catheterization for the diagnosis of AP window, unless there is difficulty making a definite diagnosis, especially with other associated defects by echocardiography, or there is a concern for increased pulmonary vascular resistance.

17.2.6 Other Imaging Studies

Cardiac CT and cardiac MRI are sometimes used to further delineate the anatomy of the defect, especially when there are associated defects and when echocardiography is unable to completely define the anatomic details.

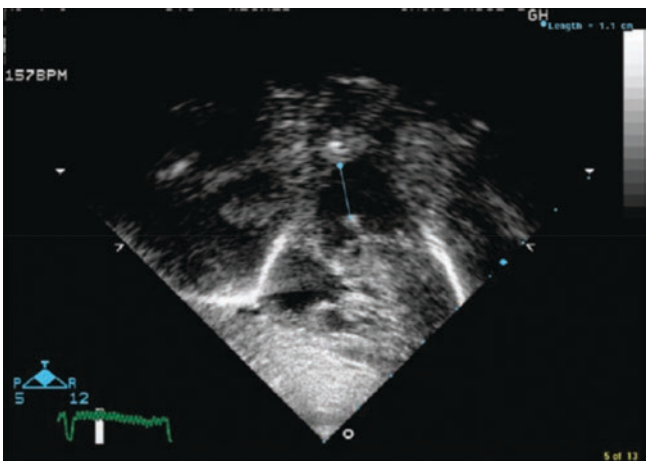

Fig. 17.2 2D echocardiogram. Subcostal view of a large proximal (type 1) AP window

17.2.7 Preoperative Management

The treatment of choice for AP window is surgical closure at the time of or soon after diagnosis. Preoperative management of patients with isolated AP window is similar to those of other left-to-right shunts, like VSD and PDA, and largely depends on the age of presentation and size of defect. Patients with moderate to large defects will likely present with symptoms associated with congestive heart failure (CHF) once pulmonary vascular resistance drops and will require medical therapy. Afterload reducing agents such as ACE inhibitors and diuretics are commonly used in outpatient setting with frequent clinic follow-ups until the surgery. Digoxin can be also used to manage congestive heart failure.

Patients presenting with severe CHF will require hospital admission prior to surgery. The key management will be optimization of the Qp:Qs. Supplemental oxygen should be avoided, which will further augment pulmonary blood flow, thereby decreasing systemic cardiac output. Patients will require intravenous (IV) diuretic therapy, as well as IV inotropic support, including milrinone, for afterload reduction. Laboratory values such as lactate, mixed venous saturation, blood gas, and NIRS are closely monitored as they provide indirect measures for cardiac output. If patients require mechanical ventilation, permissive hypercarbia can be achieved to manipulate PVR and augment systemic blood flow. With severe CHF, patients usually present with failure to thrive, requiring maximal nutritional supplementation either with total parental nutrition or enteral feeds. Enteral feeds should be planned carefully as these patients are at risk for necrotizing enterocolitis due to diastolic aortic runoff.

A small number of patients present later in life after having developed pulmonary vascular obstructive disease and are not surgical candidates. Management options include oxygen therapy, prevention of iron deficiency, and anticoagulation. Treatment of pulmonary hypertension is indicated in patients who show positive response to oxygen and nitric oxide with repeat catherization in several weeks to reevaluate hemodynamics. A subset of these patients might become surgical candidates later with a fenestrated patch repair. Some patients can be evaluated for heart-lung or lung transplantation.

17.3 Surgical Management

Since the first repair was reported in 1952 by Robert Gross, surgical techniques have evolved over the years for AP window repair [12–14]. Now the surgical repair is typically performed via a median sternotomy incision with the use of cardiopulmonary bypass and mild to moderate hypothermia. Both branch pulmonary arteries need to be controlled with tourniquets as soon as cardiopulmonary bypass is established in order to prevent excessive pulmonary runoff. Under cardioplegic arrest, the AP window is opened and occluded with a patch (Fig. 17.3). Another option is to completely divide the AP window, separating the aorta from the pulmonary artery and repairing both great vessels with separate patches (Fig. 17.4).

17.4 Postoperative Management

17.4.1 Monitoring

Patients are monitored through routine invasive monitoring, including central venous and arterial lines, which provide intraarterial pressures and facilitate frequent arterial blood gases, mixed venous saturations, and lactate levels. These measurements assist in the rapid assessment of the hemodynamic state of patients.

17.4.2 Cardiovascular Management

Inotropic support is routinely started in the operating room. At Children's Hospital of Pittsburgh, milrinone is usually initiated in the operating room and maintained for 12–24 h postoperatively and discontinued unless there is evidence of ventricular dysfunction, low cardiac output syndrome, or pulmonary hypertension, in which case milrinone can be continued until there are signs of improvement. Postoperative transesophageal echocardiographic assessment of ventricular function or residual defect will aid in determining the need for additional inotropic agents and the duration of therapy.

17.4.3 Respiratory Management

Patients with isolated and simple AP window are routinely extubated in the operating room. However, those with complex associated defects, especially with open chest or with pulmonary hypertension, would remain intubated. Chest closure usually occurs 24–48 h following surgery after effective diuresis. Extubation should be planned soon after chest closure. The occurrence of postoperative pulmonary hypertensive crises should be treated rapidly with oxygen, nitric oxide, and sedation.

17.4.4 Fluids, Electrolytes, and Nutrition

Negative fluid management is advisable during the initial 12 h after surgery, and it is important particularly in patients who have an open chest to facilitate sternal closure. Diuretics are routinely started 6–12 h after surgery. Parental nutrition

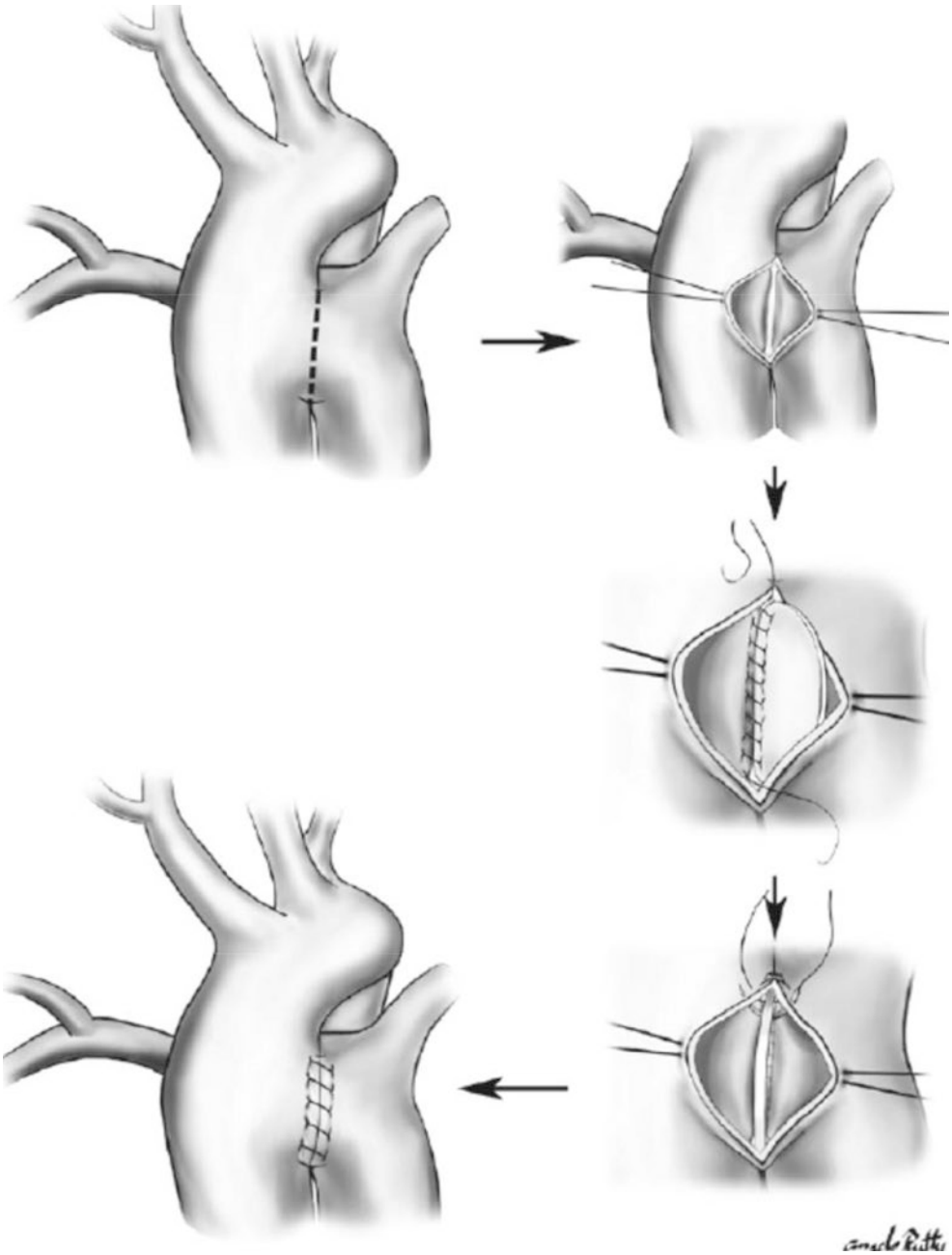

Fig. 17.3 Repair of AP window with a prosthetic patch. The anterior wall of the "window" is opened, and the patch is sawn to the edges of the defect

is initiated 24 h after surgery for patients with longer expected postoperative course, while enteral feeds are carefully planned once hemodynamic stability is achieved.

17.4.5 Sedation and Analgesia

A combination of opioid, benzodiazepine, and nonopioid agents such as dexmedetomidine are used to achieve postoperative sedation and analgesia. At Children's Hospital of Pittsburgh, dexmedetomidine is routinely started in the operating room, which has shown to facilitate early extubation and decrease opioid requirement. Other routinely used nonopioid therapy includes acetaminophen (intravenous or enteral). Nonsteroidal antiinflammatory drugs (NSAIDs) can be used as well once there is no risk of further bleeding postoperatively. For patients with evidence of pulmonary hypertension, paralytic agents are added to achieve deep sedation during the immediate postoperative period.

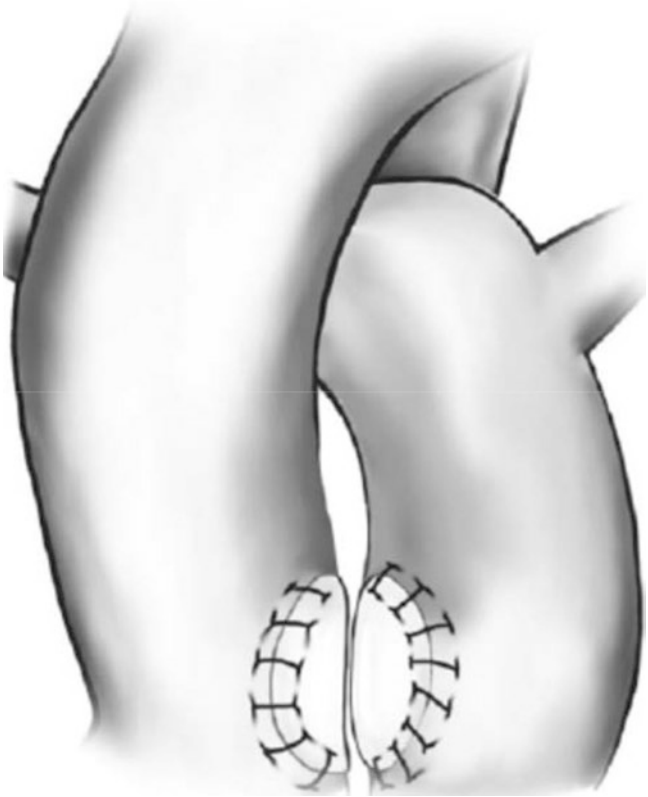

Fig. 17.4 After completely dividing the AP window, both great vessels are repaired with separate patches

17.5 Outcome

Long-term outcome is shown to be excellent for simple AP window defect repaired early in life before changes in pulmonary vascular beds. Patients with persistent pulmonary hypertension are at risk for late mortality postoperatively. The outcome of patients with significant associated lesions is variable and is determined more by the severity of the associated lesions and their candidacy for surgical repair than by the AP window that can generally be corrected easily by surgery [4, 6]. There have been reports of AP window with associated IAA to have increased risk of mortality and reoperation, but others have reported good long-term prognosis [5, 15–17]. Regardless, long-term observation is warranted for pulmonary artery stenosis, any residual defects, and recoarctation, if initially present.

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Chapter 18
Tetralogy of Fallot

Yuliya A. Domnina, Jason Kerstein, Jennifer Johnson, Mahesh S. Sharma, Traci M. Kazmerski, Constantinos Chrysostomou, and Ricardo A. Munoz

Abstract Tetralogy of Fallot (TOF) is a very common congenital heart defect occurring in approximately 15% of patients with congenital heart disease. More recently, genetic anomalies have been attributed to the development of this disease. The underlying pathology, pathophysiology, and surgical correction stem from the commonly known underlying morphologic defects: VSD, right ventricular hypertrophy, overriding aorta, and right ventricular outflow tract obstruction. Surgical correction early in infancy and appropriate postoperative care at all stages are essential to the ability of these children to live normal adult lives. However, even after correction, patients with TOF have significant considerations as they move into later childhood, adolescence, and adulthood.

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18.1 Prevalence and Anatomy

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect. Estimates for prevalence are approximately 3.26–3.4 per 10,000, with an incidence of 1 per 2518 new births per year in the United States [1–3]. Genetic anomalies have been identified in a substantial number of patients with TOF, with 22q11.2 microdeletion and trisomy 21 being the most common [4]. Additionally, heterozygous mutations in the JAG1, NKX2.5 and GATA4 genes have been associated with TOF as well [5].

The four main anatomic features of TOF include right ventricular outflow tract (RVOT) obstruction [6, 7], ventricular septal defect (VSD), aortic dextroposition overriding the VSD, and right ventricular hypertrophy (Fig. 18.1 Anatomy of TOF). Current teaching postulates that the basic pathology of TOF results from underdevelopment of the right ventricular infundibulum. This underdevelopment causes anterior malalignment of the infundibular septum, which subsequently determines the degree of RVOT obstruction, from entirely atretic in TOF pulmonary atresia with major aortopulmonary collaterals (MAPCAs) to mild stenosis with minimal clinical significance. The VSD that results is typically large and unrestrictive, leading to similar pressures between the right and left ventricles. Additionally, the pulmonary valve is often hypoplastic and thickened, and the level of obstruction may extend to the main pulmonary artery as well as the right and left pulmonary arteries.

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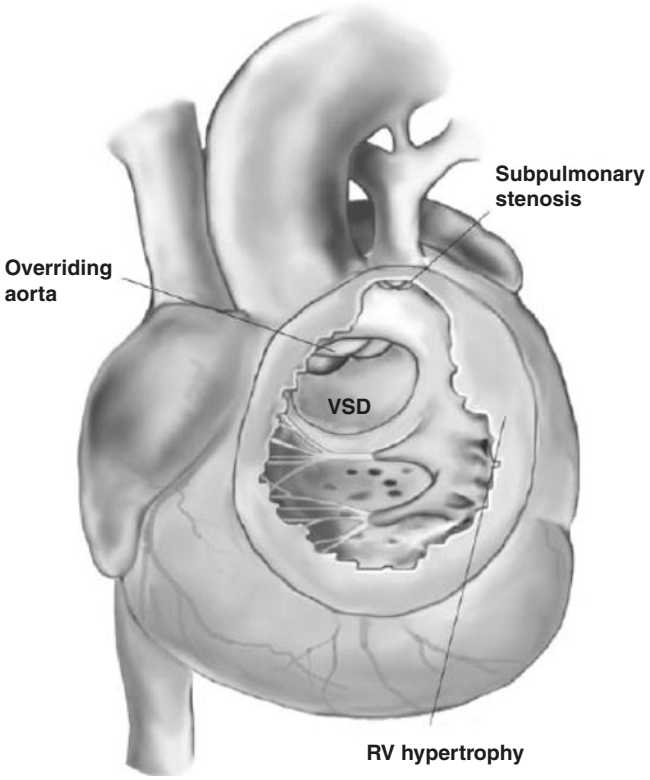

Fig. 18.1 Anatomy of Tetralogy of Fallot

Multiple defects have been associated with TOF, right-sided aortic arch (25%), coronary artery anomalies (10%), patent ductus arteriosus (PDA, 4%), atrial septal defect or patent foramen ovale, multiple VSDs, and atrioventricular septal defect [8]. All associated anomalies must be considered in surgical planning. Notably, coronary artery anomalies must be considered carefully as abnormally originating coronary can traverse the RVOT. Aberrant vessels can arise from the left anterior descending coronary (LAD), the right coronary artery (RCA), an RCA arising from the left coronary artery, or a large branch of the RCA supplying the conus region. A single right or left coronary artery may also occur [9].

18.2 Pathophysiology

As in essentially most congenital heart diseases, hemodynamics depend on the balance between pulmonary and systemic blood flow. In patients with TOF, this is mostly dependent on the severity of the RVOT obstruction, the size (and therefore the degree of restriction) of the VSD, and the level of systemic vascular resistance (SVR). Fixed obstruction at the pulmonic valve causes a certain degree of RVOT obstruction. However, the muscular component of the RVOT can be dynamic and therefore produce varying additional amounts of obstruction to the fixed pulmonary valve stenosis. The unrestrictive nature of the VSD permits the flow of desaturated blood from the right heart into the left ventricle and through the overriding aorta. SVR influences hemodynamics by determining the relative amounts of blood that flow through the overriding aorta versus through the pulmonary arteries. In general, vascular resistances, both pulmonary and systemic are normal, and pulmonary hypertension is atypical. Elevated SVR promotes pulmonary blood flow and results in increased oxygen saturations. Conversely, when SVR Is low, pulmonary blood flow is decreased and deoxygenated blood is shunted systemically, resulting in decreased oxygen saturations.

Based on these components, patients can present with varying degrees of cyanosis. In cases of severe cyanosis, patients often require an alternative source of pulmonary blood flow for survival, either through a PDA or major aorta-pulmonary collateral arteries (MAPCAs). MAPCAs are essential for patients with TOF with pulmonary atresia (discussed separately) as they are the only source of pulmonary blood flow. Additionally, patients without severe cyanosis at baseline can develop episodes of severe hypoxemia at which time the dynamic infundibulum fully obstructs pulmonary blood flow. These episodes are known as "Tet spells."

18.3 Clinical Presentation

Neonates present with a variable degree of cyanosis due to the dynamic capabilities of the muscular infundibulum. Increasing cyanosis can be a manifestation of PDA constriction. Elimination of PDA as an additional source of pulmonary blood flow can lead to severe desaturation and development of resultant oxygen debt and lactic acidosis. Worsening cyanosis may manifest in the infant as irritability, tachycardia, tachypnea, diaphoresis, and poor feeding. Blood pressure is typically well maintained; however, if acidosis persists, shock can develop where the infant develops poor pulses and may become pale and mottled.

Physical examination in TOF typically reveals a harsh, systolic murmur, caused by the RVOT stenosis. Additional components of the physical examination may include a prominent RV impulse, a single second heart sound. Of note, the absence of a murmur or disappearance of a murmur is concerning in TOF, as a constant absence may indicate pulmonary atresia, while a disappearing murmur indicates a significant increase in pulmonary obstruction.

18.4 Hypoxic Spells of Tet Spells

As mentioned above, "Tet spells" or "hypercyanotic spells" are caused by increased outflow obstruction exacerbated by infundibular hypercontractility. This leads to increased right-to-left shunting as a result of worsening obstruction. Pulmonary blood flow is decreased, resulting in hypoxia.

Tet spells are observed most in frequency at 2–3 months of age. They can be exacerbated by activity, straining, crying, or concomitant illnesses, especially respiratory infections or dehydration. During these episodes, patients are typically found overtly cyanotic and hyperventilating. Physical examination may reveal the absence of the patient's baseline murmur. The easiest way to break Tet spells is to increase both venous return and SVR. Medical management may require sedation, beta-blockers, volumes expansion, or systemic vasoconstrictors, further discussed later. Older children may accomplish this by squatting, which at the same time mobilizes systemic venous blood and increases SVR. Should patients be unable to break a spell, they can become pale, progressing to gray, and even comatose if the duration persists. These episodes may be life threatening and require recognition and intervention.

18.5 Preoperative Assessment and Management

The following should be performed as part of the initial preoperative assessment:

A. Chest X-ray: Heart size is typically normal; however, there is greater prominence of the right ventricle due to right ventricular hypertrophy. The combination of the RVH, an upturned apex, and a small main pulmonary artery segment results in the class "boot-shaped" heart.
B. Electrocardiogram: RV hypertrophy results in a right axis deviation. Persistent upright T waves are observed in the precordial leads.
C. Echocardiography: Typically sufficient to characterize anatomy. Important considerations for surgical planning include:
    - Degree and morphology of subpulmonary and pulmonary valve obstruction, including the z-score of the pulmonary valve.
    - Size of main and peripheral pulmonary arteries.
    - Size and number of VSDs.
    - Presence of PDA and/or MAPCAs.
    - Origin and proximal course of coronary arteries. It is essential to exclude a coronary artery crossing the RVOT prior to augmentation via infundibular patch.
    - Presence of PFO or ASD.
    - Aortic arch positioning.
    - Exclusion of other associated lesions, e.g., left superior vena cava.
D. SNP (single nucleotide polymorphism) microarray and FISH for 22q11 deletion: As approximately 7.4% of patients with TOF have a 22q11 microdeletion [4], all neonates with TOF should undergo genetic testing with SNP microarray or FISH analysis to evaluate for DiGeorge. If clinical criteria are few or doubtful, in particular newborn/neonate in intensive care, SNP microarray should be the first screening test to be ordered, as FISH provides information only on targeted locations and does not allow a comprehensive evaluation of the whole genome. Calcium levels should be followed carefully in any neonate with TOF as associated with DiGeorge syndrome hypoparathyroidism can result in hypocalcemia in the neonatal period.

E. Cardiac catheterization is not typically necessary prior to surgical intervention. However, in certain cases, catheterization may be needed to determine coronary artery anatomy if echocardiography is not sensitive enough to do so. Catheterization may also need to be utilized in the situation of TOF pulmonary atresia with MAPCAs, as it demonstrates the network of collaterals supplying the lungs.

18.6 Management of Special Situations

18.6.1 Newborns and Infants with Severe Cyanosis

Infants with severe RVOT obstruction can become significantly cyanotic when the PDA closes. The following should be instituted in this situation immediately:

(a) 100% oxygen.
(b) Prostaglandin E1 (Alprostadil) infusion. Start at a higher dose of 0.1 μg/kg/min. Once the ductus is patent, the dose can be weaned to a lower dose of 0.01–0.05 μg/kg/min. Beware of apnea if the patient is not mechanically ventilated.
(c) Consider intubation and support with mechanical ventilation. In the setting of severe cyanosis, the neonate will likely require mechanical ventilatory support.
(d) Intravascular access, ideally central venous access.
(e) If there is metabolic acidosis, administer sodium bicarbonate 1–2 meq/kg IV.
(f) If suspected hypovolemia, administer a crystalloid fluid bolus of 5–15 ml/kg IV.
(g) Optimize electrolytes, including ionized calcium levels.

18.6.2 "Tet Spells"

The occurrence of "Tet spells" can be an indication for surgical repair. Prior to surgical correction, the following should be considered during an acute episode:

(a) 100% oxygen.
(b) Knee-chest positioning for infants, squatting for toddlers.
(c) Sedation with morphine 0.1 mg/kg (IV, IN or PR), fentanyl 1–2 μg/kg (IV) or Dexmedetomidine 0.5–1 mcg/kg (IV). Sympatholytic effect of the latter leads to bradycardia and may cause improved relaxation of infundibulum. It has to be carefully balanced with peripheral α_2-stimulating effect that could lead to reduction of SVR and hypotension.
(d) Beta-blockers: Esmolol is ideal, given the ability to titrate between 50 and 200 μg/kg/min (IV). Intravenous propranolol can be used as an alternative.
(e) Volume expansion: crystalloid or red blood cell transfusion of 10–15 ml/kg IV.
(f) Systemic vasoconstrictors: Phenylephrine (Neosynephrine®) 2–5 μg/kg IV every 10–15 min, followed by a continuous infusion of 0.1–5 μg/kg/min as needed. Vasopressin can be used as an alternative. Vasoconstrictors are only indicated in spells refractory to oxygen, sedation, beta-blockers, and volume expansion.
(g) Sodium bicarbonate 1–2 meq/kg IV.
(h) Intubation with sedation and muscle relaxation if persistent or refractory spell.
(i) If all of the above fail, extracorporeal membrane oxygenation (ECMO support) and emergency Blalock-Taussig shunt (BT shunt) should be considered.

Although refractory Tet spells are an indication for surgery, transcatheter stent placement in the RVOT has been demonstrated to improve symptomatic neonates with TOF with significant contraindications to the operative intervention. Stenting improves arterial oxygen saturation and promotes growth of the pulmonary arteries, facilitating the ability to perform a complete repair when clinically feasible as opposed to having BT shunt as an interim procedure [10, 11].

18.7 Surgical Management

18.7.1 Timing of Surgery

Asymptomatic patients undergo an elective, one-stage surgical repair during early infancy, usually between 2 and 9 months of age, depending on the institution and the surgeon [12]. Early complete repair has surpassed palliation with a shunt as the procedural choice for the symptomatic patients requiring surgery prior to this age. The use of shunting for palliation has decreased and is now utilized only in select situations [12, 13]. Early primary repair has been found to be associated with a longer initial hospital length of stay and similar discharge mortality for neonates, but less overall hospitalizations and surgical interventions compared to palliative surgery [14, 15]. However, neonatal patients who undergo early primary repair have continued to demonstrate increased risks compared to older patients undergoing primary repairs including postoperative ventilation requirement, need for ECMO, subsequent catheter- and surgical-based interventions, ICU length of stay, hospital length of stay, and mortality [16–18].

Situations where surgical intervention needs to be planned fairly urgently include:

(a) Worsening hypoxemia, related to progressive infundibular and valvular obstruction with oxygen saturation less than 75–80%.
(b) Severe cyanotic Tet spells, as described above.
(c) Dependence on prostaglandin from early neonatal period (more likely to be observed in TOF with pulmonary atresia).

18.7.2 Surgical Technique

The TOF repair is performed via a median sternotomy incision with the use of cardiopulmonary bypass. After cardioplegic arrest, the VSD is closed via a right atriotomy and the obstructive muscle bundles in the proximal aspect of the RVOT are resected. A small interatrial communication may be left open to allow for right-to-left shunting at the atrial level, helping to offload the abnormally functioning right ventricle at the expense of mild early cyanosis. A longitudinal arteriotomy is then made in the main pulmonary artery extending into the proximal left pulmonary artery (LPA), past the area of ductal insertion, in order to prevent proximal LPA stenosis. The distal RVOT is explored via the pulmonary valve and any residual muscular obstruction is excised.

The ideal surgical repair would involve a transatrial-transpulmonary approach, avoiding a right ventriculotomy and preserving the pulmonary annulus. In the presence of severe infundibular stenosis, right ventriculotomy might be needed; some surgeons routinely close the VSD via the ventriculotomy. Data from the Society for Thoracic Surgeons note that surgery without ventriculotomy is only performed in less than 25% of patients [15]. In the absence of significant valvar stenosis, pericardial patches are used to close the pulmonary arteriotomy and the right ventriculotomy. In patients with significant pulmonary valve hypoplasia, a transannular incision is used. Latest STS data demonstrate a discharge mortality of 1.3% for primary repair [15].

Recent surgical focus has surrounded pulmonary valve preservation to avoid the long-term sequelae of chronic pulmonary regurgitation. This decision is often made based on the diameter of the pulmonary annulus with a z-score of −2 often used as the minimum for attempting to preserve the pulmonary valve [12]. Preoperative valve z-score has been shown to correlate with Technical Performance Score [19]. Bacha notes that there are multiple options for per-

forming valve-sparing TOF repair including pulmonary valve commissurotomy with or without bougie dilation, commissurotomy and intraoperative balloon pulmonary valve dilation and pulmonary cusp patch reconstruction [12]. Mavroudis also identifies that opportunities exist for pulmonary valve cusp patch reconstruction and pulmonary valve restoration during TOF repair so as not to lose the competence of the valve.

18.8 Postoperative Management

In some centers, most toddlers and children return to the cardiac ICU already extubated, and we expect a relatively uneventful postoperative course. Problems that may arise in the first 12–48 h postoperatively, especially in neonates and infants, include the following:

(a) Low cardiac output syndrome (LCOS) due to:
    1. Right ventricular diastolic and systolic dysfunction – this results from pre-repair right ventricular hypertrophy. This is likely exacerbated by ventriculotomy that is performed as part of the repair.
    2. Left ventricular dysfunction – this is expected less frequently in the postoperative course.
    3. Uncontrolled arrhythmias causing cardiac dysfunction (discussed below).
    4. Residual VSD resulting from either significant VSD patch leak or unrecognized additional VSD prior to and during surgery.
(b) Arrhythmia – The most common arrhythmias impacting hemodynamics postoperatively include:
    1. Junctional ectopic tachycardia (JET) – compared to other cardiac surgeries, JET is most frequently observed after TOF repair [20].
    2. Ectopic atrial tachycardia.
    3. Re-entry type supraventricular tachycardia (Re-SVT) – beware that the presence of a right bundle branch block, seen commonly postoperatively, may make Re-SVT appear like ventricular tachycardia.
    4. Complete AV Block – rare and, if present, mostly transient. Patients may require temporary pacing. Can be permanent in which case patient would require pacemaker.

18.8.1 Monitoring

Most patients have the following placed in the operating suite:

(a) Arterial line
(b) Central venous line – either internal jugular or subclavian
(c) Pleural and mediastinal chest tubes
(d) Peritoneal drainage tube (neonates)
(e) Foley catheter
(f) Temporary pacing wires

Though most older patients are admitted to the cardiac ICU extubated, infants often arrive intubated. Some infants may arrive with an open chest, which ideally is closed within the first 36 h postoperatively.

18.8.2 Laboratory Work

(a) Complete blood count, electrolytes, BUN, creatinine immediately after surgery and every 24 h.
(b) Arterial blood gases every 1–4 h, lactate and central venous (mixed venous) saturations every 4–6 h for the first 24 h and then as needed.
(c) Cerebral near-infrared spectroscopy (NIRS, INVOS 5100 Cerebral Oximeter Somanetics Corp., Troy, MI, USA).
(d) Continuous electrocardiogram telemetry.

Echocardiogram is not performed routinely unless patient's clinical course deviates from expected. However, the ability to do so should always be available within the cardiac ICU.

18.8.3 Management of Specific Problems

18.8.3.1 Mechanical Ventilation

Time-cycled pressure limited mode is most frequently used, aiming for approximately 8–10 ml/kg tidal volumes with ideal plateau pressures of less than 25–28 mmHg. FiO_2 is minimized to avoid potential oxygen toxicity; pO_2 levels >40 mmHg are considered acceptable in the setting of an atrial communication. Most patients postoperatively have a residual PFO or surgeon-created atrial communication to facilitate right-to-left atrial shunting in the setting of right ventricular dysfunction for preservation of cardiac output. PEEP should also be utilized at levels of 5–7 mmHg to minimize right ventricular afterload. It is equally important to prevent atelectasis and resultant V/Q mismatch.

18.8.3.2 Low Cardiac Output Syndrome

All patients are administered Milrinone for 24–72 h at a range of 0.5–1.25 μg/kg/min to support right ventricle. Since in most cases LCOS is due to RV dysfunction associated with the hypertrophic right ventricle, a higher filling pressure is needed. Many patients require CVP of 10–15 mmHg to achieve an adequate cardiac output. Ionized calcium levels are maintained between 1 and 1.4 mMol/L. Sodium bicar-

bonate at 1–2 meq/kg is given as needed to achieve a base excess and pH >7.35. If further inotropic support is needed, low-dose epinephrine at 0.05–0.1 μg/kg/min can be utilized. However, it is important to beware that epinephrine may initiate or exacerbate arrhythmias, especially JET.

18.8.3.3 Junctional Ectopic Tachycardia (JET)

The mainstay of managing JET is to decrease any adrenergic state with the goal of achieving adequate atrioventricular coordination, ideally a return to normal sinus rhythm but at least JET control with a rate of less than 170 beats/min with AV sequential pacing. JET, though transient and lasting only 3–4 days, can be a major reason for increased morbidity and mortality if not treated promptly. JET has been demonstrated to be associated with increased duration of mechanical ventilation, cardiac ICU length of stay, and a mortality ~3% [20]. The following algorithm represents the approach employed by the authors, at the Children's Hospital of Pittsburgh after immediate diagnosis and initiation of treatment:

(a) Decrease, or discontinue if possible, any inotropic agents that worsen JET (dopamine, epinephrine).
(b) Provide adequate intravascular fluid volume to optimize RV preload.
(c) Core hypothermia 34–35 °C with muscle relaxation.
(d) Amiodarone loading bolus 5 mg/kg IV slowly followed by a continuous infusion of 5–15 μg/kg/min. If there is no effect on heart rate within 60 min, a second bolus is given.
(e) Consider ECMO if JET cannot be controlled and LCOS worsens.

For treatment of other types of arrhythmia, please refer to the associated chapter.

Sedation and analgesia are managed with fentanyl and/or dexmedetomidine. Parenteral nutrition is started early after surgery, and enteral feeds are started slowly beginning 34–48 h after hemodynamic stability has been achieved. At this time, non-opioid analgesic agents (ketorolac, Motrin, Tylenol) may allow improved gut motility and reestablishment of enteral nutrition via opioid-sparing effect.

18.9 Long-Term Outlook

The overall outlook for patients with TOF remains excellent. Many patients go on to live normal lives into late adulthood. However, there are important cardiac complications that the patients born with TOF continued to struggle with later in life.

Because of the now known long-term sequelae of pulmonary insufficiency, valve-sparing repair has come to the forefront of surgical management. Pulmonary insufficiency can be a consequence of TOF repair, especially in those patients who undergo transannular patch repair. Long-standing pulmonary regurgitation can lead to right ventricular dilation and dysfunction, which has been demonstrated by MRI to occur even during preadolescence with an increase in right ventricular end diastolic volume of 9 ml/m^2/year [21]. Cardiac MRI imaging has become the gold standard for quantifying pulmonary regurgitation and right ventricular volumes [22].

The development of right ventricular dysfunction secondary to pulmonary insufficiency traditionally required reoperative intervention for pulmonary valve replacement. However, in many cases, this has been replaced by transcatheter pulmonary valve replacement with either the Melody® valve (Medtronic Inc., Minneapolis, MN, USA) or the Edwards® valve (EdwardsSAPIEN®pulmonic transcatheter heart valve, Edwards Life-science, Irvine, CA, USA). Current results are promising for transcatheter pulmonary valve replacement. Multiple studies have demonstrated both immediate relief as well as hemodynamic improvement with improvement of RV end diastolic volumes, relief of pulmonary regurgitation and pulmonary stenosis within 1 month of placement [23–25]. Sustained improvement has also been noted at 1-year post-procedure [25]. Evaluation of medium-term follow-up after Melody valve placement noted high rates of freedom from stent fracture and freedom from valve dysfunction or reintervention [23]. The use of transcatheter placement in smaller patients (<30 kg) has also demonstrated feasibility when assessed in the setting of conduit dysfunction with significant improvement in pulmonary regurgitation [26]. Short-term outcomes comparing RVOT gradient between the Melody and Sapien valves have yielded similar results [22].

An additional concern in the previously repaired TOF patient is the development of arrhythmias, especially ventricular arrhythmias predisposing to sudden cardiac death. It is thought that chronic right ventricular overload is the major risk factor for the development of arrhythmia. It is consistent with findings of pulmonary regurgitation being the most common lesion found in patients with ventricular tachycardia and sudden death. Patients who had transannular patch placement are more likely to develop sustained ventricular tachycardia and sudden death [27]. EKG findings associated with the development of ventricular tachycardia and sudden cardiac death include QRS duration (≥180 msec) and QRS rate of change [27]. Interestingly, late pulmonary valve replacement for symptomatic pulmonary regurgitation and right ventricular dilation was not found to decrease the risk of ventricular tachycardia or sudden death [28]. Patients have also been found to be predisposed to atrial arrhythmias, including atrial fibrillation and atrial flutter; in these patients, tricuspid regurgitation was the main lesion identified [27].

Adult functional health has been assessed in patients who underwent TOF repair. Analysis of adults has demonstrated

dysfunction in both the right and left ventricles [29, 30]. Hickey et al. found that 45% of adults reported cardiorespiratory symptoms (palpitations, shortness of breath, and chest pain) [29]. Adults have been shown to report decreased assessment of their own physical health compared to controls [29, 31].

Despite functional limitation later in life, the overall surgical survival and outlook for patients with TOF are excellent. Most patients enjoy an active life free of significant symptoms.

Adults report similar psychosocial quality-of-life scores compared to their age-matched controls [29, 31].

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Chapter 19
Tetralogy of Fallot with Absent Pulmonary Valve

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Abstract Tetralogy of Fallot with absent pulmonary valve (TOF-APV) compromises about 3–6% of patients with TOF. TOF-APV is a rare type of TOF with distinct anatomic features in addition to the usual anatomic defects of TOF. It is characterized by absent or rudimentary pulmonary valve leaflets, severe pulmonary regurgitation, and various degrees of aneurysmal dilatation of the main and branch pulmonary arteries leading to bronchial compression. Also with TOF-APV, there is usually a wider infundibulum with minimal right ventricular outflow tract obstruction and nearly always absent ductus arteriosus. Although minimal, a degree of right ventricular outflow obstruction occurs at the level of expected pulmonary valve annulus rather than at the infundibulum, as seen in typical TOF. Very rarely, APV can also occur as an isolated lesion without the features of TOF.

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19.1 Anatomy

Tetralogy of Fallot with absent pulmonary valve (TOF-APV) compromises about 3–6% of patients with TOF [1, 2]. TOF-APV is a rare type of TOF but with distinct anatomic features in addition to the usual anatomic defects of TOF. It is characterized by absent or rudimentary pulmonary valve leaflets, severe pulmonary regurgitation, and various degrees of aneurysmal dilatation of the main and branch pulmonary arteries leading to bronchial compression. Also with TOF-APV, there is usually a wider infundibulum with minimal right ventricular outflow tract obstruction and nearly always absent ductus arteriosus (Fig. 19.1). Although minimal, a degree of right ventricular outflow obstruction occurs at the level of expected pulmonary valve annulus rather than at the infundibulum, as seen in typical TOF. Very rarely, APV can also occur as an isolated lesion without the features of TOF [1–3].

19.2 Pathophysiology

Symptoms in TOF-APV feature a combination of problems from left-to-right shunt across the VSD and significant airway compression/obstruction due to pulmonary artery dilation. Initially there is a cyanosis at birth due to elevated pulmonary vascular resistances (PVR) secondary to a combination of VSD and nonfunctioning pulmonary valve. However, as PVR falls after birth, there is a significant increase in pulmonary blood flow due to left-to-right shunt through the VSD in a setting of minimal RVOT obstruction. This subsequent excessive pulmonary blood flow can further compromise respiratory symptoms that are already affected by airway compression in patients with TOF-APV. Severe pulmonary regurgitation from absent pulmo-

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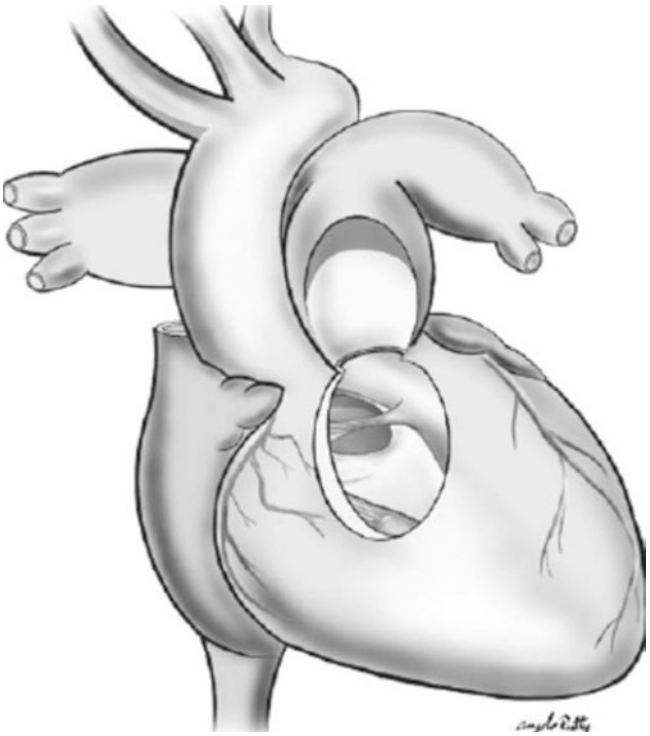

Fig. 19.1 Tetralogy of Fallot with Absent Pulmonary Valve (TOF-APV). In addition to the classic features of Tetralogy of Fallot, note the dilated main and branch pulmonary arteries, which frequently result in bronchial compression

nary leaflets leads to aneurysmal and pulsatile pulmonary arteries, which then result in bronchial compression [1, 4–6]. With a high Qp:Qs, there is an enlargement of the left atrium resulting in further compression of the left bronchus. In addition to external compression of the airway, patients with TOF-APV often demonstrate structural abnormalities with abnormal bronchial arborization, thereby further compromising lung function with severe air trapping, hypoxemia, and hypercarbia, which can persist even after surgical repair.

19.3 Clinical Presentation

There are varying degrees of respiratory distress at birth in neonates with TOF-APV due to airway compression with about 40% exhibiting respiratory distress at birth. Neonates who initially appear to have only mild symptoms may develop worsening respiratory distress as PVR starts to fall and pulmonary blood flow increases. Those with severe respiratory distress will require intubation and mechanical ventilation support.

On physical examination, there is single S2 and the characteristic "to and fro" systolic and diastolic murmur. There is cyanosis initially in addition to varying degrees of respiratory symptoms, including tachypnea, retractions, wheezing, and stridor, depending on the severity of airway compression.

19.3.1 Chest Radiography

Chest X-ray shows massively dilated pulmonary arteries with a moderate enlargement of cardiac silhouette. The peripheral vascular markings are initially normal but usually increase as PVR falls. Atelectasis, lung emphysema, and lung hyperinflation due to air trapping are often present in the chest X-ray.

19.3.2 ECG

Electrocardiogram commonly shows right axis deviation and signs of RV hypertrophy, as seen with TOF. There are no additional distinct features for TOF-APV.

19.3.3 Echocardiogram

Echocardiogram is usually sufficient to delineate the cardiac and great vessel anatomy. Specific features that need to be identified include the following:

(a) Degree and morphology of the subpulmonary and pulmonary valve area
(b) Degree of stenosis and insufficiency
(c) Size of the main and peripheral pulmonary arteries
(d) Size and number of VSDs
(e) Presence of a ductus arteriosus
(f) Origin and proximal course of coronary arteries
(g) Presence of a PFO or an ASD
(h) Aortic arch position
(i) RV function and size

Echocardiogram can help delineate between TOF-APV and the more typical TOF. In order to distinguish between the two, it is important to document the absence of the pulmonary valve or presence of pulmonary valve dysplasia with concurrent severe regurgitation, significant aneurysmal dilatation in the areas of the pulmonary arteries, and increased rather than decreased pulmonary artery pressure.

19.3.4 Cardiac Catheterization

Cardiac catheterization is usually not necessary in patients with TOF-APV. It could help to identify unusual pulmonary artery branching or distal peripheral pulmonary artery stenosis.

19.3.5 Computerized Tomography/ Magnetic Resonance Imaging

Computerized tomography or magnetic resonance imaging can provide detailed airway assessment by delineating interrelationships between the dilated pulmonary arteries and the tracheobronchial tree and the airway anatomy [7, 8].

19.4 Preoperative Management

The clinical course and short- and long-term prognosis of neonates with TOF-APV are variable, but the overall outcome is strongly related to the degree of associated airway involvement [9–11]. Initially, neonates with considerable respiratory distress may benefit from noninvasive positive pressure such as CPAP or prone positioning, which relieves the compression on the bronchi by allowing pulmonary arteries to fall forward. Patients with severe respiratory distress require immediate intubation and earlier surgical intervention. Patients requiring preoperative ventilation support are known to have higher surgical mortality and morbidity. While managing mechanical ventilator support, it is important to provide appropriate positive end-expiratory pressure (PEEP) and sufficient expiratory time. In patients with severe airway compression, it is sometimes difficult to provide adequate respiratory support even with mechanical ventilator support. Because of increased prevalence of DiGeorge syndrome among patients with TOF-APV, chromosome and FISH studies are recommended.

19.5 Surgical Management

The operative management of TOF-APV is similar to that of TOF and pulmonary stenosis, consisting of closure of the VSD and the creation of an unobstructed communication between the right ventricle and the pulmonary arteries. In addition, the diameter of the dilated pulmonary arteries needs to be reduced. At Children's Hospital of Pittsburgh, a preferred option is to perform a transannular incision with the placement of a monocusp valve and a pulmonary reduction arterioplasty (Fig. 19.2). Other options for the management of the dilated pulmonary arteries include surgical resection and replacement with a pulmonary homograft or the anterior translocation of the pulmonary arteries (Lecompte's maneuver), moving them away from the bronchi [12–14]. The foramen ovale is left open to allow for a right-to-left shunt to preserve the cardiac output during the early postoperative period.

19.6 Postoperative Management

Overall postoperative management is similar to that following a TOF operation. The challenge lies in the respiratory management given the significant airway pathology in patients with TOF-APV.

19.6.1 Monitoring

Invasive monitoring is routine, including central venous and arterial lines.

19.6.2 Cardiovascular Management

Vasoactive infusions such as milrinone are frequently employed. Lactate and central venous saturation levels are trended as a surrogate for a cardiac output.

19.6.3 Sedation and Analgesia

Deep sedation, analgesia, and paralysis should be employed in patients with severe airway compromise. This goal may be achieved by combining infusions of opioids, dexmedetomidine, and/or benzodiazepines.

19.6.4 Respiratory Management

Significant airway obstruction in TOF-APV highly complicates postoperative management and worsens overall survival when compared to typical TOF. Especially, patients requiring preoperative intubation due to severe preoperative respiratory distress are at increased risk for poor outcome [9–11]. While the main operative goal is to restore pulmonary valve competency and reduce airway compression by the pulmonary artery reduction, patients may continue to manifest evidence of postoperative respiratory compromise. They require a careful and systematic assessment of the etiology of respiratory failure and appropriate interventions to assure successful weaning from mechanical ventilation.

For those who undergo successful extubation following surgery, prone positioning can help reduce airway compression. They will mostly require noninvasive positive pressure support following extubation. If patients continue to require prolonged mechanical ventilation support, they will need further evaluation for airway compression. CT or

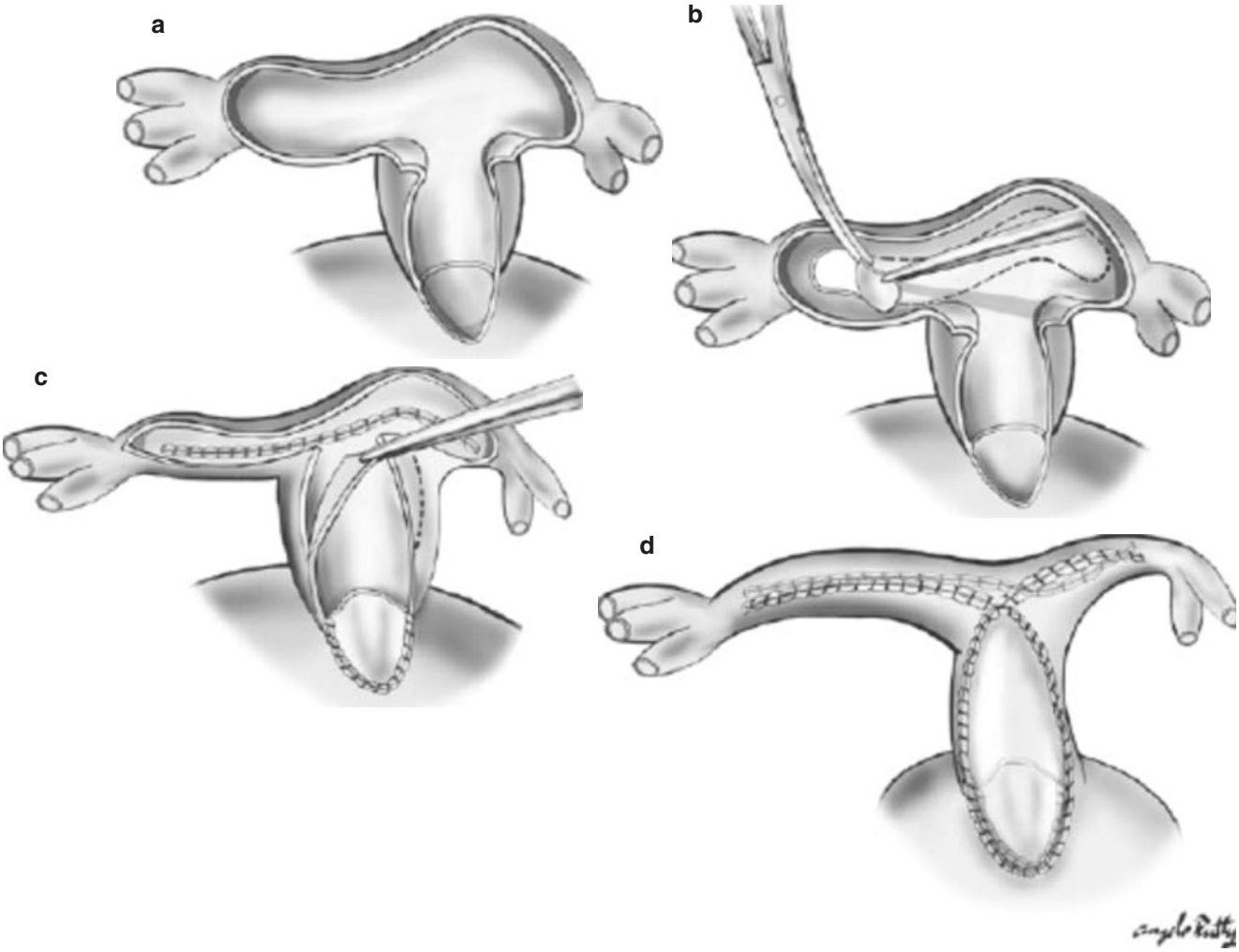

Fig. 19.2 Pulmonary Artery Reduction Arterioplasty. (**a**) The anterior wall of the main and branch pulmonary arteries is opened longitudinally. Note that the main pulmonary artery incision is extended across the pulmonary annulus (transannular incision). (**b**) A longitudinal segment of the posterior wall of the branch pulmonary arteries is excised. (**c**) The posterior wall of the branch pulmonary arteries is reapproximated with a running suture. A reduction arterioplasty of the main pulmonary artery is performed, and a monocusp pulmonary valve is placed. (**d**) A transannular patch is used to complete the repair

MRI can help to further evaluate airway anatomy and its relationship to vascular structures, including pulmonary arteries. Bronchoscopy may help identify significant tracheobronchomalacia or external compression by pulmonary vessels.

In cases of persistent vascular compression, patients will require surgical reintervention to undergo further pulmonary artery reduction/suspension. Meanwhile, bronchomalacia due to previously compressed airways may take a significant amount of time to resolve even after pulmonary artery reduction. Endobronchial expandable stents have been used for persistent bronchomalacia, but their uses are limited in terms of the total attainable diameter and inability to address distal bronchial compression. In patients with significant ongoing airway issues with repeated failed extubation, tracheostomy is often needed. Bronchomalacia and abnormal external and intrinsic airway anatomy also put patients with TOF-APV at increased risk for respiratory infection, which could be fatal if not treated. Early diagnosis and treatment for any evidence for respiratory infection are required.

19.7 Long-Term Outlook

The overall mortality in patients with TOF-APV depends on the initial severity of respiratory distress [5, 9–11, 15, 16]. Those with severe tracheomalacia and respiratory distress requiring preoperative intubation carry the highest mortality and morbidity. Those with any residual respiratory involvement usually require repeated hospitalizations for recurrent respiratory infections and reoperation to further relieve airway compression. For the rest of patients with TOF-APV, the

overall outcome has improved over the years with the overall 10-year survival rate of 80–87% [17]. For patients with less severe respiratory symptoms, their pulmonary function usually improves following surgery with growth. Nevertheless, they will need close pulmonology follow-up. Moreover, routine echocardiogram and MRI are recommended to evaluate pulmonary artery, conduit competency, RV dimensions, and function. Patients likely require late reoperation to replace RV-PA conduit or pulmonary valve.

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Chapter 20
Tetralogy of Fallot with Pulmonary Atresia

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Abstract Tetralogy of Fallot with pulmonary atresia (TOF-PA) accounts for 2% of all forms of congenital heart disease and for 20% of all forms of TOF. TOF-PA is slightly more prevalent in males than in females and is frequently associated with the 22q11 syndrome. The intra-cardiac anatomy of TOF-PA has all the features of classic Tetralogy of Fallot: ventricular septal defect, overriding of the aorta, right ventricular outflow obstruction, and right ventricular hypertrophy. The difference is in the membranous or complete atresia of the pulmonary valve and extreme variability of the architecture of the main and distal pulmonary arteries. The central pulmonary arteries can be of good size, variably hypoplastic, discontinuous, or even absent. A persistent ductus arteriosus (PDA), major aorto-pulmonary collaterals (MAPCAs), or both may provide blood flow to the pulmonary vasculature.

20.1 Anatomy

Tetralogy of Fallot with pulmonary atresia (TOF-PA)/pulmonary atresia-ventricular septal defect (PA-VSD) accounts for 2% of congenital heart disease and for 20% of all forms of TOF [1, 2]. TOF-PA is slightly more prevalent in males than in females and is frequently associated with the 22q11 deletion syndrome [3–5]. In addition to the intra-cardiac features of Tetralogy of Fallot, which include ventricular septal defect, overriding of the aorta, right ventricular outflow obstruction, and right ventricular hypertrophy, there is a complete atresia rather than stenosis of the pulmonary valve in TOF-PA with no antegrade pulmonary blood flow (Fig. 20.1). Atresia can be limited to pulmonary valve (membranous atresia) or can involve the long segment from the sub-pulmonary infundibulum to proximal main pulmonary trunk. The central left and right pulmonary arteries can be confluent or non-confluent with their sizes varying anywhere from being normal size to absent. The sources of pulmonary arterial blood flow include the patent ductus arteriosus (PDA), major aorto-pulmonary collaterals (MAPCAs), or both. With the presence of PDA, the

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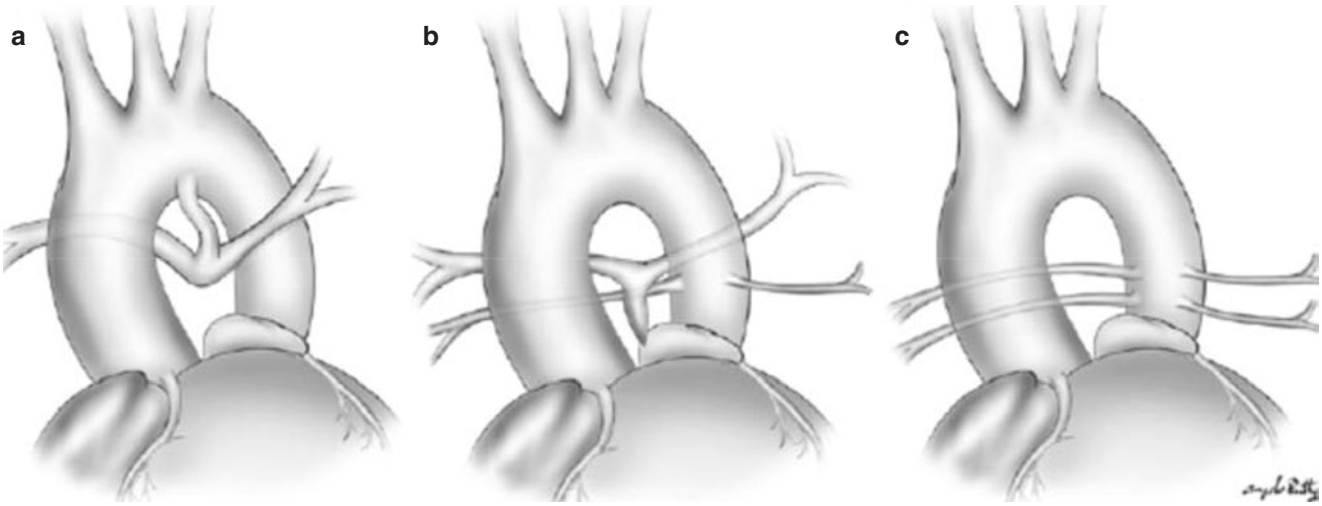

Fig. 20.1 Anatomy of the central pulmonary arteries in Tetralogy of Fallot with pulmonary atresia (TOF-PA). (**a**) Normal central pulmonary arteries, (**b**) hypoplastic central pulmonary arteries with aorto-pulmonary collaterals, (**c**) absent central pulmonary arteries with multiple aorto-pulmonary collaterals

pulmonary arteries are usually confluent. They can be hypoplastic but there is usually normal intrapulmonary arterial distribution. Collateral arteries usually arise from the descending thoracic aorta. When MAPCAs are the sole source of pulmonary blood flow, intrapulmonary arborization is abnormal. When there are non-confluent arteries, one lung is supplied by the ductus with normal arborization, while the other lung is supplied by MAPCAs with abnormal arborization [6–10].

20.2 Pathophysiology

Pathophysiology in TOF-PA depends on the source and size of vessels supplying pulmonary blood flow. Blood flow is usually provided by the PDA and/or by MAPCAs. If the PDA is the sole source of pulmonary blood flow, the neonates will present with progressive cyanosis with signs of hemodynamic decompensation as the PDA starts to close within the first 48 h of life. Prompt initiation of prostaglandin E_1 (PGE_1) to maintain the patency of ductus is critical. If aorto-pulmonary collaterals are present, the clinical presentation may vary from cyanosis with inadequate pulmonary blood flow to no cyanosis with adequate or increased pulmonary blood flow depending on the number and caliber of collateral vessels. Older infants and children commonly present with progressive cyanosis due to hypoxia. Those with worsening cyanosis with diminished pulmonary blood flow due to constriction of PDA and/or progressive stenosis of MAPCAs will require earlier surgical intervention. Not uncommonly (particularly in small birth-weight infants), patients may present with signs of heart failure with increased pulmonary flow in the presence of large collateral vessels and/or PDA as the pulmonary vascular resistance falls.

20.3 Clinical Presentation

An infant with TOF-PA is often symptomatic with cyanosis within the first hours to days of life. Severe cyanosis becomes evident as the ductus begins to close. In the presence of significant MAPCAs, cyanosis may vary. For those with limited blood flow from MAPCAs, closure of the ductus arteriosus may produce life-threatening hypoxemia and even sudden death. Some other times (especially in small birth-weight infants), patients with well-developed aorto-pulmonary collaterals and/or large ductus may present with symptoms of pulmonary over-circulation as pulmonary vascular resistance decreases and pulmonary blood flow increases, generally several weeks after birth. Infants may exhibit respiratory distress with tachypnea and poor feeding with failure to thrive. Unbalanced circulation could produce a systemic steal phenomenon and can lead to devastating complication of necrotizing enterocolitis. Growth and development are overall delayed secondary to cyanosis or congestive heart failure.

The physical exam reveals a normal first heart sound with a single loud second heart sound. There is usually lack of loud outflow systolic murmur heard in patients with TOF, but continuous murmur of PDA or MAPCA may be present.

In older patients, hemoptysis may occur as a result of rupture of extensive systemic-to-pulmonary collateral arteries. DiGeorge syndrome is a common association with TOF-PA and, therefore, requires microarray and genetic evaluation.

20.3.1 ECG

Right ventricular hypertrophy with right axis deviation is usually present. There are no additional features compared to TOF.

20.3.2 Chest Radiography

Chest X-ray reveals normal heart size with variable degree of pulmonary vascularity depending on the amount of pulmonary blood flow. A typical "boot-shaped" cardiac silhouette (*Coeur en sabot*) with right ventricular enlargement and an excavated pulmonary button may be observed. In the presence of DiGeorge syndrome with 22q11.2 deletion, a typical thymus opacity may be absent.

20.4 Preoperative Management

It is imperative to clearly delineate the anatomy of pulmonary arteries and source of pulmonary blood flow early to determine surgical planning. Echocardiogram, CT angiogram, and/or cardiac catheterization are warranted to evaluate for the presence and anatomy of native pulmonary arteries, ductus, and aorto-pulmonary collaterals. Until the evaluation is completed and the presence of collaterals is ascertained, these neonates should be considered to have ductal-dependent pulmonary blood flow and started on PGE_1.

20.4.1 Echocardiogram

Echocardiogram is an excellent diagnostic tool for initial diagnosis of TOF-PA. In addition to identifying the typical anatomic features of TOF, it can clearly demonstrate the anatomy of the atretic segment of the pulmonary artery as well as the proximal branch pulmonary arteries, including their size and confluence. The presence of MAPCAS can be detected by color Doppler even though the identification of all collaterals might be difficult. A prior study has shown that the presence of a branch pulmonary artery diameter Z score ≤ -2.5 or a PDA diameter ≤ 2 mm is the most sensitive and specific test for the presence of ≥ 1 MAPCAs [11]. Regardless, echocardiogram alone is considered insufficient to rule out the presence of MAPCAS, and a detailed definition of their anatomy is best ensured by angiography (Figs. 20.2 and 20.3), MRI/A, or CTA [12].

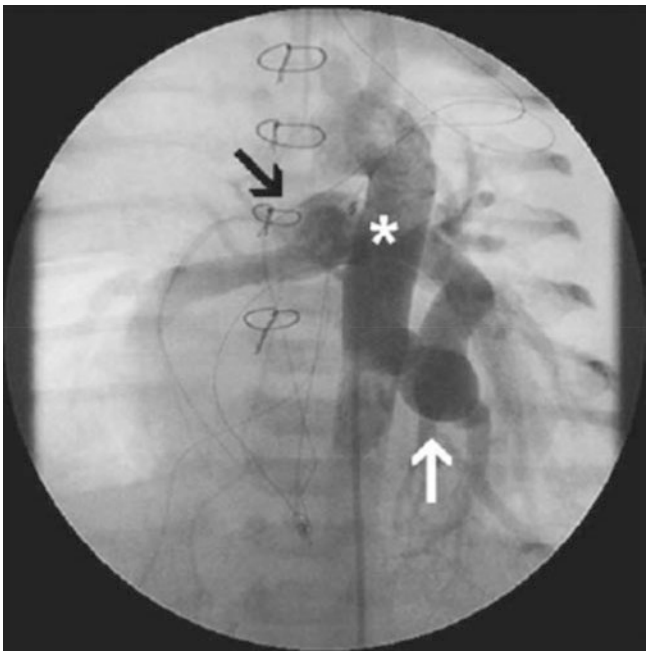

Fig. 20.2 Descending aortogram in anteroposterior projection performed in a patient after neonatal repair of TOF with pulmonary atresia with normal size central pulmonary arteries (*black arrow*) without a prior cardiac catheterization. A large aortopulmonary collateral from the descending aorta had been missed (*white arrow*), which led to severe heart failure symptoms postoperatively. In this case, the aorto-pulmonary collateral communicates with the left pulmonary artery, which is also supplied by the central pulmonary artery (*black arrow*), and thus can be ligated or embolized safely. ∗*descending aorta*

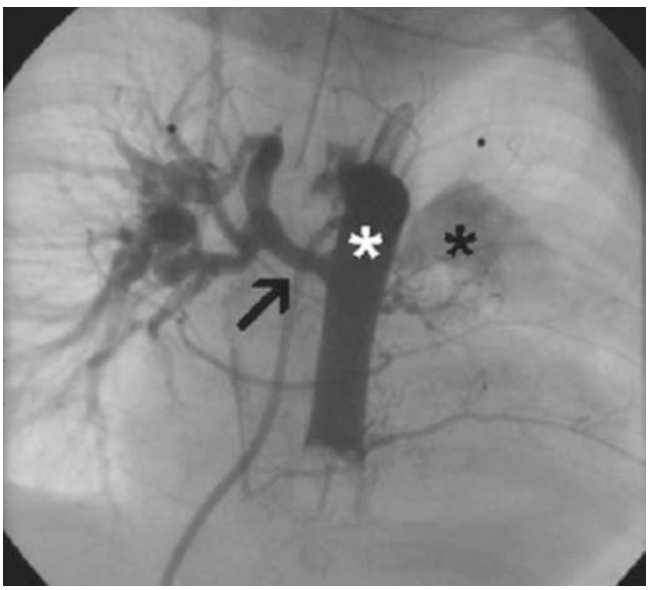

Fig. 20.3 Balloon occlusion angiogram of descending aorta (*white asterisk*) performed in a newborn with TOF-PA and absent central pulmonary arteries. There is a moderate-size MAPCA feeding the right lung (*black arrow*). The left pulmonary artery (*black asterisk*) is large and fills from the aorta as well

20.4.2 Cardiac Catheterization

Cardiac catheterization with angiogram is the gold standard for a clear anatomical delineation including pulmonary artery, lung arborization pattern, and sources of pulmonary blood flow. After initial diagnostic evaluation, interventional cardiac catheterization continues to play a key role in long-term management in patients with TOF-PA for pulmonary artery rehabilitation as well as balloon dilation and/or stenting of RV to PA conduit stenosis following surgical repair.

20.4.3 CT and MRI

Three-dimensional computed tomography or magnetic resonance angiogram also offers detailed information on pulmonary artery and collaterals anatomy. Information obtained from CTA or MRA is comparable to cardiac angiography [12, 13]. However, when patients require hemodynamic measurements or intervention, cardiac catheterization should be performed.

20.5 Surgical Management

Because of the wide variability in the native pulmonary artery development and the source of pulmonary blood flow, the surgical management of TOF-PA is more difficult than that of classic TOF. Therefore, for simplicity, these patients can be divided into three groups.

1. *Patients with normal size or minimally hypoplastic confluent central pulmonary arteries:* Most of these patients can undergo a single-stage complete repair consisting of PDA ligation, closure of the VSD, and placement of a RV to PA conduit (Fig. 20.4). In these patients, it is usually safe to close the VSD because of the well-developed pulmonary vasculature. Another alternative is to initially proceed with a systemic to pulmonary artery shunt followed by complete repair at a later time. High-risk patients with other complex congenital problems, genetic defects, or prematurity might be able to undergo cardiac catheterization and stenting of PDA to avoid surgical intervention in the neonatal period. Recently, several studies reported successful pulmonary valve perforation and right ventricle outflow track stent placement as another initial alternative procedure in high-risk patients [14, 15].
2. *Patients with hypoplastic but confluent pulmonary arteries and multiple aorto-pulmonary collaterals with multiple segments of the lungs receiving dual supply:* The surgical repair is individualized to the particular anatomy. A staged approach is frequently used consisting of sequential unifocalizations and the placement of an RV to PA conduit and/or systemic to pulmonary artery shunt (Fig. 20.5). The main goal of the initial interventions is to promote the growth of the native pulmonary arteries and of the unifocalized aorto-pulmonary collaterals. The VSD is closed once the pulmonary artery cross-sectional area is adequate (>50% of normal; the NAKTA index >160 mm^2/m^2) so that the RV pressure would be acceptable (<75% systemic) at the end of the repair [16]. Before VSD closure, the echocardiogram and/or catheterization should reveal primarily a left-to-right shunt across the VSD. A more aggressive approach would be a single-stage repair via a median sternotomy, as suggested by the Stanford group [17, 18].
3. *Patients with absent or severely hypoplastic nonconfluent pulmonary arteries and multiple aorto-pulmonary collaterals*: Commonly, a staged approach is utilized consisting of unifocalizations, followed by reconstruction of the central pulmonary arteries and placement of an RV to PA conduit with or without VSD closure. The VSD patch is fenestrated or removed if the RV pressure is >75% systemic [19]. A placement of central shunt (Melbourne shunt) or creation of aortopulmonary window has been described in patients with severe pulmonary hypoplasia

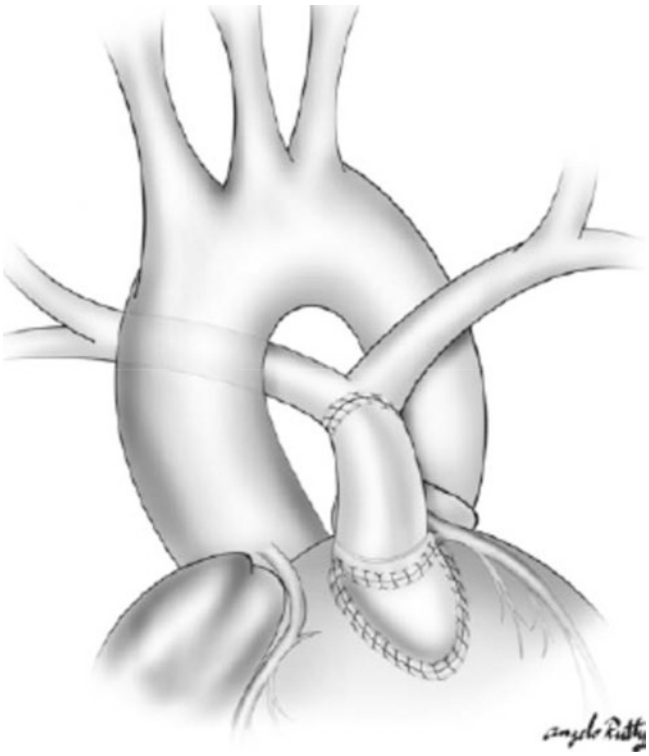

Fig. 20.4 Right ventricle to pulmonary artery conduit

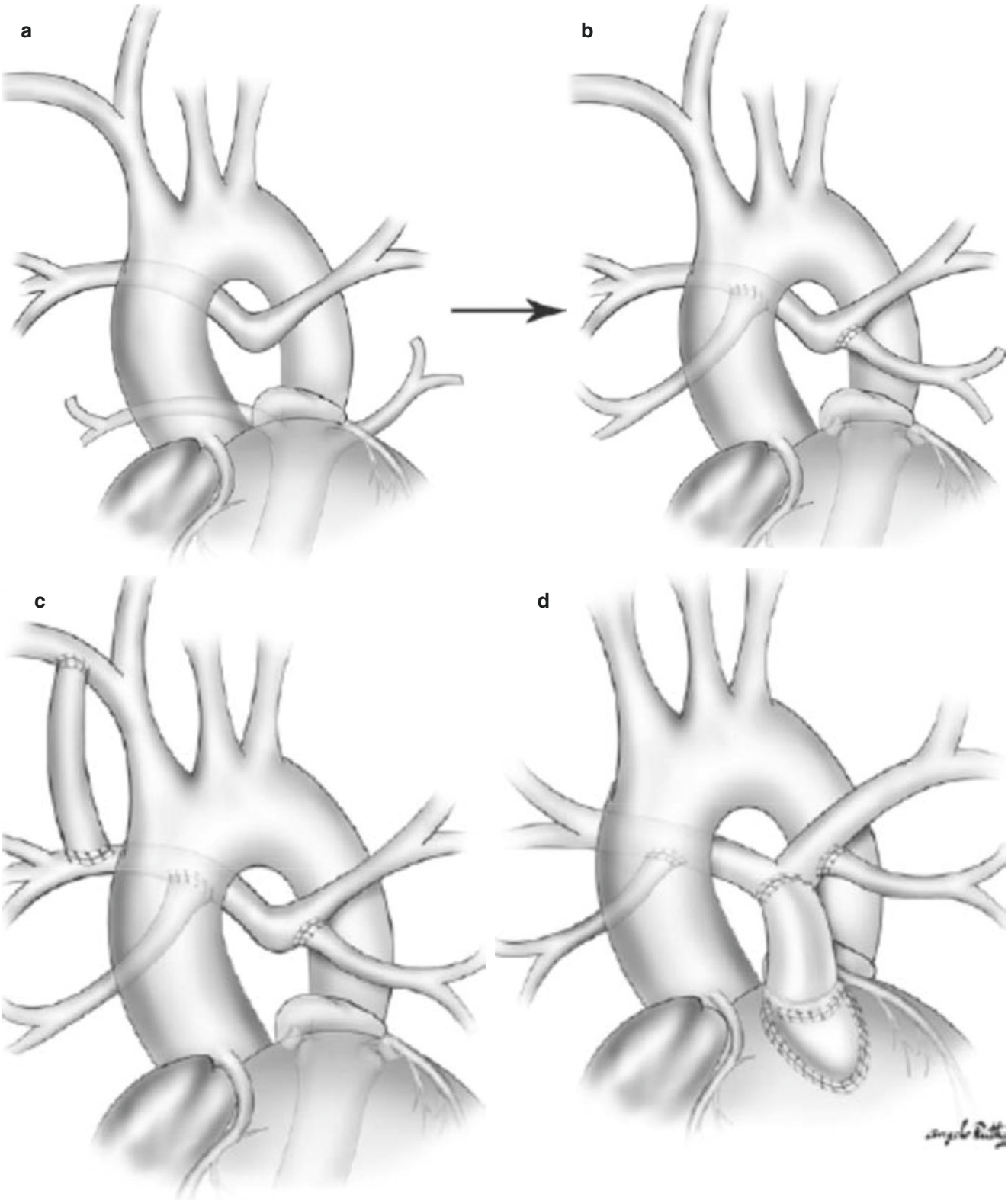

Fig. 20.5 *Unifocalization*. (**a, b**) It involves separating the aorto-pulmonary collaterals from the aorta and connecting them to the native pulmonary arteries; (**c**) a systemic to pulmonary artery shunt or (**d**) a right ventricle to pulmonary artery conduit is usually added to augment the pulmonary blood flow and promote arterial growth

or hypoxia to promote the pulmonary artery growth [20, 21]. It is important to realize that some of these patients will never achieve a complete repair because of their abnormal pulmonary arterial vasculature and excessively high pulmonary vascular resistance.

20.6 Postoperative Management

Definitive postoperative management of patients with TOF-PA depends on the individual patient anatomy and surgical stage. Overall postoperative management of TOF-PA with confluent pulmonary arteries and a PDA as the only source of pulmonary blood flow does not differ significantly from the management of patients with TOF and pulmonary stenosis.

Patients with TOF-PA and multiple aorto-pulmonary collaterals usually undergo staged repair and can present with more challenges during the immediate postoperative period. Postoperative bleeding is common, especially in the case of extensive pulmonary arterial reconstruction.

20.6.1 Monitoring

Invasive monitoring including central venous and arterial lines is standard of care.

20.6.2 Respiratory Management

Following unifocalization or full repair, patients usually arrive from the operating room intubated and remain on mechanical ventilation. The duration of mechanical ventilation mostly depends on the extent of the surgical procedure. Those who required extensive dissection of the pulmonary vasculature for unifocalization might require longer mechanical ventilation support as they are at increased risk for reperfusion injury, hemorrhage, and atelectasis. Patients undergoing full repair are at risk of pulmonary hypertensive crisis and they should be properly ventilated with a goal to permit maximal afterload reduction for the right ventricle. Nitric oxide is frequently utilized in the immediate perioperative period. In patients who fail to extubate, a high index of suspicion should arise for diaphragmatic paresis, especially in patients who underwent extensive unifocalization procedures.

20.6.3 Cardiovascular Management

Vasoactive infusions including milrinone are frequently employed in the patients with pulmonary hypertension and borderline right ventricular function. Cyanosis can be present due to right-to-left shunting at the atrial level from poor RV compliance, systolic dysfunction, and hypertrophy. In addition, in those patients palliated with an open VSD, right to left shunting can be at the ventricular level, related to high resistance or decreased functional area of distal vascular bed (remaining stenosis, kinking, or occlusion of unifocalized collaterals).

20.6.4 Sedation and Analgesia

Deep sedation, analgesia, and paralysis should be employed in the patients exhibiting signs of pulmonary hypertension. This goal may be achieved by a combination of dexmedetomidine, opioids, and benzodiazepines.

20.7 Complications and Long-Term Outcome

Most patients with TOF-PA will need multiple cardiac catheterization procedures after initial surgical palliation or complete repair, for rehabilitation of pulmonary arteries as well as in preparation for VSD closure. Many postoperative issues can be managed in the Catheterization Laboratory, with coil embolization of residual collaterals, or with transcatheter interventions for thrombosed or stenotic unifocalized vessels. The development of novel catheter techniques to deal with lesions resistant to traditional techniques (ultrahigh-pressure balloons, cutting balloon, stent implantation) has led to an increased success rate of these interventions, especially in the last decade [6, 19] (Fig. 20.6).

The prognosis of TOF-PA depends on the specific anatomy as well as the number, type, and result of interventions. Long-term follow-up data are not widely available. The results of published surgical series are not necessarily applicable to other patient groups, as there is significant heterogeneity in the anatomy, in addition to variable institutional expertise in surgery and interventional cardiology. Evolving and improving surgical techniques in combination with sophisticated cardiac catheter interventions will undoubtedly lead to ongoing improvement in survival and decreased morbidity [14, 18, 20, 22–26].

These patients are followed closely with regular electrocardiographic and full echocardiographic evaluations for the potential development of right ventricle to pulmonary artery conduit obstruction and stenosis of reconstructed pulmonary arteries, progressive right ventricular dysfunction, and evidence of arrhythmia.

Most patients with TOF-PA and small or absent central pulmonary arteries will require multiple cardiac catheterizations as a nonsurgical complement of the staged repair (Fig. 20.5). They are usually evaluated for pulmonary artery obstruction and persistent undesired collateral supply of pul-

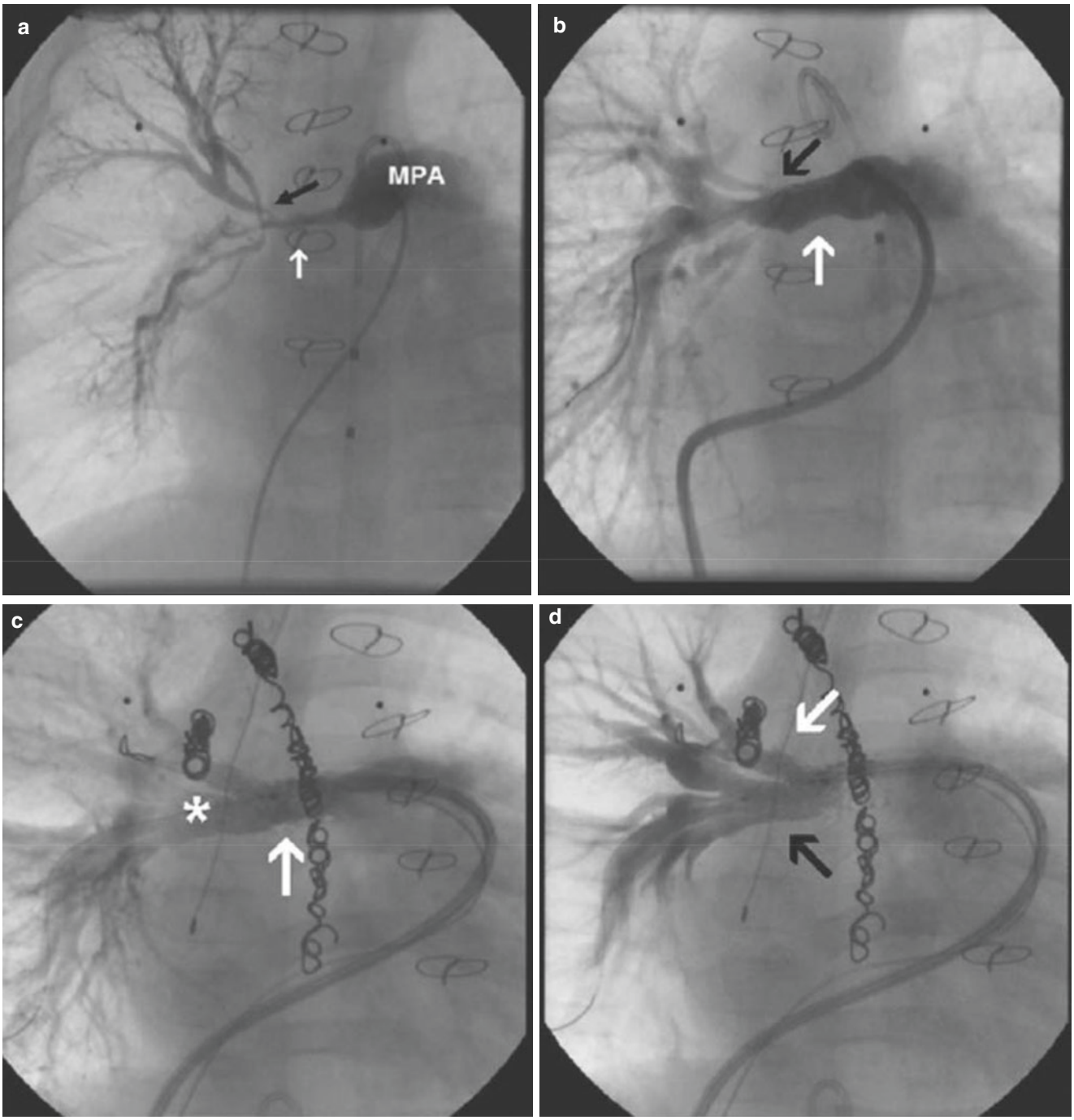

Fig. 20.6 Series of angiograms performed on a patient with absent central pulmonary arteries, multiple collaterals, status post-staged unifocalization with a right ventricle to pulmonary artery homograft, and fenestrated patch closure of the ventricular septal defect. (**a**) Note the severe distal hypoplasia, long-segment proximal RPA stenosis (*white arrow*), and segmental right upper lobe stenosis (*black arrow*) after unifocalization of right pulmonary artery collaterals (this is on the same patient as shown in Fig. 20.3). (**b**) Following multiple transcatheter interventions including high-pressure pulmonary angioplasty and proximal RPA stenting (*white arrow*), there is significant improvement in the distal and proximal vessel diameters of the right upper lobe (*black arrow*) and remaining segments; (**c, d**) after additional transcatheter intervention in the right pulmonary artery (*asterisk*), including balloon angioplasty and stenting plus coiling of remaining aortopulmonary collateral flow, the vessel has been rehabilitated, with significant improvement in diameter of the right upper lobe, distal right lower and middle lobes, as well as proximal RPA (*arrows*)

monary blood flow. Interventions include balloon angioplasty with or without stent placement and coil embolization of residual aorto-pulmonary collaterals. The window of opportunity to achieve the most growth in the vascular bed is during the first 2 years of life. Thus, surgical and catheter interventions should be started early in life.

Patients who undergo placement of a right ventricle to pulmonary conduit will require multiple conduit replacements during their lifetime, secondary to progressive conduit stenosis and/or insufficiency. Stent implantation in the stenotic homograft may delay the need for surgery; however, if the conduit was originally very small, surgical replacement is needed. The development of transcatheter valve technology has offered an alternative to surgical conduit replacement for older children with stenotic or dysfunctional homograft conduits [27, 28].

A few patients may never reach the stage of complete repair because of very hypoplastic pulmonary arteries. In such cases, there is ongoing right to left shunting at ventricular level, associated with variable degrees of cyanosis, reduced exercise tolerance, and propensity for fatal arrhythmia which all lead to overall poor quality of life.

There are few patients with absent central pulmonary arteries and multiple collaterals who have a balanced degree of pulmonary blood flow and who survive relatively well without intervention until the second or third decade of life. Still, the risk of chronic cyanosis and polycythemia with stroke is significant in long term to warrant an intervention, if still feasible. In addition, these patients are at risk of irreversible pulmonary hypertension (affecting the pulmonary segments without stenosis) as well as progressive loss of lung segments from stenosis and occlusion of pulmonary collaterals. Late failure in this setting can only be managed with heart–lung transplantation. Thus, a management approach aimed at intervention during early childhood is preferred whenever feasible.

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Chapter 21
Pulmonary Atresia, Intact Ventricular Septum

Yolandee Bell-Cheddar, Jacqueline Kreutzer, Constantinos Chrysostomou, and Victor O. Morell

Abstract Pulmonary atresia with intact ventricular septum is a rare, initially ductal-dependent congenital cardiac lesion. It occurs at a rate of 4 per 100,00 live births [1]. There are many associated intracardiac anomalies that may occur in pulmonary atresia with intact ventricular septum. It generally occurs in a patient with atrioventricular and ventriculoarterial concordance. There are varying right ventricular morphological changes, and depending on what is present management may vary. The presence of deleterious coronary anomalies presents a major challenge to the management of such patients. In fact, extremes of patient may be offered cardiac transplantation from the very beginning.

21.1 Introduction

Pulmonary atresia and intact ventricular septum was first described in 1783. It was described by Hunter [2]. This cardiac pathology is by no means homogenous. There is a wide range of right ventricular morphological changes. This ranges from severely hypoplastic right ventricle to a right ventricle of adequate size.

The right ventricular outflow tract is not patent at all. This lack of patency can be due to a membranous covering or a muscular obstruction of the outflow region. Conceivably by extrapolation of the concept of "no flow no grow"; one may imagine that since there was no egress of blood into the main pulmonary artery, the blood that would've been flowing through the tricuspid valve would diminish over time. Hence, there is usually an association with tricuspid valve anomaly. The tricuspid valve may leak or become so hypoplastic that there is the resultant near tricuspid atresia.

21.1.1 Embryology

The extent of the right ventricular development varies widely. Kutsche and Van Mierop postulated that this cardiac lesion occurred later in embryologic development [3].

This lesion is thought to occur after septation of the heart has occurred. The pulmonary valve is derived from the endocardial tissue. When the valve fails to develop normally, there may be thickening of the valve leaflets with associated sino-tubular junction abnormalities. On the other hand, there may be a fibrous dimple formed with muscular thickening—without adequate development of the valve leaflets.

21.1.2 Genetic Associations

It may be associated with an autosomal dominant form of inheritance. It is also seen associated with Noonan's syndrome and Williams syndrome.

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21.2 Other Cardiac Associations

21.2.1 ASD

Patients with pulmonary atresia and intact ventricular septum need an atrial level communication.

This could be a secundum ASD or a PFO. This allows for blood flow from the right atrium to the left atrium.

21.2.2 TV Anomalies

As stated before, there is usually tricuspid valve anomalies associated with pulmonary atresia and intact ventricular septum. The tricuspid valve may either be stenotic or regurgitant. In the case of a stenotic tricuspid valve, the annulus is hypoplastic and not well formed, while in the case of very regurgitant tricuspid valve the annulus is usually dilated, and there can be an association with an Ebsteinoid type of tricuspid valve. The general rule of thumb is that a patient with a small right ventricle usually has a hypoplastic tricuspid valve. Patients with a large right ventricle usually will have a regurgitant, Ebstenoid type of tricuspid valve. The latter usually represents a poor prognosis.

21.2.3 Right Ventricular(RV) Anomaly

By definition, the morphologic right ventricle in PA IVS is hypoplastic. The most frequently used description of the morphologic RV is that it is tripartite. By that it means that it has three portions: an inlet/sinus, a trabeculated portion, and then an infundibular/outflow portion. The degree of hypoplasia of the right ventricle is highly dependent on how much of the RV was formed. Some patients have pulmonary atresia intact ventricular septum in which the right ventricle is well formed with all three portions developed; others have no outflow portion of very small trabecular portion and only an inlet developed portion of the RV [4]. In general, hypoplastic and hypertrophic morphological right ventricle has been described in over 50% of patients with PA IVS.

21.2.4 Pulmonary Arteries/PDA

Branch pulmonary arteries are usually confluent. These are supplied by a patent ductus arteriosus.

21.2.5 Coronary Artery Anomalies

Coronary anomalies may be intramural or extramural. They may be congenital or acquired.

There are several changes that can occur. There is an association with the development of ventricular coronary connections. Fistulas between the right ventricle and coronary arteries are one of the most frequent coronary anomalies that can be found.

Usually when the fistula is present, the coronary arteries and right ventricle communicate via sinusoids. Where the fistula and sinusoids meet this area is called a coronary cameral fistula.

These sinusoids are thought to be persistence of embryologic tributaries that supply the myocardium with blood prior to the development of true coronary arteries. In the literature, it has been noted that these connections do not disappear in patients with PA IVS.

Persistence of high pressure within the right ventricle in utero can result in the development of blood tributaries from the right ventricle to the subepicardial space. Due to the high pressure of blood flowing within these tributaries or embryologic blood vessels, there may be development of fibrotic changes and stenosis within the vessels. This may result in atresia or total interruption of these vessels. Hence, the circulation through the vessels become highly dependent on high right ventricular pressure, and so the vicious cycle continues. In general, the diastolic pressure, which is usually sufficient to supply blood flow through the coronary arteries, may no longer be able to do so and hence the high dependence on increased RV pressures. This high-pressure dependence is what is known as right ventricular dependent coronary circulation (RVDCC). Retrograde coronary perfusion then becomes necessary. As would be expected, these lesions tend to occur when the RV is most hypertrophied. Conceivably, therefore, the smaller is the size of the right ventricular cavity, the more predisposed one would be to the development of right ventricular dependent coronary circulation. By extrapolation, a tricuspid valve with a normal or more positive Z score is unlikely to have associated right ventricular dependent coronary circulation [5]. There are several other coronary anomalies that may be associated with pulmonary atresia and intact ventricular septum. One may have single coronary from the aorta or absent coronary from the aorta. Coronary ostial stenosis or coronary ostial atresia may occur. There may be underdevelopment of 1 or 2 or even 3 of the main coronary arteries.

21.3 Clinical Presentation

Because of the development of fetal echocardiographic techniques, most patients are diagnosed in utero. The patients who were not diagnosed in utero would present with hypoxemia and cyanosis. This lesion is a ductal-dependent lesion, and as there is functional and later structural closure of the

patent ductus arteriosus, blood supply to the branch PAs becomes limited, hence the resulting hypoxemia and cyanosis. More profound hypoxemia occurs with later structural closure of the PDA.

On examination, the infant is usually tachypneic and tachycardic. There is usually an active precordium with evidence of left ventricular enlargement, though there may be right ventricular enlargement as well. Typically heart sounds 1 and 2 are single. Initially an S3 or S4 sound is not generally heard. The initial murmur appreciated is that of patent ductus arteriosus; however, a pansystolic murmur in keeping with tricuspid valve regurgitation may be appreciated.

21.3.1 Chest XRAY

The chest x-ray may be normal but may also have increase in size of cardiac silhouette. The increased cardiac silhouette size in this disease is due to ventricular enlargement. This may be right ventricular or left ventricular enlragement. The right border of the cardiac silhouette, which represents the right atrium, may also be enlarged.

21.3.2 EKG

There is no classic EKG finding for pulmonary atresia with intact ventricular septum. These patients usually have normal sinus rhythm with sinus tachycardia. Right ventricular forces are diminished. There may or may not be ST or T-wave changes consistent with subendocardial ischemia. And these ST or T-wave changes may fluctuate over time (Fig. 21.1).

21.3.3 Echocardiogram

Echocardiogram will usually make a clear diagnosis of the cardiac anatomy. It can usually clarify the nature of pulmonary atresia—membranous or fibromuscular. Echocardiography can be used in determining if the pulmonary valve is functional atretic or truly atretic; usually true pulmonary atresia is associated with tricuspid valve regurgitation. It will also clarify the morphology of the right ventricle and tricuspid valve. The biggest limitation of echocardiography in this cardiac anomaly is delineation of the coronary anatomy. Hence, it is recommended that all patients with a diagnosis of pulmonary atresia intact ventricular septum have a cardiac catheterization procedure performed and undergo angiographic study prior to decompression of the right ventricle (Fig. 21.2).

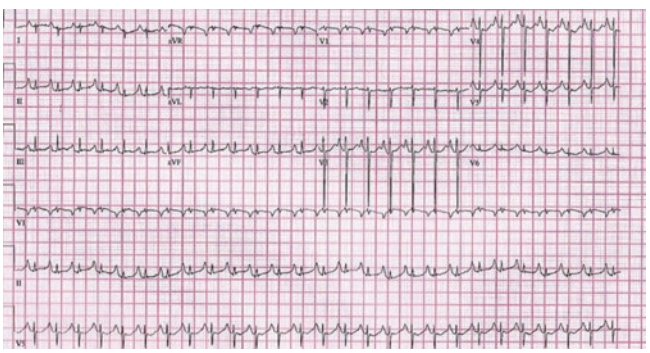

Fig. 21.1 Typical EKG of patient with PA and IVS – Note the paucity of RV forces and right atrial enlargement

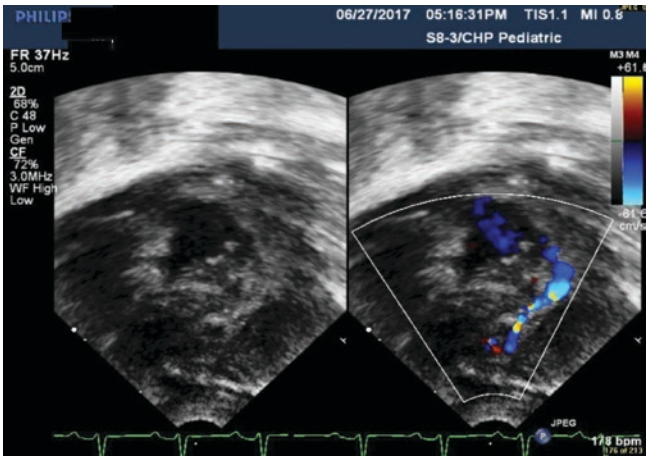

Fig. 21.2 Echocardiography in PA/IVS—showing RV sinusoid, small RV cavity, and minimal outflow tract

21.3.4 Cardiac Catheterization

Cardiac catheterization in this group of patients is used to determine the presence of stenosis within the coronary artery system or the presence of atresia. In general, a tricuspid valve Z score of less than 2.5 predicts clinically important coronary anomalies.

Confirmation of a nonrestrictive atrial level communication is important. In the cardiac catheterization lab one seeks to verify that the A-wave equalizes in going from right atrium to left atrium.

RV pressure is usually suprasystemic but can be subsystemic. Subsystemic RV pressure is usually seen in the face of severe tricuspid valve regurgitation. A cardiac catheterization will confirm the type of pulmonary atresia membranous versus muscular. One may perform selective coronary angiography or angiography of the ascending aorta, as well as a right ventricular angiography to delineate coronary anatomy.

Unfortunately, the invasive procedure for cardiac catheterization is the only means to determine the presence of clinically significant coronary abnormalities in this population of patients—especially RV-dependent coronary circulation.

21.4 Initial Management

Initial management of such patients involves the usual management of any cyanotic patient. Intravenous access should be obtained. Ideally, placement of an umbilical arterial and venous lines would be preferred, and these patients should immediately be started on prostaglandin (PGE).

The next order of management, if the patient had been stable prior, is to ensure continued stability of the respiratory function. Determine the need or lack thereof for respiratory support.

At times, though the patient may be stable from a respiratory perspective, one may need to intubate the patient in order to assist in balance in QP:QS as pulmonary vascular resistance falls.

It is important to assess the pH milieu of these patients and avoid acidosis.

And of course, if the patient is significantly hemodynamically unstable and extracorporeal membrane oxygenation is offered at the institution, one must assess the need for ECMO cannulation.

In patients who are predisposed to coronary ischemia, avoid hypotension. One may need to add inotropic support in order to increase systemic vascular resistance. This could be in the form of epinephrine or phenylephrine.

21.5 Initial Intervention

Whatever we do initially for this rare but potentially very ill group of patients must be done with the goal of minimizing complication, minimizing mortality, and striving to obtain biventricular physiology.

The initial intervention on these patients may be surgical or via cardiac catheterization.

Initial order of business is to determine whether or not the RV can be decompressed, and this can be done either surgically or through cardiac catheterization procedure.

One also needs to determine a way in order to establish a more long-term form of pulmonary blood flow. This can be done in the cardiac catheterization lab through placement of a stent/stents within the patent ductus arteriosus or surgically through the performance of the aorta to pulmonary shunt, such as a Blalock-Taussig shunt.

Patients with significant RV-dependent coronary circulation usually would be shunted only, without RV decompression.

In most cases, however, patients who receive a shunt tend to go on to a univentricular pathway.

In patients without significant RV-dependent coronary circulation, the options for intervention may include the relief of RV obstruction only, RVOT obstruction relief with placement of an aortopulmonary shunt, or only placement of an aortopulmonary shunt.

The literature is rich in reports of the association of increased mortality with smaller tricuspid valve. That is, tricuspid valve annular with a Z score that is less than 2.5 has been associated with increased mortality rate. This increased mortality rate, however, is seen in such patients who undergo RV decompression.

Studies exist that show that fetal tricuspid valve score and rate of growth can assist in in the determination of postnatal outcome. Fetal studies have noted that the extent of tricuspid valve regurgitation can be associated with postnatal outcomes.

Dr. Frank Hanley in his research on outcomes and factors contributing to death has found that lower birth weight, tricuspid valve size, and the presence of significant RV-dependent coronary circulation are all risk factors for death in this population [6].

It is important to know what significant RV-dependent coronary circulation means. If one of the three major coronary artery is atretic, then this is considered significant. If more than two major coronary vessels are affected, this is also considered significant. And of course if the LV myocardium is supplied by RV fistula, then that is also considered to be a significant coronary anomaly. In the presence of any of these three things, RV decompression is not recommended. It must be noted that the presence of fistulas or sinusoids alone does not equal a poor prognosis.

There are institutions that have these patients listed for cardiac transplantation, when there is significant RV-dependent coronary circulation. These patients, while waiting for cardiac transplant, will remain on PGE or receive a PDA stent or undergo placement of an aortopulmonary shunt. There is a group of patients in whom one may decide to perform a tricuspid valve closure as part of the initial management.

21.6 Surgical Management

The surgical management is based on the degree of right ventricular hypoplasia and on the coronary anatomy, mainly the presence or absence of right RVDCC [6, 7]. There are a number of surgical strategies available, including the following.

1. Two Ventricle Repair

This strategy is used in patients with mild RV hypoplasia, with a tricuspid valve Z-score > -2, in the absence of RVDCC. Initially, these patients undergo placement of a right ventricular outflow tract patch with or without the addition of a systemic to pulmonary artery shunt (Fig. 21.3). The interatrial communication is left open. Subsequently, they

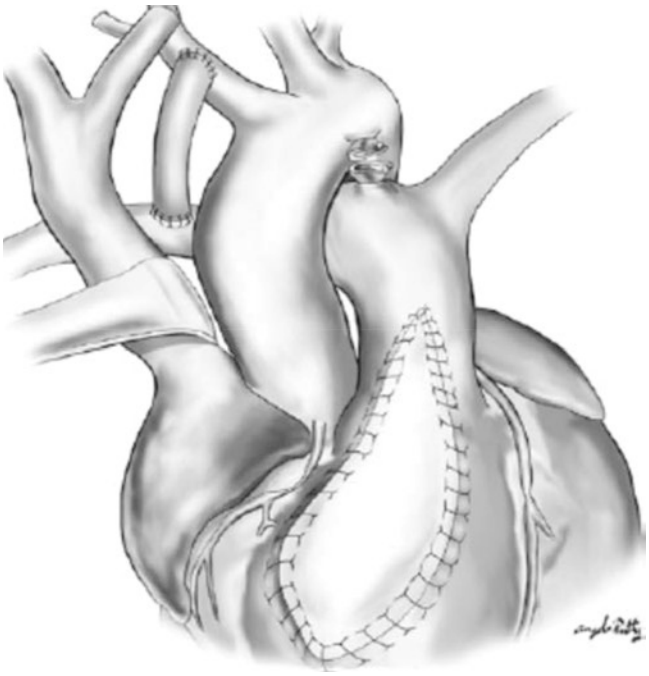

Fig. 21.3 Right ventricular outflow tract patch and a right systemic to pulmonary artery shunt. The PDA has been ligated and divided

undergo ASD closure and shunt occlusion in order to achieve a biventricular repair.

2. Single Ventricle repair

This strategy is used in the presence of severe RV hypoplasia, with a tricuspid valve Z-score <−5 and/or RVDCC. Initially, a systemic to pulmonary artery shunt is placed, followed by a bidirectional Glenn. Eventually, the patient will undergo a Fontan procedure.

3. One and One-Half Ventricle Repair

This strategy is used in the presence of moderate RV hypoplasia, with a tricuspid valve Z-score >−2 but <−5, in the absence of RVDCC. Initially, the patient undergoes placement of a RVOT patch and a systemic to pulmonary artery shunt. Subsequently a bidirectional Glenn is performed with closure of the ASD and shunt occlusion.

4. Cardiac Transplantation

This strategy is used in the presence of RVDCC with aorto-coronary atresia. Patients with this coronary anatomy have a very high incidence of sudden death [7].

21.7 Cardiac Catheterization Management

Patients with membranous pulmonary atresia and good-sized tripartite right ventricles can undergo wire, laser, or radio-frequency-assisted valve perforation, followed by balloon valvotomy [8–10]. The technique of radiofrequency perforation has been perfected and expanded worldwide with the use of the Baylis-Nykanen catheter system. Fig. 21.4a–d.

Although successful perforation mostly using this technique has been reported in up to 75–90% of selected patients, the procedure is definitive for only 35% of cases [4, 5, 7] as they commonly require additional intervention either transcatheter or surgical (placement of Blalock-Taussig shunt or PDA stenting) [8]. Given that most patients with pulmonary atresia have hypoplastic right ventricular outflow tract and pulmonary annulus, many believe that in order to achieve adequate right ventricular decompression and to maximize right ventricular growth, a surgical right ventricular outflow tract patch is necessary. Thus, in the presence of marked pulmonary annular and right ventricular outflow tract hypoplasia, surgical management is preferred rather than transcatheter therapy as the best method to achieve maximal right ventricular outflow tract decompression.

Following initial right ventricular outflow tract decompression, some patients will be able to wean from prostaglandins. Those who do not after 2 weeks will require an additional source of pulmonary blood flow, either as a BT shunt or a PDA stenting.

During follow-up, additional transcatheter interventions may be indicated, such as transcatheter closure of atrial septal defect with device and coil embolization of a BT shunt.

21.8 Postoperative Management

Postoperative care of these patients is highly dependent on what procedure is performed.

21.9 Overall Prognosis

Lower birth weight, tricuspid valve size, and the presence of significant RV-dependent coronary circulation are all risk factors for death in this population [7].

In a recent Multicenter study looking at reinterventions after RV decompression in patients with pulmonary atresia intact ventricular septum, it was found that these patients have a high risk for reintervention. One positive finding, however, was that these patients mostly achieved a biventricular physiology. This study noted that patients with mild tricuspid valve regurgitation prior to RV decompression are of higher risk for reintervention procedures; these were the patients who ended up being univentricular or with 1–1/2 ventricular circulation over time. This study suggested that the degree of TR and its physiology were more of a determinant than the

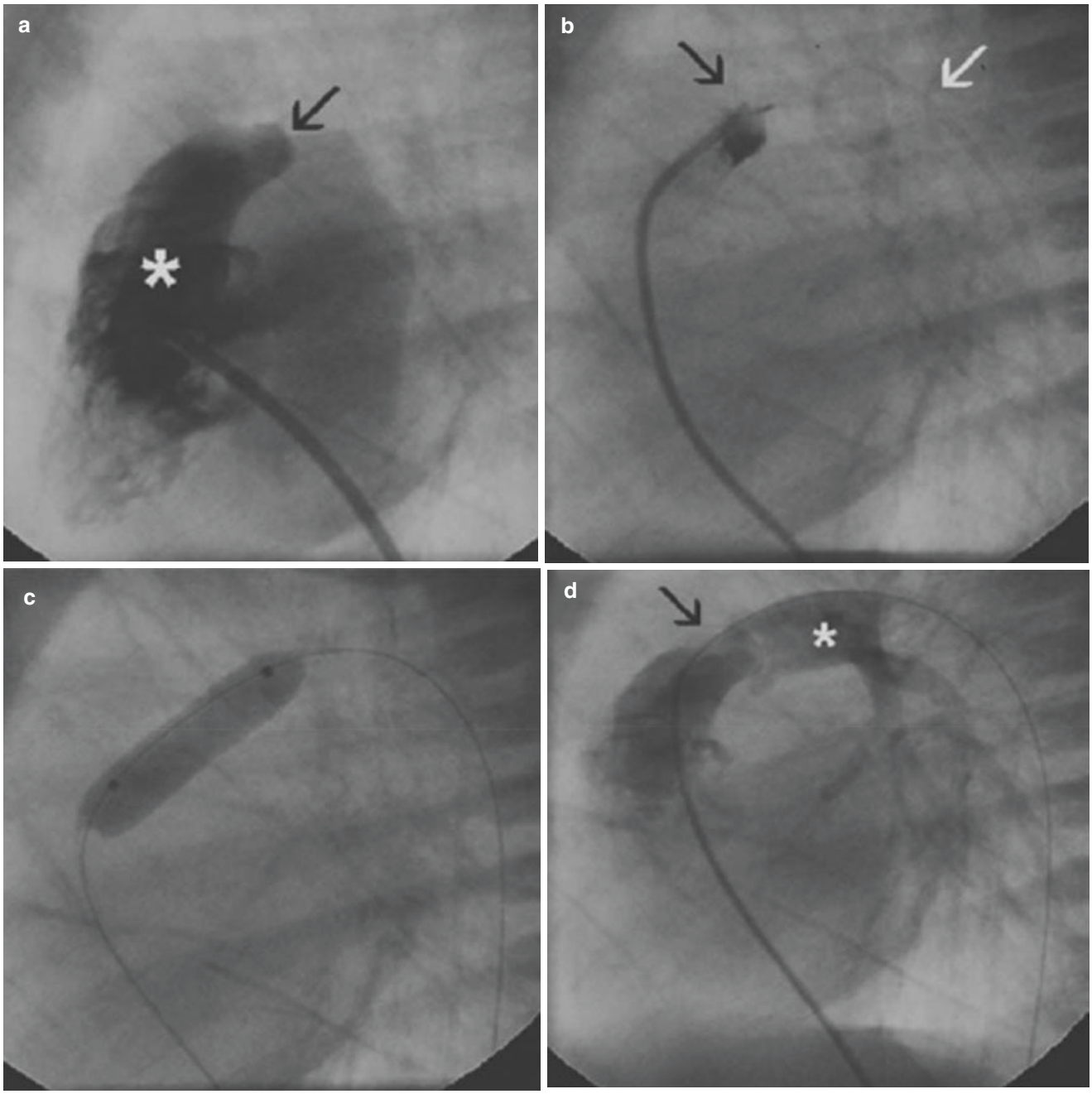

Fig. 21.4 (**a**) In lateral projections, a right ventriculogram demonstrates a membranous pulmonary valve atresia (*black arrow*), with a reasonable size right ventricle (*white asterix*) and no evidence of any right ventricular to coronary artery connections. As commonly seen, there is tricuspid valve regurgitation so that contrast fills backward the right atrium, (**b**) Using a 4F right coronary artery JR2 catheter, the radiofrequency wire is activated, aimed at the membranous valve. The aortic pigtail catheter (*white arrow*) is positioned across the PDA or in the descending aorta for angiography to document the anatomy of the main pulmonary artery. Following radiofrequency burn through the membranous valve, the tip of the wire is seen across the valve plate (*black arrow*); (**c**) following radiofrequency perforation, a guidewire is advanced across the valve down to the descending aorta through the PDA and a balloon catheter is used then for the valvotomy; (**d**) angiography of the right ventricular outflow tract following radiofrequency perforation of the pulmonary valve demonstrates wide open pulmonary valve (*black arrow*), with unobstructed filling of the main pulmonary artery (*white asterix*)

actual tricuspid valve annular size, as had been described in previous studies [11]. PA IVS is a cyanotic heart disease that generally portends a bad prognosis. However, there are subpopulations within this group of patients who can achieve favorable outcomes.

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Chapter 22
Pulmonary Stenosis

Yuliya A. Domnina, Ricardo A. Munoz, Jacqueline Kreutzer, and Victor O. Morell

Abstract Pulmonic stenosis refers to an obstruction at or distal to the right ventricular outflow. Due to various possible levels of obstruction, this disease is not a homogeneous entity. Obstruction can be found at the valvar level, the RV infundibulum, and/or the supravalvular level within main pulmonary artery or distal to it at multiple levels. It is also found in association with VSD and overriding aorta as in Tetralogy of Fallot (TOF) (see associated chapter). Twenty-five to thirty percent of patients with congenital heart disease suffer from some form of pulmonary stenosis (Latson LA, Prieto LR. Pulmonary stenosis. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ, eds. *Moss and Adams' Heart Disease in Infants, Children, and Adolescents*, 6th ed. Lippincot Williams & Wilkins; 2001:820–821). Various forms of pulmonary stenosis are found in association with genetic syndromes such as Noonan's, Williams and Alagille.

Subvalvular PS, which is a rare condition in its isolated form. Lesions of pulmonary artery stenosis can present at the level of the main pulmonary artery, in right and left branch pulmonary arteries, at bifurcation sites, or at the distal branches.

Untreated pediatric or adult PS usually becomes a progressive condition with the gradient across pulmonary valve and hypertrophied infundibulum increasing over time.

Balloon pulmonary valvuloplasty is the treatment of choice for the relief of valvular PS.

Surgical management is reserved for those patients in whom a balloon valvuloplasty and/or arterioplasty was not successful. Life expectancy in mild, moderate, or severe pulmonary stenosis after repair is within normal limits.

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22.1 Anatomy

22.1.1 Pulmonary Valve Stenosis (PS)

Valvular PS with intact ventricular septum typically is an isolated anomaly and accounts for 5–10% of all congenital heart defects [1]. The valve leaflets are usually thin with fused comissures. A 1–2 mm central opening is seen, and the valve presents as a doming structure projecting into the main pulmonary artery. The right ventricle is typically hypertrophied, and there is poststenotic dilation of the main pulmonary artery. Valvular dysplasia is found in 10–20% of patients with all forms of PS. Dysplastic valves are trileaflet with markedly thickened cusps comprised of myxomatous tissue and little, if any, commissural fusion. Reduced mobility is exhibited, and the valve annulus is usually hypoplastic. This entity is frequently found in patients with Noonan's syndrome [1].

22.1.2 Subvalvular Pulmonary Stenosis

Subvalvular PS is a rare condition in its isolated form. There are two distinct lesions described within this diagnostic entity. The first occurs when an obstructive fibrous or

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muscular band divides the right ventricle into two chambers (main body and infundibulum) and is called a double-chambered right ventricle. The second is a diffuse fibromuscular narrowing of the infundibular portion of the right ventricle. Clinically, the disease is usually progressive with patients closely resembling those with isolated valvular PS. The treatment is surgical with approach through a right atriotomy for the excision of the obstructive muscle bundle or through a right ventriculotomy for infundibular muscle resection.

22.1.3 Pulmonary Artery Stenosis

Lesions of pulmonary artery stenosis can present at the level of the main pulmonary artery, in the right and left branch pulmonary arteries, at bifurcation sites, or at the distal branches. Peripheral pulmonary artery stenosis (PPS) occasionally occurs at a single level and refers to a narrowing in a branch pulmonary artery; however, multiple sites of obstruction are more characteristic. PPS is frequently a benign condition that presents most commonly with a systolic ejection murmur auscultated in infancy (physiologic PPS). It is seen in neonates due to discrepancy in the size of the main pulmonary artery and the left and right branch PAs. This is usually a mild condition with no significant health consequences. The murmur usually disappears within a few months. PPS can also be pathologic and associated with genetic syndromes and congenital infections. In Rubella syndrome, there is peripheral stenosis of the pulmonary arteries associated with patent ductus arteriosus (PDA) [2]. An intervention for this PPS is rarely needed. Peripheral pulmonary stenosis may be seen, and branch pulmonary arteries could also be diffusely hypoplastic in Noonan's syndrome. This syndrome is associated with lymphedema, webbed neck, dysmorphic features, and hypotonia [3]. Patients with William's syndrome develop PPS in association with supravalvar pulmonary and aortic stenosis with or without coarctation of the aorta or peripheral systemic arteriopathy; pulmonary valvar stenosis occurs less frequently [4–5]. In Alagille syndrome, there is extensive pulmonary stenosis at various levels. Mutations in either jagged-1 (*JAG1*) or notch-2 (*NOTCH2*) have been reported in patients with Alagille syndrome. Pulmonary valvar stenosis and diffuse main and branch pulmonary artery stenosis are usually present [6]. There is no specific genetic linkage found for an isolated pulmonary stenosis.

22.2 Pathophysiology

22.2.1 Pulmonary Valve Stenosis (PS)

In PS, right ventricular (RV) pressure increases to overcome the stenosis of the pulmonary valve. In the case of critical PS (ductal dependent), there is not enough antegrade flow across the pulmonary valve to allow a normal cardiac output. Thus, the patent ductus arteriosus (PDA) needs to remain open to allow pulmonary blood flow via a left-to-right shunt. In addition, decreased compliance of the RV may occur and lead to mandatory right-to-left shunting across the patent foramen ovale (PFO) to ensure adequate systemic blood flow. The later hemodynamic situation will lead to systemic desaturation and cyanosis. The neonatal myocardium undergoing hyperplasia and hypertrophy is capable of generating increased intraventricular pressure necessary to overcome fixed obstruction. However, compliance of the RV decreases shortly after birth, and signs of RV failure manifest as the complete cardiac output is expected to go through the stenotic valve orifice. The noncritical PS is rarely seen in the intensive care unit, except in the rare cases of postintervention recovery period complicated by congestive heart failure and other postprocedural events (see below).

Untreated pediatric or adult PS usually becomes a progressive condition with the gradient across pulmonary valve and hypertrophied infundibulum increasing over time. Continued elevation of right ventricular end-diastolic pressure as a result of RV hypertrophy compromises diastolic RV myocardial perfusion. Ventricular arrhythmias and sudden death can occur. Evidence of RV subendocardial ischemia/infarction and fibrosis can be seen in postmortem cases with severe PS.

22.2.2 Branch Pulmonary Artery Stenosis

In the presence of branch pulmonary artery stenosis, there is an increase in the afterload to the right ventricle with subsequent right ventricular hypertension and dysfunction. The impact of increased afterload is more deleterious in patients with associated pulmonary regurgitation (for example, patients who have had TOF repair with transannular patch) as the RV suffers from additional pressure and volume overload. The RV of patients with dysfunctional contractility patterns (poor coordination between the sinus and the infundibular portion of the RV) becomes dilated, and it may lead to an increased risk of ventricular arrhythmias and sudden death. The degree of RV hypertension is dependent upon the severity of the arteriopathy (multiple versus single and unilateral versus bilateral stenosis). In the presence of any intracardiac septal defect, patients may exhibit significant arterial oxygen desaturation due to right-to-left shunting via PFO. Occasionally, desaturation may also be seen due to severe V/Q mismatch in the absence of a septal defect. The effect of branch pulmonary artery stenosis on blood flow distribution leads to increased flow to the unaffected branches with the potential development of segmental pulmonary artery hypertension in those branches without stenosis.

22.3 Clinical Findings

The clinical presentation of pulmonary stenosis is diverse due to variable severity of the obstruction. Valvular pulmonary stenosis presenting in the neonate as critical PS will typically appear with cyanosis that is apparent at birth due to suprasystemic RV pressure and right-to-left atrial shunting through a PFO. Infants may also become hypoxemic and acidotic due to inadequate pulmonary flow and decreased cardiac output as the PDA begins to close. Patients with mild-to-moderate degree of stenosis are usually asymptomatic initially but, as the gradient increases, may present with fatigue and dyspnea precipitated by exertion. As the disease progresses and the obstruction become more severe with increasing age, untreated patients may become symptomatic at rest with manifestations of right heart failure: hepatomegaly, peripheral edema, dyspnea, angina, syncope, arrhythmia, and sudden death.

On physical examination, a careful palpation of the chest demonstrates a prominent RV impulse. In the case of valvular stenosis, auscultation elicits a normal first heart sound, (S1) followed by an ejection click, best heard at the upper sternal border. The pulmonary stenosis is typically more severe the shorter the distance from S1 to the click. An early systolic click is noted in all cases of pulmonary stenosis except those with dysplasia of the pulmonary valve (more commonly seen in patients with Noonan's syndrome). A diamond-shaped ejection murmur is best heard at the left upper sternal border with radiation into the lung fields and the back. It is typically harsh and usually IV/VI or more. As the severity of the stenosis increases, the peak of intensity of the murmur occurs later. If bilateral obstruction is present, the murmur will be heard throughout the chest. A soft P2 secondary to decreased PA pressure due to severe stenosis may be noted. In mild cases of PS, the second heart sound (S2) can be normally split and, as the severity increases, can become more widely split. In critical PS, S2 becomes single.

ECG reveals right axis deviation and several degrees of RVH, according the severity of the stenosis. An RsR' pattern may be seen in V1. Right atrial enlargement may be noted in severe cases. In the case of severe valvular pulmonary stenosis associated with right ventricular hypoplasia (a condition similar to that of pulmonary atresia with an intact ventricular septum), the right ventricular forces will be decreased and left axis deviation may be seen in the newborn.

Chest radiography usually demonstrates normal heart size. Mild-to-moderate pulmonary stenosis is associated with dilatation of the main pulmonary artery and left pulmonary artery. Severe or critical pulmonary stenosis will result in oligemic lungs and an increased cardio-thoracic ratio. In branch pulmonary artery stenosis, if unilateral, differential/asymmetric flow distribution may be observed in the chest radiograph.

In echocardiogram, the pulmonary valve is typically best assessed from the parasternal short-axis view. The right ventricular outflow tract (RVOT) is best interrogated from the parasternal short axis view and subcostal position [7]. The gradient across the pulmonary valve will determine the severity of the RVOT obstruction and/or PS. The maximum instantaneous pressure pulsed wave Doppler gradient is often at least 10% higher than the instantaneous peak-to-peak gradient measured in the cardiac catheterization laboratory. This discrepancy is due to a phase delay between peak velocities and pulmonary artery systolic pressure. In the presence of proximal branch pulmonary artery stenosis, gradients and anatomic narrowing can be documented in the branch pulmonary arteries. If the stenosis is distal, the lesion cannot be assessed by echocardiography.

22.4 Management

22.4.1 Preintervention

In neonates with severe pulmonary valve stenosis with profound hypoxemia and cyanosis, PGE is necessary to preserve ductal patency and allow left-to-right shunting. Mechanical ventilation may be utilized in the setting of coexistent lung disease, cardiogenic shock, and profound cyanosis until the patient's stabilization and restoration of appropriate pulmonary blood flow. While prostaglandin infusion is used to stabilize these infants and transition to ex-utero life, it also allows for less-urgent timing of intervention. Within the first day or two of life, though, intervention that is more definitive must occur. Balloon pulmonary valvuloplasty is the treatment of choice for the relief of valvular PS. When planning for balloon dilatation of pulmonary valve, the nature of the valve leaflets and diameter of pulmonary valve annulus has to be studied by 2D echocardiography to determine the size of the balloon needed. In patients with branch pulmonary artery stenosis, a lung perfusion scan can assess blood flow distribution and assist in the management approach. This test should be performed before and after the intervention to evaluate the success of the procedure.

22.4.2 Intervention

22.4.2.1 Valvular PS: Balloon Pulmonary Valvuloplasty

Mild pulmonary valve stenosis does not require therapeutic intervention. However, as stated above, balloon pulmonary valvuloplasty is the treatment of choice for children with moderate to severe stenosis. Cardiac catheterization should be performed to balloon-dilate the stenotic pulmonary valve,

and it is generally recommended that the procedure be performed for peak-to-peak gradients in excess of 40 mmHg. The decision to intervene should not rest solely on the PV gradient in the setting of RV dysfunction or critical stenosis, in which case intervention may be indicated regardless of the gradient. The procedure is performed under general anesthesia or intravenous sedation. In newborns and young infants, general anesthesia is indicated. The femoral artery and femoral vein are catheterized for hemodynamic measurements and right side angiography (Fig. 22.1a). The technique involves crossing the stenotic valve with a floppy guidewire, exchanging the catheter for a balloon catheter, and inflation of the balloons with diluted contrast material for a few seconds (Fig. 22.1b). The currently recommended balloon/

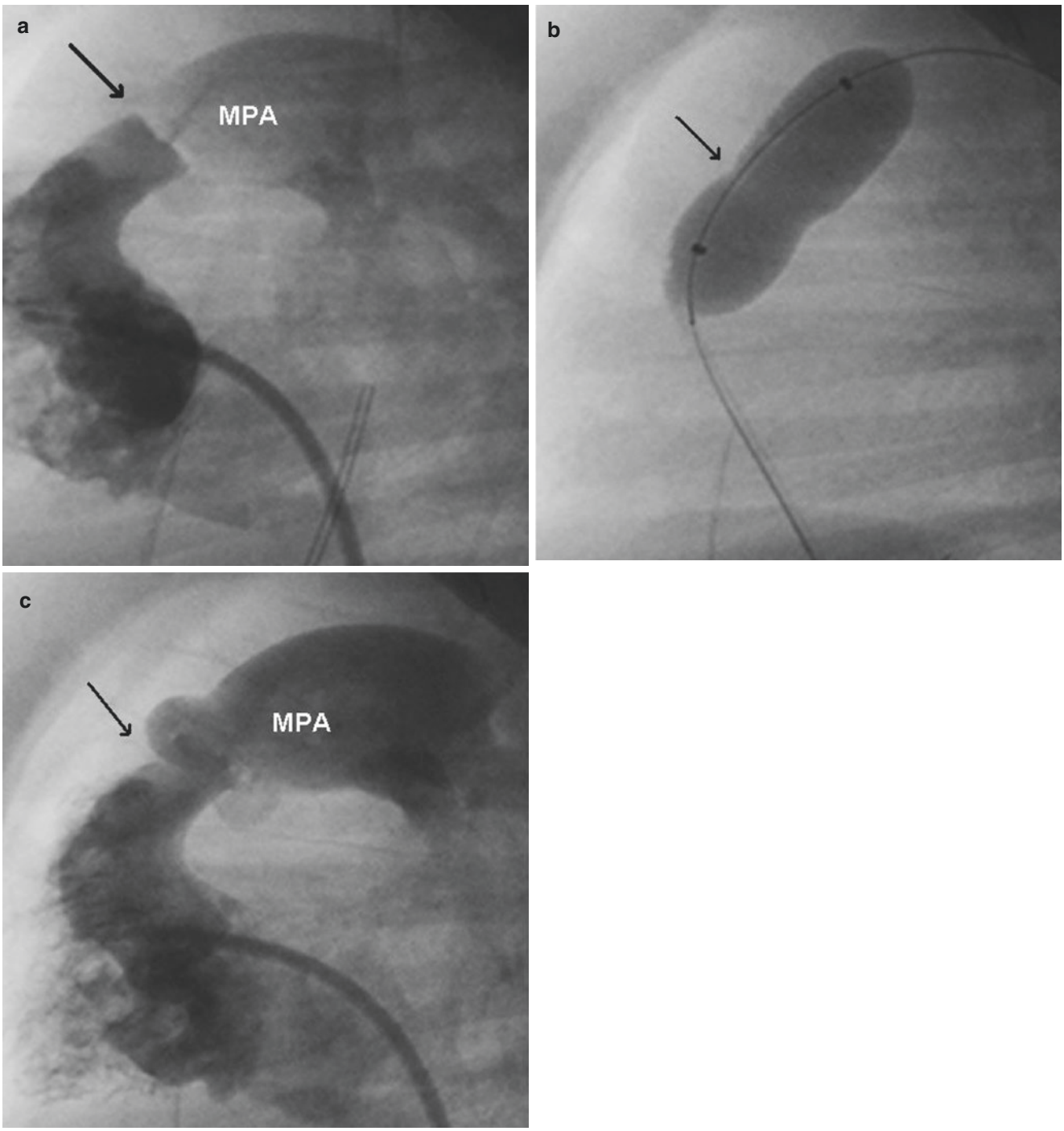

Fig. 22.1 (**a**) Right ventriculogram performed in lateral projection demonstrates a severe degree of pulmonary valve stenosis, with a tiny jet of contrast crossing the valve (arrow). The main pulmonary artery (MPA) is large with some poststenotic dilation. There is no supravalvar obstruction. (**b**) Balloon valvotomy of pulmonary valve. (**c**) Right ventriculogram following balloon procedure demonstrates significant increase in valve orifice (arrow), with no evidence of residual obstruction. MPA is main pulmonary artery

annulus ratio is 1.2 to 1.25 with a maximum of 1.4. The pressure gradient is determined post valvotomy. If significant, it is important to identify if the gradient is due to residual valvar PS or dynamic subpulmonary stenosis post valvotomy. Ventricular angiography can help with this diagnosis (Fig. 22.1c).

Immediate reduction of gradient, increase in jet width, and free motion of the pulmonary valve leaflets with less doming have been observed following balloon dilatation. Improvement of right ventricular function, tricuspid insufficiency, and right-to-left shunt are also observed. Restenosis, defined as a gradient of ≥50 mmHg, has been observed in nearly 10% of children. Predictors of restenosis include balloon/annulus ratio <1.2 and immediate postvalvuloplasty gradient of ≥30 mmHg, small pulmonary valve annulus, and postsurgical complex pulmonary stenosis. Redilatation with balloons that are larger than those used at the time of initial balloon valvuloplasty produces excellent results and is the procedure of choice. Balloon pulmonary valvuloplasty is equally successful in neonates, as well as in adult subjects. However, the chances of repeat intervention in the newborn with critical PS are higher than those for the infant, child, or adult presenting electively with moderate to severe PS. Lifelong follow-up to identify the significance of residual pulmonary insufficiency is indicated [8–9].

Complications during and immediately after balloon valvuloplasty have been rare (0.35% major complication rate by the VACA registry) [10]. However, the complication rate is higher in the newborn with critical PS. Reported complications include balloon rupture, blood loss requiring transfusion (especially in newborns), bleeding/hematoma at the catheter site, arrhythmias (including complete heart block), cardiac arrest, perforation of the right ventricular outflow tract with tamponade, and death. In the case of extensive wire perforation of the right ventricular outflow tract, emergency surgical intervention is indicated. If a small guidewire perforation occurs, pericardioscentesis and transfusion may be all that is needed [11]. "Suicidal" right ventricle (severe right ventricular contractility failure associated with severe right ventricular outflow tract obstruction) could be seen in patients post balloon dilatation of the pulmonary valve in the presence of severe right ventricular hypertrophy. Immediately following the balloon procedure, there is an acute drop in cardiac output related to a lack of ejection of the right ventricle due to post dilation dynamic subpulmonary muscular obstruction. This can also be seen post surgical relief and is more likely in patients with an initial right ventricular pressure of over 100 mm Hg with severe infundibular hypertrophy. As the development of hyperdynamic right ventricular outflow tract obstruction cannot be predicted with certainty, preemptive intervention such as hydration and beta-blockade therapy should be instituted prior to balloon dilatation in cases of severe right ventricular hypertrophy.

Previous surgery and pulmonary valve dysplasia are not contraindications for balloon valvuloplasty. Indeed, the use of high pressure balloons for resistant pulmonary valves can increase success rate greatly.

22.4.2.2 Supravalvular and Peripheral Pulmonary Artery Stenosis

Supravalvular and peripheral lesions can be a challenge for effective management. Surgery can be performed for proximal lesions; however, the recurrence rate for branch lesions can be high, especially if there is a diffuse arteriopathy. The distal lesions are impossible to access surgically, and thus transcatheter interventional strategies have become the standard of care. Patients with diffusely hypoplastic pulmonary arteries and/or discrete or multiple areas of branch stenosis may benefit from one or serial interventional catheterizations (single and multiple balloon dilations during the same or multiple procedures).

The management options for patients with PPS include the following:

1. Balloon pulmonary arterioplasty (BPA)
2. Stent implantation
3. Surgical pulmonary artery plasty

Indications for intervention include the following:

1. Right ventricular hypertension
2. Abnormal differential blood flow distribution on lung perfusion scan (less than 30% of flow to the affected lung)
3. Segmental pulmonary artery hypertension in the unaffected vessels (mean distal pulmonary pressure of >25 mmHg).
4. Inadequate pulmonary blood flow distribution precluding corrective surgery (such as PPS associated to unrepaired TOF variants) or associated with cyanosis.
5. Presence of pulmonary artery distortion associated with single ventricle physiology in the form of cavopulmonary shunt or Fontan procedure.

22.4.2.3 Balloon Pulmonary Arterioplasty (BPA)

Since the results of surgical pulmonary artery plasty have been quite unsatisfactory in patients with peripheral pulmonary artery stenosis, transcatheter intervention remains the first-line therapy (Fig. 22.2). However, surgical plasty continues to be the procedure of choice for specific conditions (such as stenosis associated with shunt anastomosis in patients undergoing further surgery), as well as for patients who have failed transcatheter management attempts for surgically reachable lesions.

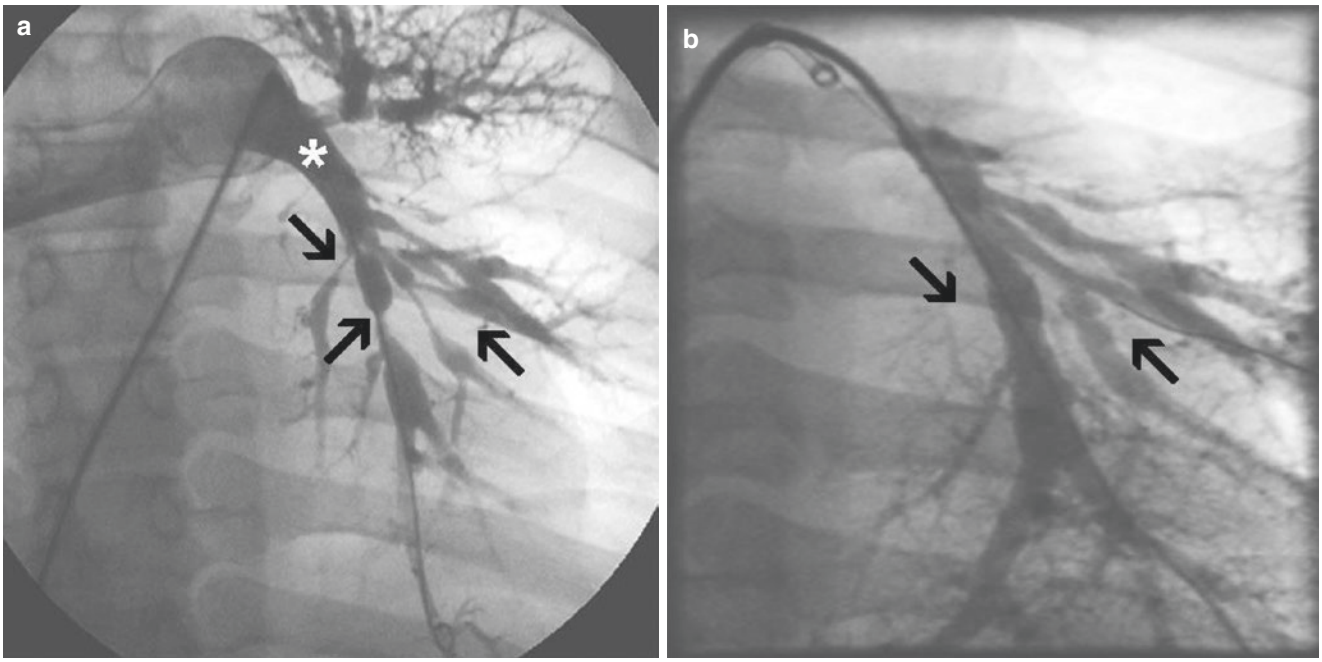

Fig. 22.2 (**a**) Left pulmonary artery angiogram performed in a patient with severe peripheral pulmonary artery stenoses. The arrows point to some of the areas of stenosis. The proximal left pulmonary artery (∗) is mildly hypoplastic, but the worse stenosis is at the lobar, segmental, and subsegmental levels. (**b**): following multiple pulmonary artery balloon dilation procedures in the left lower lobe, angiogram demonstrates significant angiographic improvement in vessel diameter post intervention (arrows)

In current practice, high pressure balloons are almost always used to address both discrete and long-diffuse lesions of pulmonary artery stenosis (Fig. 22.2a). Reported results indicate a success rate of 50 to 75%. Following the advent and availability of the cutting balloon (a bladed balloon sized up to 8 mm in diameter), the success rate has increased to over 90%. Restenosis post-balloon dilation has been reported in up to 15 to 35% of cases, but the degree of restenosis is unpredictable as the underlying disease processes are variable. For example, the peripheral pulmonary arteriopathy of the Williams syndrome is quite different from isolated discrete "coarctation" of the left pulmonary artery. In the latter, the results of BPA +/− stenting are excellent, while the former may produce disappointing results. In addition, the definition of restenosis can be highly variable in different studies. This can be demonstrated in pediatric literature where lack of vessel growth may be considered restenosis when, in truth, it may have been the natural course of the disease.

The incidence of complications reported varies from 6 to 10% and includes nonfatal pulmonary artery tears, pulmonary hemorrhage, reperfusion injury/pulmonary edema, distal vessel aneurysm formation, and deep vein thrombosis. The procedure-related mortality is reported to be 1%. Death occurs from vessel rupture (tears) or cardiac arrest in patients with suprasystemic RV pressure and poor right ventricular function. Immediate transcatheter management of unconfined tears (coil embolization of bleeding vessel or tear itself) is used as an approach to reduce morbidity and mortality. Reperfusion injury/pulmonary edema occurs in about 4% of cases, and aneurysm can be seen in <5% [12].

High risk factors for BPA-related complications are as follows

- Suprasystemic right ventricular pressure
- Associated right ventricular dysfunction
- History of vessel trauma/hyperperfusion edema at prior transcatheter procedures
- Williams syndrome
- Low cardiac output
- Multiple peripheral distal lesions

Various measures can be utilized to avoid or lessen potentially fatal complications, including the use of general anesthesia for the procedure, inotropic support if needed, and blood transfusion to treat any anemia. For those patients with right ventricular dysfunction and suprasystemic right ventricular pressure, the creation of an interatrial communication prior to the balloon procedures may be advantageous as it will lead to right-to-left shunting and, thus, preserve the blood pressure during balloon inflations. For high-risk patients, recovery in the intensive care unit should be planned. A close follow-up of BPA-induced tears (particularly uncontained) should be planned in a form of chest CT angiography, recatherization, or both.

22.4.2.4 Intravascular Stent Implantation

Balloon expandable intravascular stents implanted into the sites of pulmonary artery stenoses have been found to significantly improve the effectiveness of balloon angioplasty (Fig. 22.3).

Multiple reports in the literature have confirmed high success rates for pulmonary artery stenting (above 90%) and promising long-term results [13]. Stents are especially indicated and preferred when the stenosis is due to external compression (Fig. 22.4). Fractures, thrombosis, aneurysm formation, or stent migration is extremely rare. Stent redilation

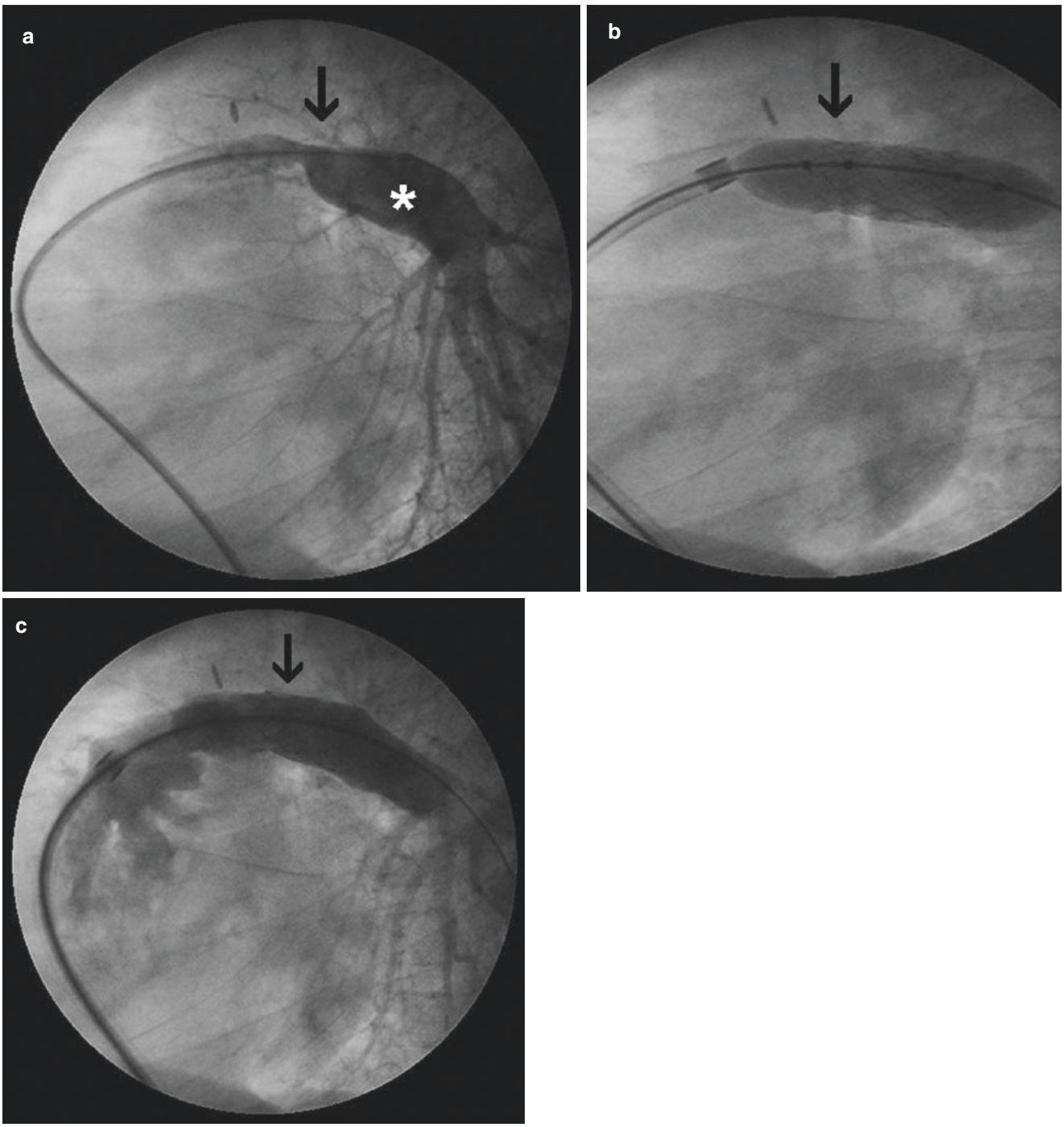

Fig. 22.3 (**a**) In the lateral projection, selective left pulmonary (∗) angiogram demonstrates severe proximal stenosis (arrow). (**b**) Implantation of a stainless steel stent over a BIB balloon across the area of stenosis (arrow). (**c**) Following stent implantation, there is significant angiographic improvement

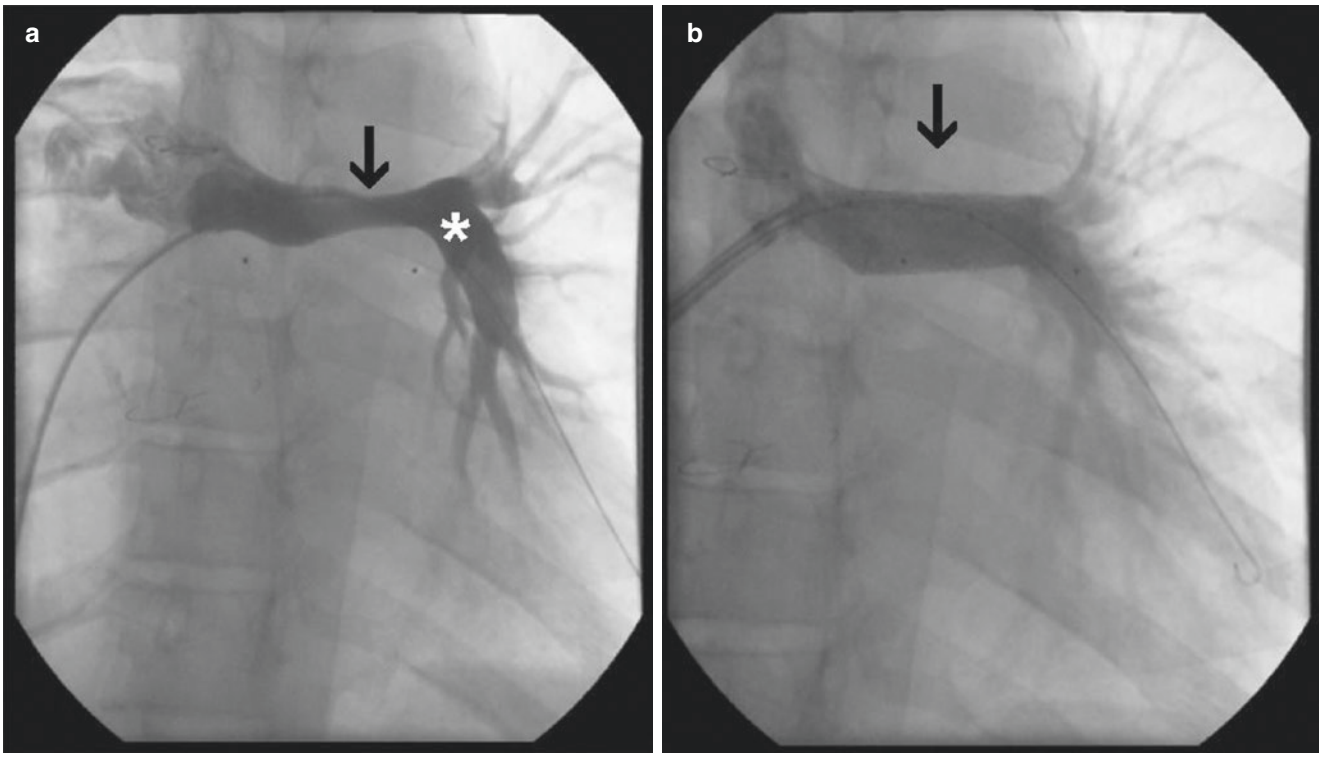

Fig. 22.4 (**a**) Selective left pulmonary artery (∗) angiogram performed in a patient following Fontan after neonatal Norwood procedure. Note that there is stenosis at the proximal left pulmonary artery (arrow), which is related to inferior compression by the augmented neo-aortic arch. (**b**) Following stent implantation, the stenosis is resolved (arrow)

can be performed with success up to 10 years. However, stent implantation has theoretical disadvantages over BPA. These include a need for larger introducer sheaths and subsequent dilations to keep up with somatic growth, the possible occlusion of branching vessels, and surgical implications. Significant restenosis is quite rare, except for that related to a lack of growth. In-stent restenosis (ISR) is usually a result of neo-intimal proliferation or rarely stent fracture.

In the past few years, drug-eluting stents (DES) have emerged as one of the most promising technologies in the field of interventional cardiology. Loaded with antiproliferative and anti-inflammatory agents, these stents have the potential to reduce ISR significantly. Sirolimus- and paclitaxel-eluting stents (PES) have been shown to be remarkably effective in preventing restenosis post coronary interventions in adults. Paclitaxel-coated balloons are also available to address particularly refractory vascular lesions. Presently, pediatric applications of DES are off-label innovative therapy [14].

22.4.3 Postintervention

22.4.3.1 Valvulopasty

Most patients outside of the newborn period who undergo balloon pulmonary valvuloplasty do not need intensive care monitoring. Typically, only overnight observation is required and patients are discharged the following day. In rare cases, patients develop "suicidal" right ventricle and need ICU monitoring with intravenous infusion of beta blockers, followed by transition to oral propranolol to be weaned during the few weeks thereafter.

In newborns with critical pulmonary valve stenosis, cyanosis commonly persists for at least 10 weeks following RV decompression, and often patients need to be kept on prostaglandins for that period of time. Some patients require a surgical Blalock-Taussig shunt, or ductal stent placement, given their inability to wean from prostaglandin. As the RV hypertrophy regresses, RV compliance improves and more antegrade flow is seen across the pulmonary valve with less right-to-left shunting at the atrial level, which manifests as improvement in saturation.

22.4.3.2 Pulmonary Artery Angioplasty

As mentioned above, some patients undergoing extensive pulmonary artery interventions are admitted to the cardiac intensive care unit due to the high risk of developing segmental pulmonary edema and bronchial bleeding (reperfusion injury). Patients with intraprocedural hemoptysis need to be very closely observed due to concern of development of uncon-

tained tear that could result in massive pulmonary hemorrhage and hemothorax in severe cases. Most of these patients must remain at least 24 h on mechanical ventilation. Diuresis and positive end expiratory pressure (PEEP) is particularly beneficial in this subset of patients. For some patients, muscle relaxants are indicated until the extent of tear is ascertained and appropriately treated with stent or pulmonary artery embolization. An admission chest X-ray must be obtained to assess endotracheal tube placement, the magnitude of pulmonary edema, and stent placement. Successful extubation is usually accomplished 24–48 h after admission. In patients who have undergone stent placement, aspirin should be started after 24 h and once the bleeding has subsided. A few doses of first-generation cephalosporin (Ancef) may be indicated after intervention. Aspirin is continued for 6 months in patients with pulsatile pulmonary arterial blood flow. Follow-up lung perfusion scans can help assess the success of the intervention in patients with unilateral lesions [15].

22.4.4 Surgical Management

Surgical management is reserved for those patients in whom a balloon valvuloplasty and/or arterioplasty was not successful. Anatomically, these patients tend to present with a hypoplastic pulmonary valve annulus and a very dysplastic valve. Also, there could be a significant component of subvalvar and/or supravalvar stenosis. Balloon pulmonary valvotomy could also be unsuccessful due to technical difficulties and inability to catheterize the hypoplastic right ventricular outflow tract [16]. The repair requires cardiopulmonary bypass and is usually performed at normothermia or with mild hypothermia. An open surgical valvotomy via a main pulmonary artery incision is routinely performed. In the presence of a very small pulmonary annulus with or without subpulmonary stenosis, a transannular patch is required. Supravalvar pulmonary stenosis is managed with a patch arterioplasty.

In a report by Hanley et al. based on a prospective 27-institution study of 101 neonates with severe-to-critical pulmonary stenosis, percutaneous balloon valvotomy and certain types of surgical valvotomy were identified as optimal initial procedures. The outcomes were similar, and there was no difference in freedom from reintervention after the first procedure at 4 years of follow-up care [17].

22.4.5 Postoperative Management

22.4.5.1 Pulmonary Valvotomy

Postoperative management is usually uncomplicated due to the relatively benign postoperative course. Patients are routinely admitted to the cardiac intensive care unit postoperatively for monitoring and care and usually arrive with an arterial line and central venous line (typically right internal jugular line) and occasionally with temporary pacing wires (in cases of right ventriculotomy and extensive infundibular muscle resection). The smallest or severely preoperatively ill patients will arrive intubated with a goal of extubation within the next 24 h. Excessive bleeding and cardiac arrhythmias are infrequent.

A small group of patients continue to have some degrees of cyanosis after a successful balloon dilation of the stenotic pulmonary valve. If oxygen saturations remain consistently below 70%, prostaglandins should be restarted and beta blockers may be required for several weeks. Occasionally, patients persist with refractory cyanosis despite the therapies and they may need a BT shunt. The origin of cyanosis is secondary to poor RV compliance and right-to-left atrial level shunting. Residual pulmonary regurgitation is initially well tolerated.

22.5 Long-Term Outlook

Untreated PS patients with a pressure gradient across the pulmonary valve of less than 25 mm Hg rarely suffer from poor outcomes. Patients with a pressure gradient of 26–49 mm Hg have a 21% chance of developing a progressive increase in this gradient. Patients with a pressure gradient of 50–79 mm Hg across the valve have a 79% chance of becoming worse, and patients with 80 mm Hg or higher pressure have a 97% chance of developing severe consequences [18]. Patients treated with balloon pulmonary valvuloplasty (BPV) for isolated pulmonary stenosis seems to enjoy excellent outcomes.

Long-term outcome and cumulative incidence of reintervention following BPV were described by Devanagondi et al. for 103 patients, who underwent procedure between 1982 and 2011. Overall, 15/103 patients (15%) required surgical intervention following BPV to relieve PS or augment pulmonary blood flow, including pulmonary valvotomy (N = 3), transannular patch (N = 9), and modified Blalock-Taussig shunt (N = 7), with some patients having multiple surgical procedures. Three of 103 patients had surgical pulmonary valve replacement at 16.8–22.2 years following BPV for symptomatic severe PR. Freedom from repeat BPV or surgical intervention was 80% at 10 years and 78% at 20 years post-BPV. Authors reported that at the time of the latest follow-up, 60% of patients had moderate PR [19]. Studies demonstrated that RV volume overload secondary to PR is usually well tolerated for decades before leading to right heart failure.

Surgical correction of pulmonary stenosis was the treatment of choice until three decades ago, when balloon valvuloplasty was introduced. But it seems that long-term outcomes and quality of life for surgical patients are similarly good. Ninety consecutive patients who underwent surgery for pulmonary stenosis between 1968 and 1980 were

examined by Roos-Hesselink et al. Quality of life was found to be good (25 years 93% survival, 67% of the patients was in NYHA Class I, and maximal exercise capacity was 90% of normal). Pulmonary regurgitation was found in a third of the patients 22–33 years after surgical repair for isolated pulmonary stenosis, and reoperation for pulmonary regurgitation was necessary in 9%, especially after the transannular patch technique [20].

Tricuspid and pulmonary annuli are expected to grow with the child's growth, and the PV demonstrates catch-up growth [20]. It has been concluded that life-long follow-up is essential, but excellent outcome can be anticipated. Life expectancy in mild, moderate, or severe pulmonary stenosis after repair is within normal limits.

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Chapter 23
Left Ventricular Outflow Tract Obstruction

Michael D. Tsifansky, Ricardo A. Munoz, and Victor O. Morell

23.1 Introduction

Left ventricular outflow tract obstruction (LVOTO) accounts for 3.5–10% of all congenital heart defects [1, 2], with the majority of patients being male. LVOTO occurs at the valvar (70%), subvalvar (14%), and supravalvar (8%) levels, and several levels of obstruction often coexist (8%) [3]. LVOTO may be further compounded by other left-sided anomalies (small left atrium, abnormal mitral valve, small – or even hypoplastic – left ventricle (LV), aortic coarctation (CoA), or interrupted aortic arch) [4]. Often seen in this context is Shone's complex – a combination of a parachute mitral valve, supra-annular mitral ring, subaortic stenosis, and CoA [5]. Ventricular septal defects, abnormal attachments of the mitral or tricuspid valve apparatus, and pulmonary venous anomalies may coexist with LVOTO. Critical LVOTO presents as shock in the early neonatal period, while less severe defects may only become clinically significant later in childhood, or even remain silent into adulthood [6].

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23.2 Valvar Aortic Stenosis

23.2.1 Anatomy

The normal aortic valve has an area of about 2 cm^2/m^2 of body surface area and is trileaflet (right, left, and noncoronary cusps) and tricommissural [7]. The stenotic aortic valve can be monocuspid or, more frequently bicuspid due to the fusion of the right and the left cusps (see Fig. 23.1); morphologically, such valves are gelatinous and incompletely developed [8]. Bicuspid valves are commonly associated with left-sided cardiac abnormalities and CoA.

The severity of aortic stenosis (AS) can be trivial, mild, moderate, or critical, depending on the orifice size and either echocardiography-measured peak systolic ejection gradient (PSEG) or catheter-obtained peak-to-peak transvalvular gradient (Table 23.1). In neonates with valvar AS, the valve is usually gelatinous with thickened and poorly formed leaflets. In severe disease, left-ventricular (LV) filling is restricted, and the atrial-level right-to-left shunt decreases, thereby decreasing the LV contribution to systemic cardiac output (CO). This may lead to the underdevelopment of the left-sided structures described earlier, especially hypoplastic ascending aorta and the arch, and increase the risk of CoA.

23.2.2 Pathophysiology

LV wall stress is directly proportional to the LV pressure and the LV cavity diameter, and inversely proportional to twice the LV wall thickness [9]. Therefore, the immediate consequences of LV hypertension in the context of LVOTO are the development of concentric myocardial hypertrophy (to maintain contractility and CO, and minimize wall stress) and increased myocardial O_2 consumption. Progressive LV hypertrophy eventually leads to subendocardial ischemia, interstitial fibrosis, and diastolic – and then systolic –

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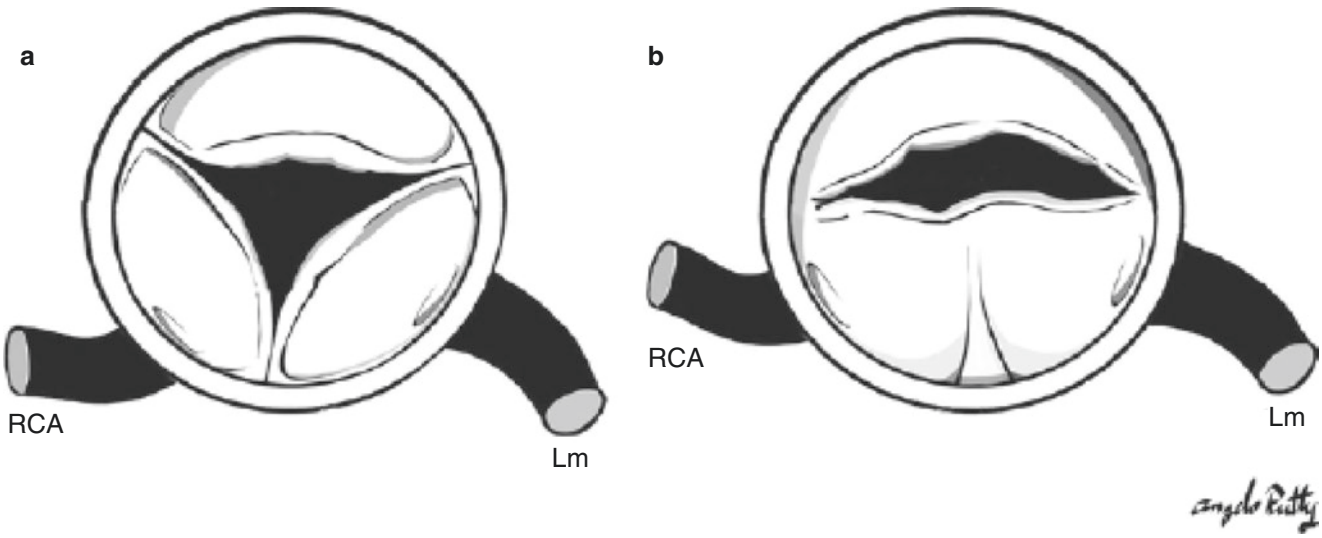

Fig. 23.1 (**a**) Normal trileaflet aortic valve. (**b**) Bicuspid aortic valve

Table 23.1 Classification of valvular aortic stenosis

Classification	Echo PSEG, mmHg∗	Catheter gradient, mmHg[a]	Valve Area, cm^2/m^2 BSA[b]
Trivial	<25	<10	>0.7
Mild	25–50	11–40	>0.7
Moderate	50–80	41–80	0.5–0.7
Severe	>80	>75	<0.5
Critical	30–80		

[a]All gradients assume normal CO; in the setting of ventricular dysfunction, transvalvar gradients may be underestimated. Echocardiographic gradients are usually estimated in patients without sedation and catheter gradients are estimated in sedated patients. The latter measurement is the most precise indicator of obstruction
[b]Body surface area

dysfunction, and atrial and ventricular arrhythmias. The stiff LV requires atrioventricular synchrony for adequate stroke volume, so patients with AS and arrhythmias are predisposed to hemodynamic instability, syncope, and sudden death.

In neonates with critical (*ductus arteriosus*-dependent) AS, the above processes start in utero, leading to LV endocardial fibroelastosis (EFE) and systolic and diastolic failure, and compromising the forward flow across the aortic valve. Consequently, in these infants, systemic CO remains at least in part dependent on the right ventricular output and right-to-left shunt at the level of the *ductus arteriosus*, and closure of the *ductus* shortly after birth leads to sudden increase in the LV wall stress, ventricular dilation, and cardiogenic shock. About 10% of infants with AS present with critical AS [10].

Infants with severe but not critical AS may develop congestive heart failure (CHF) over the first few weeks of life. Their pathophysiology is similar to that outlined above; however, in them, EFE is uncommon, systemic perfusion is not ductal-dependent, and frank cardiogenic shock is rare. Those with milder AS present later and are less likely to develop CHF. However, LV hypertrophy, ischemia, and limited reserve of CO may lead to angina or syncope on exertion.

23.2.3 Clinical Presentation

Neonates with AS presenting in cardiogenic shock and respiratory distress after the *ductus arteriosus* closure are often misdiagnosed with septic shock. They are hypotensive, tachypneic, and poorly perfused; and their pulses are often faint. There may be no murmur on the physical examination. They are oliguric and severely acidotic [11].

Older infants with severe AS present in CHF with feeding difficulties and failure to gain weight. They display decreased peripheral perfusion, tachypnea, a gallop with a harsh systolic murmur, and hepatomegaly.

Children with a milder obstruction usually present with an asymptomatic murmur (described below) or, much less frequently, with anginal chest pain and exertional syncope. However, serious events, including cardiorespiratory arrest on exertion, have also been reported in this population [12].

The typical adult presentation is the triad of *angina pectoris,* syncope, and CHF. The physical examination shows *pulsus parvus et tardus* (a delayed and slow-rising pulse), narrow pulse pressure, and a harsh crescendo-decrescendo murmur at the second right intercostal space, radiating to the sternal notch. An early systolic click and a single or reversely split S_2 typically accompany the murmur. The presence of the reversely split S_2 may indicate severe AS associated with bundle branch block and/or LV dysfunction. In the setting of severe LV dysfunction, the stroke volume falls and the systolic ejection murmur becomes softer. Some patients with AS may have aortic insufficiency (AI), which produces a decrescendo murmur immediately following S_2 [13].

23.2.4 Chest Radiography

In neonates and infants, the chest X-ray typically shows cardiomegaly and pulmonary edema, which is secondary to LV dysfunction, LA hypertension, and pulmonary venous congestion. In older children and adults, mild cardiomegaly and a prominent aortic arch are present.

23.2.5 ECG

In infants with mild AS, electrocardiography may be normal. In older children and adults, left ventricular hypertrophy and ST-T changes are present.

23.2.6 Echocardiography

Echocardiography is usually diagnostic and sufficient to plan a catheter-based or surgical intervention, although some prefer to also obtain a cardiac CT. The decision to proceed with catheter or surgical intervention is based on the analysis of anatomic details and the severity of ventricular dysfunction. The relevant anatomic information includes the size and function of the aortic and mitral valves, size of the atrial communication, presence of other intracardiac defects (especially those contributing to the LVOTO), and the size of the aorta.

Neonates with significantly underdeveloped left-sided structures may require a univentricular repair. Antegrade systolic flow into the ascending aorta and the transverse arch is sine qua non to biventricular repair, while retrograde flow from the *ductus arteriosus* into the aortic root implies that the left-sided structures are inadequate for biventricular repair. Gradients in neonates with AS may underestimate the severity of LVOTO due to the presence of patent *ductus arteriosus* and severe ventricular dysfunction. In the setting of cardiogenic shock soon after delivery, echocardiographic assessment should focus on ruling out restrictive atrial septal defect, inadequately sized ductus arteriosus, left-sided structural abnormalities, and hypoplastic arch.

23.2.7 Cardiac Catheterization

Cardiac catheterization is performed if significant questions about cardiovascular anatomy remain after non-invasive cardiac imaging (this is infrequent), or if percutaneous balloon dilation of the stenotic aortic valve is planned. The technique typically involves retrograde approach via the femoral (or, in infants, umbilical) artery. Carotid artery cutdown and jugular, femoral, or umbilical vein (transseptal) approaches have also been described but are not commonly used [14]. In addition to the transvalvular gradient, narrowed pulse pressure in the ascending aorta and elevated LV end-diastolic pressure are found. Aortography is remarkable for a thickened, fused, and domed valve that restricts the contrast.

Other patients with AS who may benefit from catheter-based studies include those with angina with ST-T wave changes (to evaluate the LV pressure and the coronary arteries) and those with syncope (to evaluate LVOTO), although these indications are not universally accepted. Balloon valvuloplasty of the aortic valve is described separately.

23.2.8 Preoperative Management and Indications for Intervention

23.2.8.1 Neonates and Young Infants

Neonates with critical AS who present in shock and CHF require emergent infusion of prostaglandin E_1 (PGE) to re-establish ductal patency and ductal-dependent systemic CO, and to alleviate pulmonary hypertension. The PGE dose should be kept low (0.01–0.025 mcg/kg/min) so as to avoid apnea, fever, and hypotension.

Gas exchange and acid-base status should be normalized because these infants do not tolerate acidosis. Mechanical ventilation with the tidal volume of 8–12 ml/kg and adequate positive end-expiratory pressure (6–8 cm H_2O) are frequently required to address pulmonary edema and hypoxia. Bicarbonate infusion may be required to correct acidosis; however, ongoing acidosis implies inadequate CO, and reasons for this should be sought. Inotropic support (most commonly a low-dose epinephrine infusion) may be required.

If the LV or the mitral valve is too small, an atrial-level left-to-right shunt as well as patent *ductus arteriosus* may be required to maintain CO. Those with an inadequate atrial-level communication may need an emergent balloon atrial septostomy. A small group of such patients may need extracorporeal membrane oxygenation (ECMO) support prior to the balloon atrial septostomy.

It is prudent to abstain from enteral feedings in unstable infants with *ductus*-dependent systemic circulation (especially if umbilical arterial lines are in place), and parenteral nutrition should be started when feasible. Many centers administer H_2-blockers or proton-pump inhibitors to the fasting infants, although their utility has not been shown. Electrolytes and fluid balance should be optimized.

There is no role for prophylactic antibiotics in such infants, but antibiotics are often started before the diagnosis is established because of concerns for septic shock. In this case, it is reasonable to finish 48–72 h of broad coverage while awaiting cultures.

Gentle sedation may be used to decrease the metabolic needs and improve infants' comfort. Among other agents, dexmedetomidine has gained popularity in this and other pediatric cardiac populations due to the predictability of its hemodynamic effects, lack of respiratory suppression, and overall ease of use [15, 16].

Head and renal ultrasonography should be performed, and karyotype should be checked before the AS repair, if time allows.

Timing of the AS repair is dictated by the stability of the patient on one hand, and the presence of ductal-dependent systemic circulation or the development of CHF (the only definitive indications for AS repair in this group) on the other. Indeed, if an infant who originally required PGE ultimately tolerates PGE discontinuation, has no respiratory distress, and is able to grow, an intervention may be safely delayed.

Concurrently with the stabilization, a decision needs to be made for each infant as to whether to proceed along the univentricular or the biventricular pathway. In infants with isolated AS and normal left-sided structures, as well as in those with clearly hypoplastic LV, this is straightforward, but many patients fall into the gray zone between the two extremes. Nevertheless, it is important to make the correct decision for each infant, because a failed trial of the two-ventricular repair will likely result in a debilitated, chronically critically ill child with long-standing elevated LA pressures and secondarily elevated pulmonary vascular resistance that would greatly increase the risk of univentricular conversion or heart transplantation [11, 17, 18].

There exist several sets of predictors of failure of the biventricular pathway (and mortality) in patients with AS, including the "Rhodes Score" [17] with its subsequent modification [19], the Congenital Heart Surgeons' Society (CHSS) Calculator [20], and others [21]. The presence of more than one "Rhodes Factors" predicts the failure of aortic valvotomy (and thus the biventricular repair) with 95% certainty in the context of isolated AS, but the Score performs less well in the context of multiple left-sided lesions. The original "Rhodes Factors" include:

- Mitral valve area <4.75 cm^2/m^2 of BSA.
- Long-axis LV length/Long-axis heart length <0.8.
- Aortic root diameter <3.5 cm/m^2.
- LV mass <35 g/m^2.

In addition to the "Rhodes Factors," the following features have been associated with failure of the biventricular repair in neonates with complex left-sided lesions: [19]

- Moderately large VSD.
- Unicomissural aortic valve.
- Hypoplastic mitral valve or LV (Z score <−2).

Other investigators [22, 23] have reported the following additional risk factors for biventricular repair:

- Mitral valve orifice <9 mm.
- Aortic annulus diameter <5 mm.
- Non-apex forming LV.

The CHSS Calculator (www.chssdc.org) is an evolving web-based decision tool that compares predicted likelihood of survival after univentricular repair to that after biventricular repair across the full spectrum of critical LVOTO for each individual patient based on a large dataset of patient outcomes and morphologic, functional, and pathologic variables from the late 1990s [20, 24].

23.2.8.2 Older Infants and Children

In these patients, the left-sided cardiac structures are adequate for the maintenance of CO, and they usually do not require intensive preoperative management. Early intervention before the onset of irreversible myocardial changes is desirable, though the exact timing should be individualized and is difficult to predict. Percutaneous balloon aortic valvuloplasty is the procedure of choice in this age range [11]. An intervention is typically indicated in the presence of peak echocardiographic Doppler gradient >30–40 mmHg or peak-to-peak catheter-derived gradient >20–30 [11], especially in the presence of symptoms, notable LV hypertrophy or EKG changes.

23.2.9 Surgical Management

23.2.9.1 Surgical vs. Catheter-Based Intervention

There has been no prospective study comparing the surgical and the interventional approaches in neonates, infants, or older children with AS, and in the existing retrospective studies the overall results of the two approaches are overall comparable. As a general rule, patients undergoing open valvotomy are more likely to have residual AS, whereas those undergoing a balloon aortic valvuloplasty are more likely to have aortic insufficiency (AI), and a reintervention will be required regardless of the nature of the procedure initially performed [25–36]. The advantages and disadvantages of either intervention appear to depend on institutional expertise, making the procedure of choice largely a matter of institutional preference. In particular, in neonates appropriate for a biventricular repair, the results balloon aortic valvuloplasty are quite acceptable [14, 37]. Therefore, in unstable neonates with very poor LV function, the interventional route may be

particularly appealing, although in this population the complications of balloon aortic valvuloplasty are more frequent than in the less acutely ill patients [29, 37].

23.2.9.2 Aortic Valvotomy

Once on cardiopulmonary bypass, the *patent ductus arteriosus,* if present, is ligated to prevent retrograde flow into the pulmonary arteries. After aortic cross-clamping and the administration of cardioplegia, the proximal ascending aorta is opened approximately 1 cm above the right coronary artery. Then, the valvotomy is performed by opening the intercommissural raphes almost to the aortic annulus (Fig. 23.2).

23.2.9.3 Aortic Valve Replacement

There are several options for aortic valve replacement in pediatric patients (Table 23.2).

23.2.9.4 Mechanical Valves

On cardiopulmonary bypass and under cardioplegic arrest, a proximal aortotomy is performed. The native aortic valve leaflets are excised, and the mechanical prosthesis is implanted with non-absorbable sutures. In the presence of annular hypoplasia, an aortic root enlargement procedure is performed in order to place an adequate size valve.

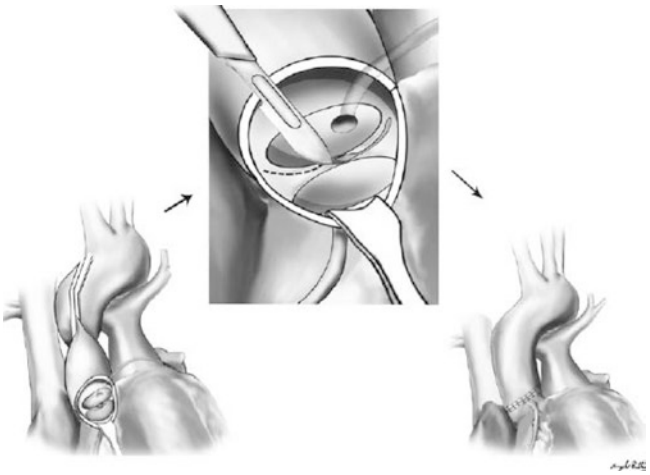

Fig. 23.2 Open surgical valvotomy. Via a transverse aortotomy the aortic valve is inspected and the valvotomy performed

23.2.9.5 Aortic Allografts

On cardiopulmonary bypass and under cardioplegic arrest, the coronary buttons are harvested, and the proximal aortic wall and the aortic valve are excised. The allograft is then sutured to the aortic annulus proximally and to the ascending aorta distally. Finally, the coronary arteries are reimplanted.

23.2.9.6 Pulmonary Autograft (Ross Procedure)

This procedure involves the harvesting of the pulmonary root (pulmonary valve and proximal main pulmonary artery), which is then used to replace the aortic root [Fig. 23.3]. The RV to pulmonary artery continuity is reestablished with a conduit, most frequently a pulmonary homograft. This procedure also requires coronary artery reimplantation [11].

23.2.9.7 Aortic Annular Enlargement Procedures

Some patients have a component of aortic annular hypoplasia contributing to their aortic stenosis. Several surgical techniques (Fig. 23.4) addressing this problem have been described [11] including:

- **Manouguian**: a posterior longitudinal aortotomy extending through the commissure between the left and noncoronary aortic cusps into the anterior leaflet of the mitral valve. The annulus is then enlarged with a prosthetic patch.
- **Nicks**: the aortotomy is extended into the noncoronary sinus and aortic annulus, but not into the mitral valve. A prosthetic patch is then used to enlarge the annulus.
- **Konno:** a vertical aortotomy is extended through the aortic root into the interventricular septum to the left of the

Table 23.2 Comparison of aortic valve replacement options

[38]	Need for anticoagulation	Growth potential	Option for neonates and infants	Freedom from reoperation for valve-related problems at 10 years
Mechanical valves	Yes	No	No[a]	40–80% [38–40]
Homograft	No	No	Yes	50–80%[b] [39–41]
Pulmonary autograft	No	Yes	Yes	85–95% [39, 41]

[a]The smallest commercially available mechanical valve is 15 mm in diameter [42]
[b]Lower longevity is associated with younger patient age at implantation

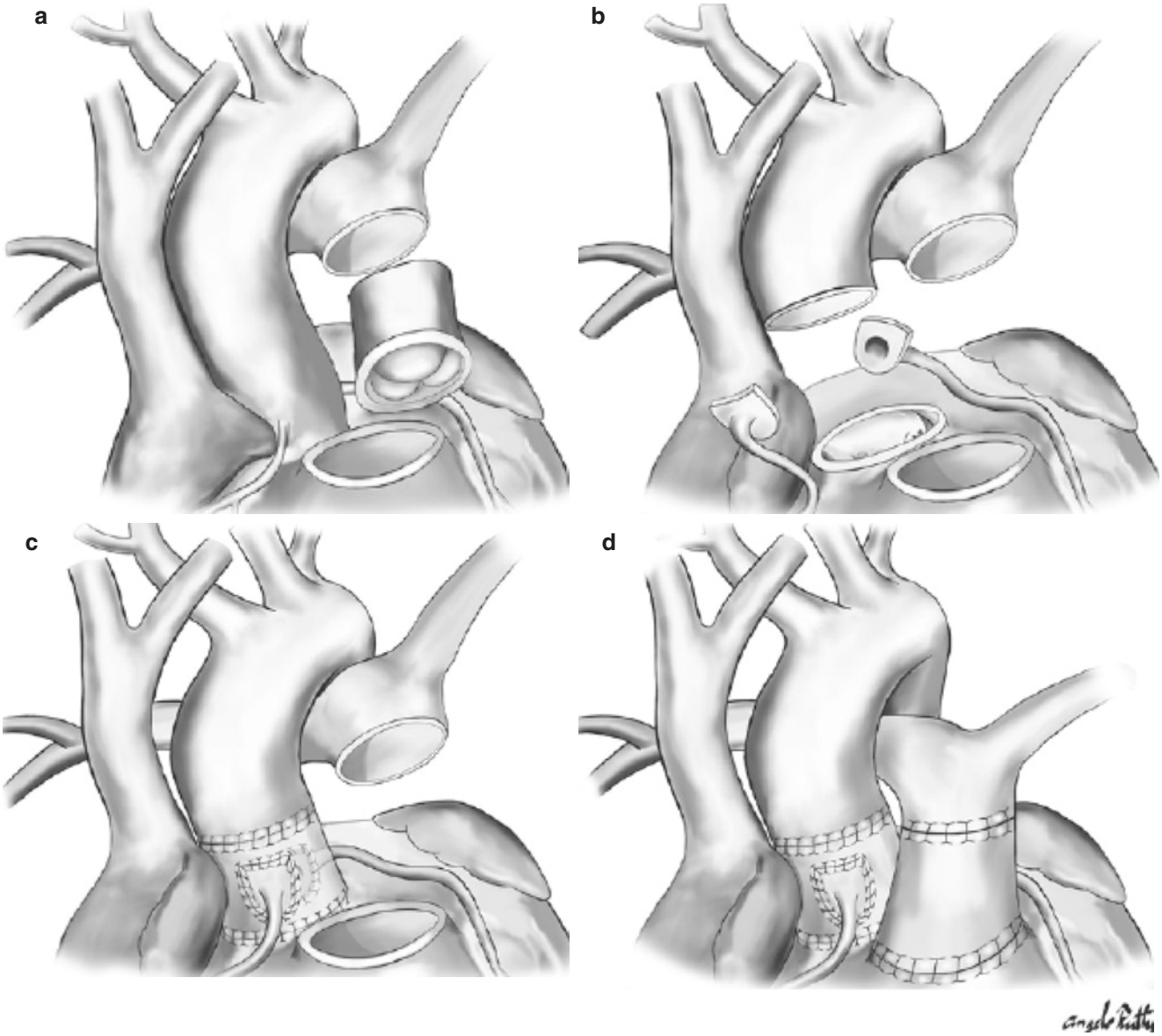

Fig. 23.3 Ross procedure. (**a**) The pulmonary autograft is harvested. (**b**) After harvesting the coronary buttons, the proximal aortic wall and the abnormal aortic valve are excised. (**c**) Aortic continuity is reestablished using the pulmonary autograft; note that the coronary buttons have been reimplanted. (**d**) A pulmonary homograft is placed in the pulmonary position

right coronary artery. The incision is closed with a prosthetic patch. This is a very useful technique in the context of multi-level obstruction.

23.2.9.8 Balloon Valvuloplasty of the Aortic Valve

In patients with more than mild AI, catheter intervention should not be performed. Approach for the procedure is as described for diagnostic catheterization. A 3–4 F sheath is used in infants and a 4–8 F sheath in older children and adults. Long, low-pressure balloon of the diameter roughly equal to that of the aortic annulus is used to minimize injury to the valve and residual AI. Adenosine may be used during the procedure to achieve a short-lived and reversible cardiac standstill.

23.2.10 Postoperative Management

23.2.10.1 Neonates

Neonates recovering from surgical or interventional repair of critical AS often have pulmonary hypertension and myocardial dysfunction, and may need significant support, including

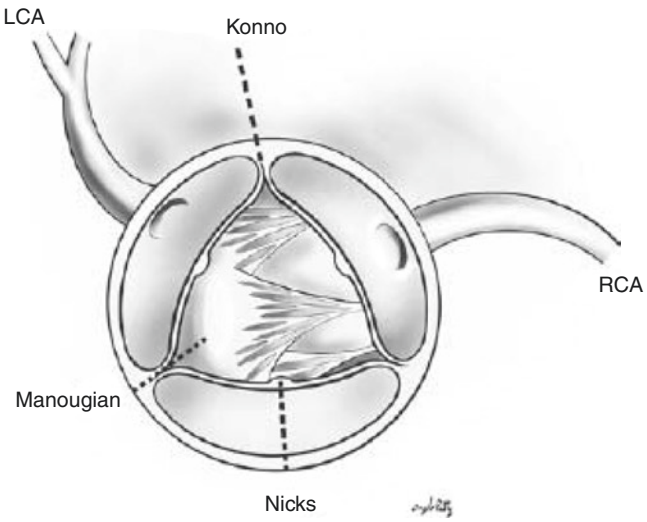

Fig. 23.4 Annular Enlargement Procedures

mechanical ventilation, inotropic support, and diuretics. Inhaled nitric oxide (NO) therapy may be considered in selected patients with critical hypoxic pulmonary vasoconstriction; however, NO may increase pulmonary venous return and overload the failing LV.

Monitoring

After the surgical or interventional repair of the aortic stenosis, the hemodynamic management in the ICU is largely guided by echocardiographic findings, including right- and left-ventricular function, volume status, residual lesions (AS or AI), and the presence of procedure-specific complications. An echocardiogram should be done in the operating room or catheterization suite and repeated frequently, because as the LV function improves, the transvalvular gradient may change. Intraoperative placement of a left-arterial line should be considered, especially if the size of the left-sided structures is small.

Cardiovascular Management

Low-dose epinephrine and/or milrinone infusions are typically started in the operating room and continued for several days in the ICU. The inotropes are usually weaned off after extubation, and the infant is transitioned to an angiotensin-converting enzyme inhibitor for long-term treatment, especially in the presence of residual AI. However, aggressive afterload reduction is contraindicated in the presence of significant residual AS. In some centers, *ductus arteriosus* may be left open if the adequacy of left-sided structures is in question. If ductal patency is required for more than 3–5 days or left-atrial/pulmonary venous hypertension persists for more than several days, the adequacy of left-sided structures for systemic CO should be questioned, and the cardiac anatomy should be reevaluated. Previously, unappreciated CoA and/or arch hypoplasia should be specifically sought and excluded by echocardiography or MRI.

Patients with significant pulmonary hypertension, failing myocardium, and/or cardiogenic shock may be supported by ECMO if improvement is expected. Otherwise, alternative approaches should be considered, including univentricular repair and cardiac transplantation.

Respiratory Management

Mechanical ventilation may be needed for several days after the procedure. Goals of the ventilatory support are the same as during the preoperative period. The infant is weaned to extubation when hemodynamically stable. Inotropes are usually continued through extubation. Failure to wean from the ventilator should alert the intensivist to the possibility of persistent left-atrial/pulmonary venous hypertension as a result of poorly compliant, small LV, and/or residual AS or AI.

Some, but not all, centers restrict fluids to ½ –2/3 maintenance and minimize the sodium load immediately after surgical repair. If instituted, these restrictions are gradually lifted over the following few days as the infant's hemodynamics and renal function normalize. Such restriction is unnecessary after a catheter-based intervention. Diuretics are started within 6 h of the surgical or interventional procedure in many centers, while others prefer to postpone them for 12–18 h. Feedings are started slowly when the hemodynamics are stable, the infant has bowel sounds, and the abdominal exam is benign. When the infant is no longer significantly fluid overloaded, the diuretics are decreased and administered enterally.

Coagulation Management

Pre-cardiopulmonary bypass platelet dysfunction has been described in the context of various congenital heart defects [43]. Infants and children with bicuspid aortic valve may have abnormal platelet morphology (increased mean platelet volume), which, theoretically, may predispose them to thrombosis [44]. The practical implications of this phenomenon, if real, are unclear.

23.2.10.2 Older Infants and Children

These patients are usually much easier to care for than neonates, and their recovery is rapid. With uncomplicated repair, cardiopulmonary bypass and aortic cross-clamp times are brief, and significant inotropic support is unnecessary. Typically, these patients leave the operating room with a

combination of a milrinone and a vasodilator. When the procedure involves reimplantation of the coronary arteries, nitroglycerin may be initiated and continued for the 24–48 h after surgery. These patients may be extubated soon after the procedure; this also facilitates pain and control and sedation. Because LV systolic function is typically preserved, relief of AS is commonly followed by systemic hypertension. If surgical correction was undertaken, aggressive control of hypertension is desirable in the first 1–2 days so as to protect the aortic sutures. Vasodilators and β-blockers are usually effective. Pulmonary hypertension and myocardial dysfunction are infrequent beyond the immediate neonatal period, but, if present, they are treated similarly to those in neonates. Of note, if epidural catheters are used after valve replacement and anticoagulation is planned, the epidural catheter should be removed at least 3 h before commencing anticoagulation.

23.2.10.3 Complications

Procedure-appropriate complications should be looked for and identified prior to discharge from the ICU. Complications of balloon valvuloplasty include AI, residual AS, and ventricular dysfunction. Ventricular arrhythmias may transiently occur during the procedure, and rarely complete heart block may follow it. Anemia from blood loss during access is not uncommon in small infants. Complications of surgical valvotomy and valve replacement are mentioned elsewhere.

23.2.10.4 Long-Term Outcomes

As mentioned earlier, balloon aortic valvotomy often results in AI, while surgical valvuloplasty frequently leaves a residual AS. In the long term, children tolerate residual AS much better than AI [45]. The incidence of significant AI in the intermediate term is 13%, and that in the late term is 40% [46–48]. Once present, AI progressively worsens over time, leading to significant ventricular dysfunction and necessitating early reintervention [46, 49].

23.3 Subaortic Stenosis

23.3.1 Anatomy

Subaortic stenosis (subAS) is LVOTO below the aortic valve annulus; it may coexist with valvar and suravalvar obstruction. SubAS comprises several anatomic types: [3].

- *Discrete anterior subvalvar membrane* (most frequent): occurs in children and adolescents because of subtle distortion of the LVOT and resulting turbulent blood flow which causes endocardial damage and fibrosis.
- *Diffuse tunnel-like obstruction* involving the muscular septum: occurs mostly as a secondary lesion following a resection of a simple subaortic membrane and is due to post-surgical scarring and progressive fibromuscular proliferation in the context of a distorted LVOT.
- *Discrete projection of the conal septum into the LVOT.*
- *Hypertrophic obstructive cardiomyopathy* (described separately).
- *Other unusual space-occupying lesions*: duplication of the anterior mitral leaflet, accessory endocardial cushion tissue, anomalous choral or papillary-muscle insertion into the septum: most of these occur in the setting of another congenital heart disease, such as partial atrioventricular canal or L-transposition of the great arteries. CoA, interrupted aortic arch and ventricular septal defects could also be associated with this anomaly.

23.3.2 Pathophysiology

Pathophysiology of subAS is similar to that of AS in that subAS results in pressure overload of the LV and concentric LV hypertrophy. In addition, subAS causes blood flow acceleration across the subaortic area, which generates a jet that damages the aortic valve, which leads to the development of AI.

23.3.3 Clinical Presentation

Symptomatic isolated subAS is rare, but with severe obstruction, fatigue and dyspnea may be present. Its first presentation may be syncope and anginal pain or sudden death. Physical exam is similar to that of valvular AS; in fact, clinical differentiation between valvular and subvalvular AS is usually impossible. AI often coexists with subAS and adds a soft early-diastolic component to the typical AS murmur. When present, AI in the context of subAS carries a high risk of endocarditis.

23.3.4 Chest Radiography and ECG

Chest X-ray and electrocardiography findings are indistinguishable from those of AS.

23.3.4.1 Echocardiography

Echocardiography is diagnostic and sufficient to plan the surgery. Parasternal long-axis, apical long-axis, and apical five-chamber views best display the subaortic membrane. Parasternal long-axis and parasternal short-axis views best display the tunnel-like obstruction. Particular attention should be paid to the competence of the aortic valve, since

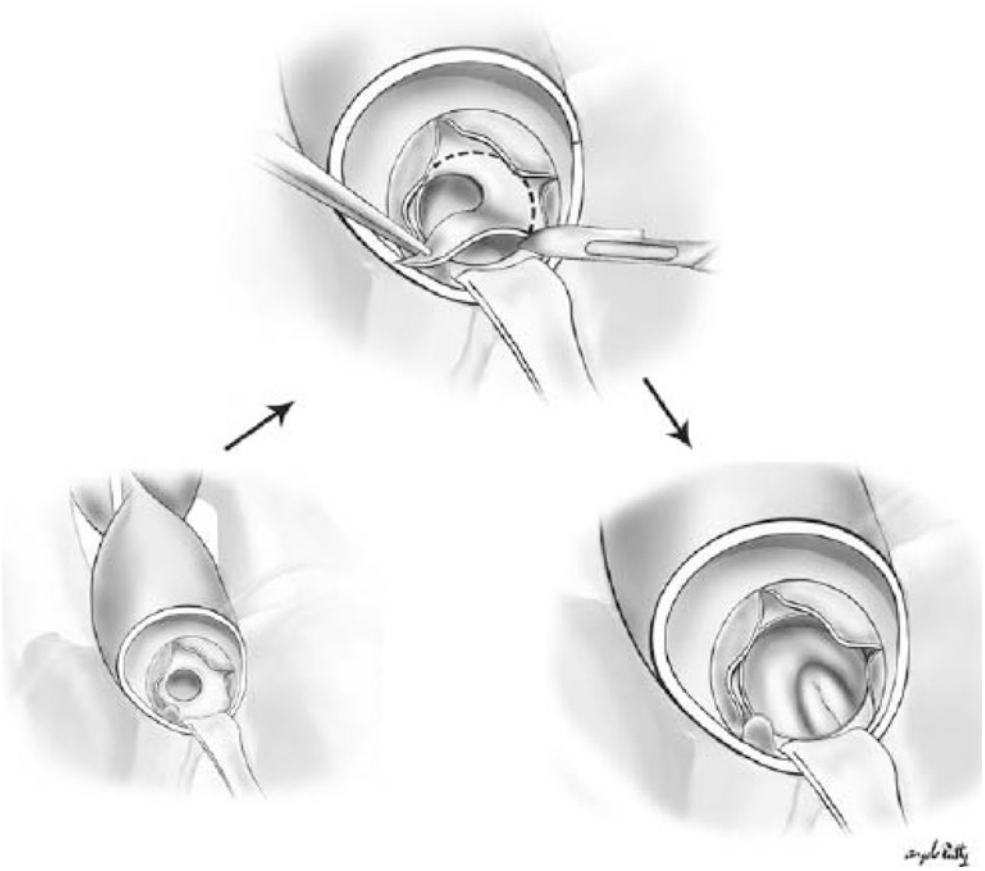

Fig. 23.5 Repair of subaortic stenosis**.** The fibromuscular membrane is sharply excised from the distal left ventricular outflow tract. Note that the membrane is very close to aortic valve

new-onset significant AI is an indication for surgery. Diagnostic catheterization is rarely done for subaortic stenosis alone, and catheter-based interventions are ineffective. If a catheterization is done, access is as for the catheterization for AS. A typical aortography of subaortic stenosis shows a jet of contrast without doming of the aortic valve.

23.3.5 Preoperative Management and Indications for Intervention

Unless these patients present with sudden death, they are rarely severely ill or unstable. They undergo elective repair and do not require preoperative management. Aside from finding new-onset AI, indications for repairing an isolated subaortic membrane are unclear. In general, surgical treatment is indicated in the presence of a mean echocardiographic gradient of 40–50 mmHg. Recurrence of the subaortic membrane is still a significant challenge especially when the first surgery is performed in patients younger than 10 years.

23.3.6 Surgical Aspects

The surgical approach involves a median sternotomy, cardiopulmonary bypass, and cardioplegic arrest. Via a proximal aortotomy, the membrane is visualized and sharply excised (Fig. 23.5). We routinely perform a myomectomy (resection a segment of left ventricular outflow tract muscle, underneath the right coronary cusp) in order to enlarge the LVOT and reduce the incidence of recurrence.

In cases were the obstruction is more diffuse, a modified Konno procedure is utilized. Through a right ventriculotomy, an incision is made in the interventricular septum, underneath the aortic valve. The obstructing LVOT muscle is resected, and the interventricular septal incision is closed with a patch, enlarging the LVOT. The mortality rate associated with simple subaortic resection is less than 2% [11].

23.3.7 Postoperative Management and Complications

Typically, these patients are extubated in the operating room and have an uncomplicated recovery in the ICU. Meticulous attention should be paid to the electrocardiogram especially to new onset of left bundle branch block, third-degree atrioventricular block, and ventricular arrhythmias. If the repair included reimplantation of the coronary arteries, a careful comparison with the preoperative EKG should made to detect S-T segment and T waves abnormalities. If coronary ischemia is suspected, serial troponin levels should be obtained, and an echocardiogram

must be completed to rule out ventricular dysfunction and/or regional motion abnormalities. Nitroglycerin can be initiated in the presence of myocardial ischemia, while the patient is emergently transferred to the cardiac catheterization laboratory to define the nature of the myocardial ischemia. The hypertrophic LV is particularly sensible to ischemia and infarction. Hypertension and hypotension should be avoided in this setting. Control of the systemic blood pressure can be achieved with beta-blockers and vasodilators. Essentially, all patients should have a transesophageal echocardiogram in the operating room, with the data regarding ventricular function and residual AS and AI readily available postoperatively.

23.4 Supraaortic Stenosis

23.4.1 Anatomy

Supraaortic stenosis (supraAS), an LVOTO at the level of the sinotubular junction or proximal ascending aorta, is the least common type of LVOTO. SupraAS may be part of Williams syndrome; it may occur sporadically; or it may display an autosomal-dominant inheritance. When valvar and subvalvar AS coexist with supraAS, the associated valvar disease correlates strongly with the need for reoperation. The sinotubular junction is usually quite thick, creating a wedge-like projection at the junction of the sinuses of Valsalva with ascending aorta and giving the region an hour-glass appearance. Occasionally, aortic valve leaflets adhere to the sinotubular junction, although normally they are unaffected. The coronary ostia are usually thick and sometimes stenotic. The coronary arteries are dilated, tortuous, and aneurismal even in young children. In Williams syndrome, the entire ascending aorta, including the aortic arch branches, may be thick and narrow; pulmonic stenosis is frequently present, and the main pulmonary artery may also be narrow. Coarctation of the abdominal aorta and subclavian and renal artery stenosis may also be seen [50].

23.4.2 Pathophysiology

Pathophysiology of supraAS is similar to that of AS and subAS. SupraAS results in pressure overload of the LV and concentric LV hypertrophy. Additionally, because the coronaries originate proximal to the supraaortic obstruction, they are exposed to high pressure (which accounts for their morphology) and perfused during systole rather than diastole. However, coronary flow may also be compromised by obstruction at the sinuses of Valsalva and the coronary ostia. Distorted coronary morphology coupled with myocardial O_2 supply/demand mismatch (for reasons described under AS) may put these patients at significant risk for sudden death [50].

23.4.3 Clinical Presentation

Patients with the familiar form of supraAS present in infancy with signs of mild CHF; severe CHF is rare. Patients with Williams syndrome present with stigmata of Williams syndrome (elfin faces, prominent forehead, long philtrum, enamel hypoplasia, friendly personality, and frequently hypercalcemia, hyperacusis and unusual affinity for music, peripheral pulmonic stenosis, CoA, subclavian artery stenosis, renal artery stenosis). These patients may be asymptomatic or display a variety of clinical findings, such as systolic ejection murmur, syncope, systemic hypertension, cerebral vascular accidents, myocardial infarction, syncope, and sudden death.

Physical exam findings are similar to those of AS; however, the systolic murmur is best heard along the right upper sternal border and the click is absent. Systolic hypertension is frequent and may be more pronounced in the right arm.

23.4.4 Chest Radiography

Chest X-ray findings are similar to those of AS; however, the ascending aorta is usually not dilated.

23.4.5 ECG

Electrocardiographic findings are similar to those of aortic stenosis. Right ventricular hypertrophy may also be present if RVOTO or branch pulmonary artery stenosis is present.

23.4.6 Echocardiography

Echocardiography is diagnostic and sufficient to plan the surgery. Parasternal long-axis and apical long-axis views best display the supraaortic narrowing, while the suprasternal view best shows the diffuse hypoplasia of the ascending aorta and the aortic arch. The morphology of the aortic valve and the gradient across the obstruction should

be investigated. Similarly, the morphology of the RVOT should be investigated and RV pressure assessed. Particular attention should be paid to the morphology of the coronary arteries, although magnetic resonance may provide higher quality images than echocardiography [50]. Diagnostic catheterization is rarely necessary; MRI may be advisable to further define the aortic arch and other vascular anatomy.

23.4.7 Preoperative Management and Indications for Intervention

Preoperatively, these patients are rarely severely ill or unstable, so they undergo an elective repair and do not require involved preoperative management. The goal is to treat the supraAS before the development of severe LV hypertrophy and progressive coronary stenosis. Generally, Doppler gradient of 30–40 mmHg and evidence of sinotubular junction narrowing necessitate surgical repair [11]; whereas, a child with a smaller gradient and without evidence of significant LV hypertrophy may be closely followed.

23.4.8 Surgical Aspects

In patients with supraAS, the area of narrowing tends to be circumferential ("napking ring") and appears as a fibrous ridge at the level of the sinotubular junction. The fibrous process that affects the aortic wall can involve the origin of one of both coronary arteries, at times causing coronary ischemia. Therefore, it is important to visualize the origin of both coronary arteries at surgery.

The surgical approach involves a median sternotomy incision, cardiopulmonary bypass, and cardioplegic arrest. First, the ascending aorta is opened longitudinally across the area of narrowing. Then the fibrous ridge is excised and the aorta augmented with a patch that extends across the area of narrowing and into the aortic sinuses [Fig. 23.6]. An inverted "Y"-shaped patch is commonly utilized, extending into the two anterior sinuses [Fig. 23.7]. Occasionally, all three aortic sinuses may need enlargement [Fig. 23.8]. In patients with diffuse ascending aortic narrowing, a long-segment patch aortoplasty will be required [11]. The mortality rate associated with surgical management of supraAS is less than 5%.

23.4.9 Postoperative Management and Complications

Patients with discrete supraAS are typically extubated in the operating room or soon after arriving in the ICU, and their postoperative course is uncomplicated. Patients with more diffuse forms of supraAS can have a more complex postoperative course and are managed similarly to the patients with repaired valvular AS. As in the other types of LVOTO, careful attention should be paid to adequate sedation and control of hypertension to protect the aortic sutures for the first 1–2 days.

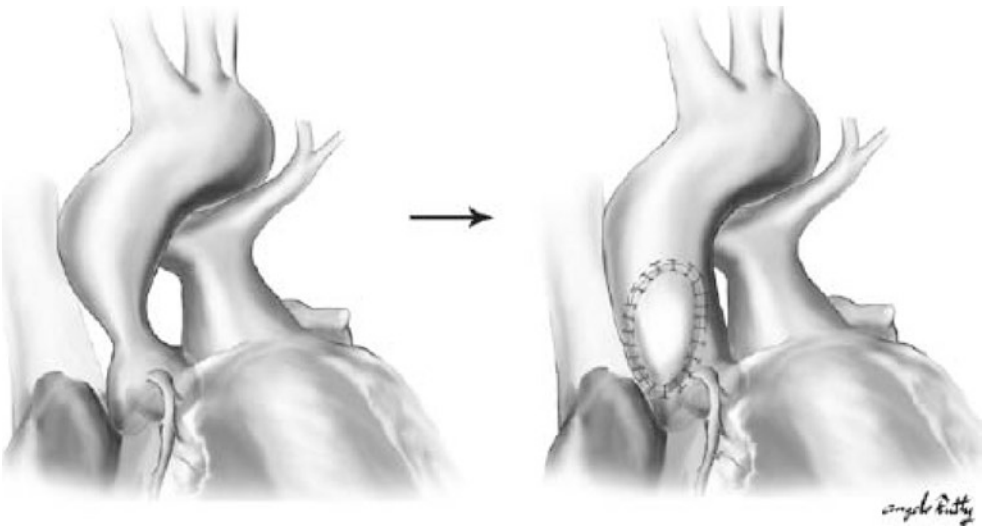

Fig. 23.6 Single-patch technique

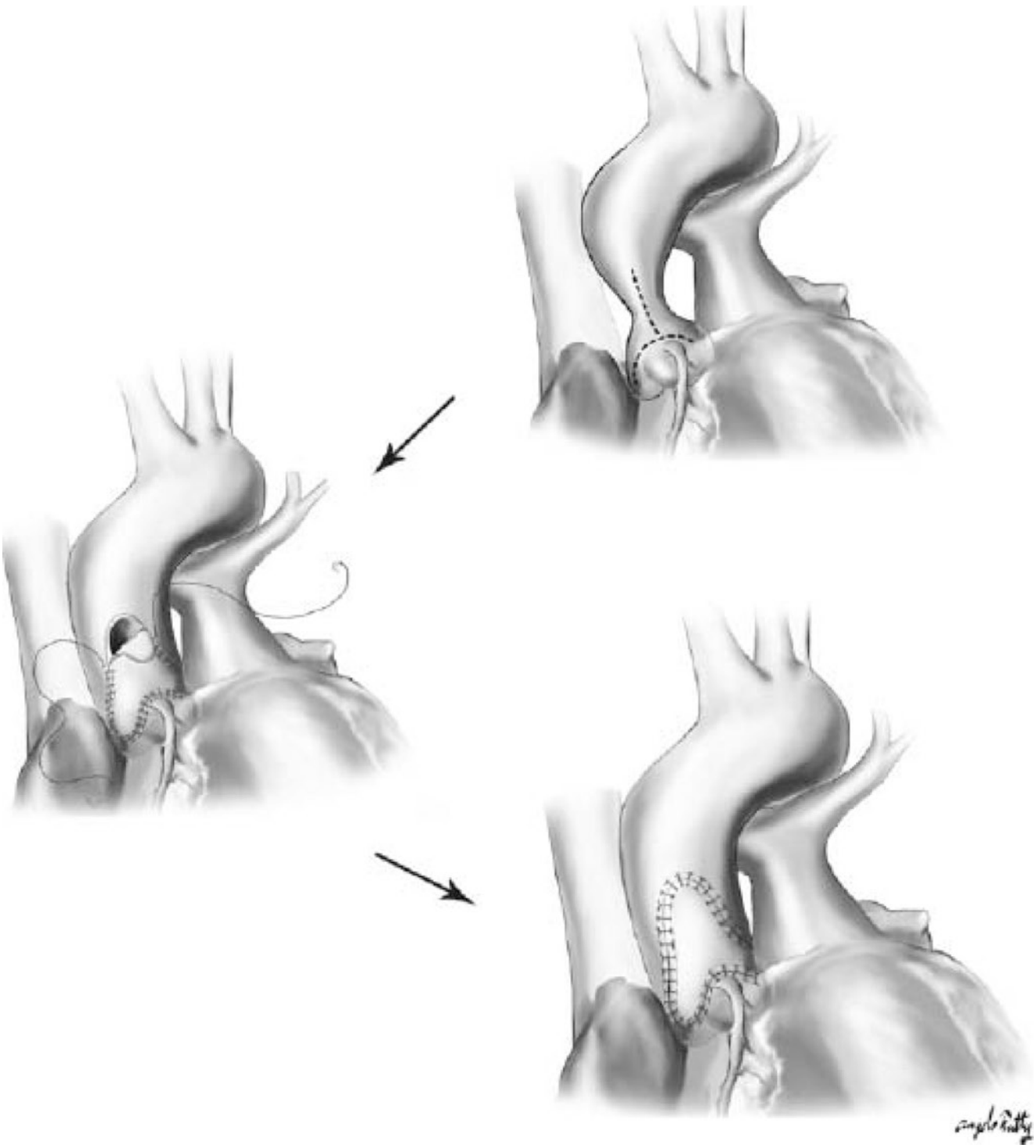

Fig. 23.7 Repair of SupraAS with an inverted Y-shaped patch. The aortotomy is extended into the two anterior aortic sinuses. After resection of the fibrous ridge, the aorta is repaired with an inverted "Y"-shaped patch

Several issues specific to the repair of supraAS should be kept in mind. After the relief of the supravAS, the coronary perfusion pressure (and thus, the coronary flow) may actually decrease, creating "coronary insufficiency", and afterload-increasing agents (e.g., α1-agonists) may need to be employed to correct that. On the other hand, if the aortic arch narrowing is inadequately addressed, the supraaortic gradient will in effect be transferred more distally, and this possibility should be investigated if the patient is exhibiting low CO.

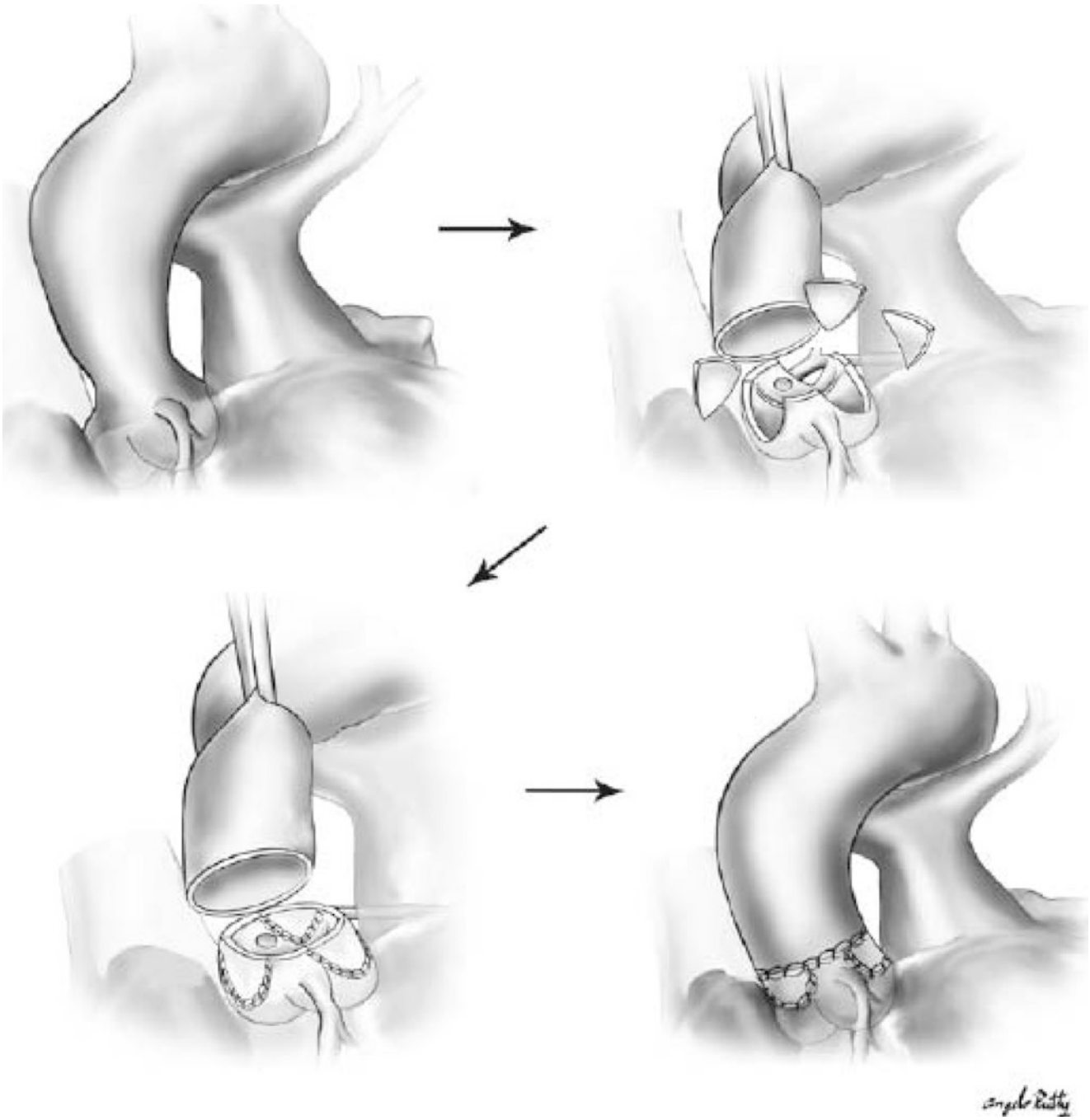

Fig. 23.8 Three-patch technique. After transecting the aorta, just above the area of narrowing, all three aortic sinuses are augmented with patches

Finally, patients with Williams syndrome may show RV hypertension due to main or branch pulmonary artery stenosis; therefore, it may be advisable to dilate and/or stent the pulmonary arteries prior to surgical intervention.

Sedating the patients with Williams syndrome may be challenging because of their hyperacusis and unique personality. Dexmedetomidine and low-dose benzodiazepines are useful in this setting.

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Chapter 24
Coarctation of the Aorta

Michael D. Tsifansky, Ricardo A. Munoz, Jacqueline Kreutzer, and Victor O. Morell

Abstract Coarctation of the aorta (CoA) and interrupted aortic arch represent two ends of a spectrum of extracardiac obstruction to the left ventricular (LV) output. CoA refers to a discrete narrowing of the descending aortic lumen (usually seen as a single posterior shelf of tissue at the level of the *ductus arteriosus*); "aortic hypoplasia" implies a narrowed aortic segment of some length in the absence of such a discrete shelf; "atretic arch" defines an interruption to the patency of the aortic arch lumen with the two blind ends of the arch connected only by a fibrous strand; and finally, "interrupted aortic arch" describes the complete discontinuity between the proximal and the distal ends of the aortic arch. As with other causes of obstruction to LV output, these lesions may coexist and be further compounded by intra- and extracardiac defects [1, 2].

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24.1 Introduction

Coarctation of the aorta (CoA) and interrupted aortic arch represent two ends of a spectrum of extracardiac obstruction to the left ventricular (LV) output. CoA refers to a discrete narrowing of the descending aortic lumen (usually seen as a single posterior shelf of tissue at the level of the *ductus arteriosus*); "aortic hypoplasia" implies a narrowed aortic segment of some length in the absence of such a discrete shelf; "atretic arch" defines an interruption to the patency of the aortic arch lumen with the two blind ends of the arch connected only by a fibrous strand; and finally, "interrupted aortic arch" describes the complete discontinuity between the proximal and the distal ends of the aortic arch. As with other causes of obstruction to LV output, these lesions may coexist and be further compounded by intra- and extracardiac defects [1, 2].

Congenital CoA is a frequent cardiovascular lesion, especially among Caucasian boys. It is less common among African-American boys and even less among African-American girls. CoA is not commonly associated with genetic anomalies, except for girls with Turner syndrome, in whom it is frequent. Notably, CoA can also be acquired, e.g., after Takayasu arteritis or as a result of cardiac surgery.

24.2 Embryology and Anatomy

Anatomically, CoA is usually found in the thoracic descending aorta at the level of the *ductus arteriosus* ("juxtaductal"), just distal to the origin of the left subclavian artery (Fig. 24.1). The actual narrowing is due to a ridge-like infolding of the *tunica media* along the posterior aortic wall, creating a posterior shelf. The left subclavian and intercostal arteries are often dilated, whereas the right subclavian artery sometimes originates below the coarctation. Other vascular anomalies often found in patients with CoA include berry aneurysms of the circle of Willis [3] and other congenital and acquired cerebrovascular pathology [4], as well as coronary [5–10] and renal [11] artery anomalies.

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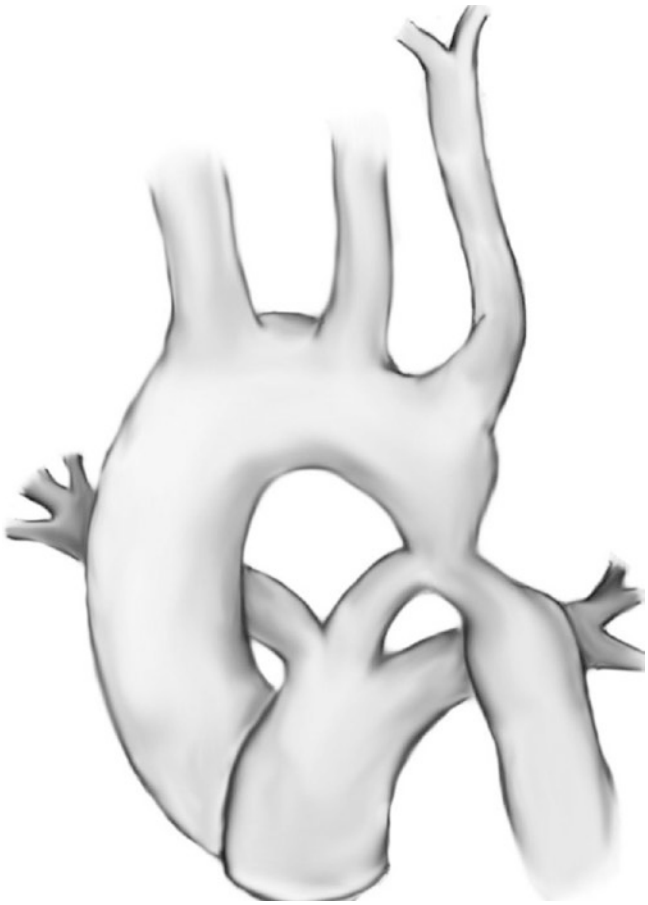

Fig. 24.1 Aortic coarctation. Note the area of narrowing in the proximal descending aorta, just distal to the left subclavian artery

There are three embryologic theories regarding the formation of CoA. (1) Ectopic ductal tissue, potentially present in the aorta around the *ductus arteriosus* insertion site, may contract as the *ductus arteriosus closes*, forming CoA. (2) In the setting of reduced LV output (usually due to abnormal anatomy; and indeed, CoA is often associated with left-sided cardiac underdevelopment and intracardiac obstruction), lack of forward flow through the proximal aorta may result in CoA. Finally, (3) anomalies in migration, development, and apoptosis of neural crest cells, which form parts of aorta and cardiac valves, may contribute to the genesis of CoA [12–14] and perhaps also explain the association between CoA and aortic valve and other left-sided cardiac anomalies.

CoA presenting in neonates is often a "complex CoA," i.e., it is complicated by congenital intracardiac anomalies, including hypoplasia of the mitral valve, the left ventricle, the aortic valve, and the aorta itself. The aortic valve is often bicuspid, and subaortic stenosis is also present. Many infants with severe CoA also have a ventricular septal defect (VSD). Furthermore, CoA may be part of the Shone complex [15] (combination of parachute-type mitral stenosis, a supra-mitral ring, and a subaortic stenosis). Less frequently, double-outlet right ventricle, *truncus arteriosus*, aorto-pulmonary window, and single ventricle may be present. However, right-ventricular outflow tract obstruction in association with CoA is rare.

On the other hand, CoA presenting beyond infancy is usually a "simple CoA," i.e., an isolated lesion. However, such patients develop a rich network of engorged collateral vessels in order to supply organs distal to the coarctation. These vessels erode the lower edges of the ribs, producing the appearance of rib-notching on chest X-rays, and may result in increased bleeding after the repair of CoA via lateral thoracotomy.

24.3 Pathophysiology

In neonates with critical CoA, closure of the *ductus arteriosus* results in cardiogenic shock from severe obstruction to LV output with resultant LV failure leading to elevated left-atrial (LA) pressure, left-to-right shunting across the *foramen ovale,* and pulmonary edema. Important systemic sequelae of LV failure in these patients include renal failure and necrotizing enterocolitis (NEC).

Infants and children with milder CoA do not develop acute heart failure. In these patients, the heart compensates by several mechanisms, including (1) concentric myocardial hypertrophy (to maintain normal wall stress), (2) increase in LV end-diastolic volume, mobilizing preload-recruitable cardiac output (Frank-Starling Law), (3) increase in sympathetic outflow, resulting in increased inotropy, and (4) development of the previously described collateral circulation, which decreases the LV afterload. If the CoA is not addressed, however, many patients will ultimately develop congestive heart failure (CHF) during the first 6 weeks to 6 months of life. CoA compounds the hemodynamic effects of coexisting LV outflow track obstruction (aortic and/or mitral stenosis, etc.) and left-sided regurgitant lesions (aortic and/mitral regurgitation, etc.). While complex coarctations of the aorta typically result in worse outcomes, a coexisting ventricular septal defect may actually protect the LV from failure by providing an alternative outflow as the *ductus arteriosus* closes.

The pathophysiology of the older child and adult with CoA is similar to that of infants with non-critical CoA. In them, LV pressure overload also results in concentric hypertrophy, increased sympathetic tone, multiple collaterals, and, if unaddressed, congestive heart failure. However, the progression to CHF is much slower.

24.4 Preoperative Management and Indications for Intervention

24.4.1 Neonates

Newborns with CoA presenting in shock require aggressive medical management, including an infusion of prostaglandin E_1

(PGE_1, alprostadil) to re-establish ductal flow and systemic perfusion and to alleviate the pulmonary hypertension seen in severe LV failure. In any CoA, the pre-ductal saturation will reflect the saturation in the LV (which, in turn, will reflect the pulmonary venous saturation and should be 90–100% in simple CoA). If opening the *ductus arteriosus* is sufficient to re-establish some antegrade flow across the coarctation, perfusion of the post-ductal vasculature will come from two sources – the pulmonary artery (lower oxygen saturation) and LV (higher oxygen saturation). Thus, in simple CoA, the pre-ductal saturation will reflect solely the pulmonary venous saturation, whereas the post-ductal saturation will depend on the relative contribution of each source (antegrade aortic flow vs. retrograde pulmonary artery flow). This should be kept in mind when generating the differential diagnosis of desaturation in a patient with CoA.

In an unstable neonate with critical CoA, PGE_1 should be started at a relatively high dose (0.1 mcg/kg/min) and lowered to 0.01–0.03 mcg/kg/min as cardiogenic shock resolves. Conversely, in a stable neonate (with a prenatal diagnosis of CoA, for instance), the dose of PGE_1 should be kept low (0.01–0.03 mcg/kg/min) to avoid side effects (apnea, fever, hypotension, and decreased pulmonary vascular resistance).

The ratio of systemic-to-pulmonary blood flow (Qp:Qs) should be optimized. Room air (or rarely subambient inspired oxygen concentrations) may be required, and blood pCO_2 of 40–45 is desirable. Gas exchange and acid-base status should be corrected, because these infants may not tolerate hypoxia or acidosis. Fluid restriction to 75% of maintenance is beneficial during the acute phase, although an occasional small fluid bolus may be needed. As these infants stabilize, judicious use of diuretics may be required.

Severe ventricular failure, frequent apneas due to PGE_1, or inability to balance Qp:Qs may necessitate mechanical ventilation. Tidal volume of 8–12 ml/kg and positive end-expiratory pressure (PEEP) of 6–8 cm H_2O are frequently needed to treat pulmonary edema secondary to left atrial hypertension and hypoxia. Bicarbonate infusion and inotropic support of the myocardium may be needed until cardiogenic shock resolves. However, ongoing acidosis and cardiogenic shock need to be investigated, including careful reanalysis of the cardiac and vascular anatomy and function. Most important in this setting is to ascertain that the ductus arteriosus is indeed open (usually by echocardiography); and if not, that the PGE_1 is infusing appropriately through a functioning line. The very rare patient with cardiogenic shock unresponsive to appropriate medical therapy necessitates an emergent repair or the use of extracorporeal membrane oxygenation for stabilization followed by a delayed repair. On the other hand, those who respond to medical treatment should be physiologically stable prior to the surgical repair.

Due to the risk of NEC, infants with critical CoA should not be fed enterally (especially in the presence of an umbilical arterial catheter) and may need parenteral nutrition. These patients should be monitored for abdominal distension and bloody stools, which would signify the development of NEC. Many centers administer H2-blockers or proton-pump inhibitors to fasting infants, although their benefit has not been clearly shown. Electrolytes and fluid balance should be optimized. While there is no role for prophylactic antibiotics, they are often started before the diagnosis is established because of concerns for septic shock. In such cases, it is reasonable to complete 48–72 h of therapy while awaiting cultures. Sedation with low-dose fentanyl and midazolam or dexmedetomidine may be useful to decrease the infants' metabolic needs and improve comfort.

24.4.2 Older Infants, Children, and Adults

These patients present much less acutely and often undergo an elective surgical repair without the need for preoperative hospitalization. Common sequelae of longstanding unrepaired CoA include stroke, systemic arterial hypertension, and heart failure.

24.5 Surgical and Interventional Aspects

24.5.1 Timing of Surgery

In general, all patients with severe CoA should undergo elective surgical repair within a week or two of their diagnosis, but those with signs of LV failure may need a more urgent intervention. It is appropriate to allow sick neonates to recover (resolution of shock, renal failure, NEC, etc.) before proceeding with surgical repair. Finally, whether associated anomalies are repaired at the time of the CoA repair or in a separate procedure is dictated by the nature of the anomalies as well as the clinical status of the infant. It is not infrequent, for example, to perform the repair of a VSD associated with CoA as a follow-up surgery, [16] although many centers would repair both defects at once [2].

24.5.2 Surgical Technique

Several surgical techniques are utilized in the management of isolated CoA [2]. These procedures are usually performed via left posterolateral thoracotomy and require a period of aortic clamping. A medial sternotomy approach is commonly used in the presence of associated intracardiac anomalies.

24.5.2.1 Resection and End-to-End Anastomosis

After mobilization of the aorta, the *ductus arteriosus* is ligated and divided. The aorta is clamped proximally and distally and the area of coarctation excised. The two ends of

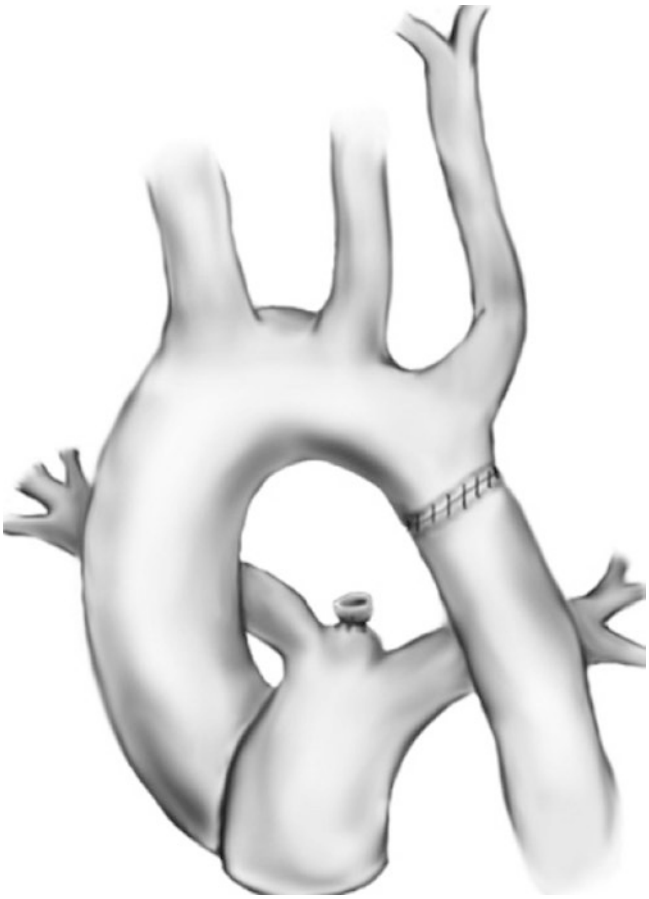

Fig. 24.2 Completed end-to-end coarctation repair

the aorta are then approximated with a running suture (Fig. 24.2).

24.5.2.2 Resection and Extended End-to-End Anastomosis

The undersurface of the proximal aortic end is opened longitudinally up to the takeoff of the left common carotid artery. A counter-incision is then made along the greater curvature of the descending aorta, and the two ends are then sutured together (Fig. 24.3). This repair is especially useful in patients with distal aortic arch hypoplasia.

24.5.2.3 Prosthetic Patch Aortoplasty

A longitudinal incision is placed through the area of coarctation and extended proximally and distally. The aortotomy is then repaired with a synthetic patch (Fig. 24.4). This repair is appropriate for the management of patients with poor aortic mobility and in the redo setting.

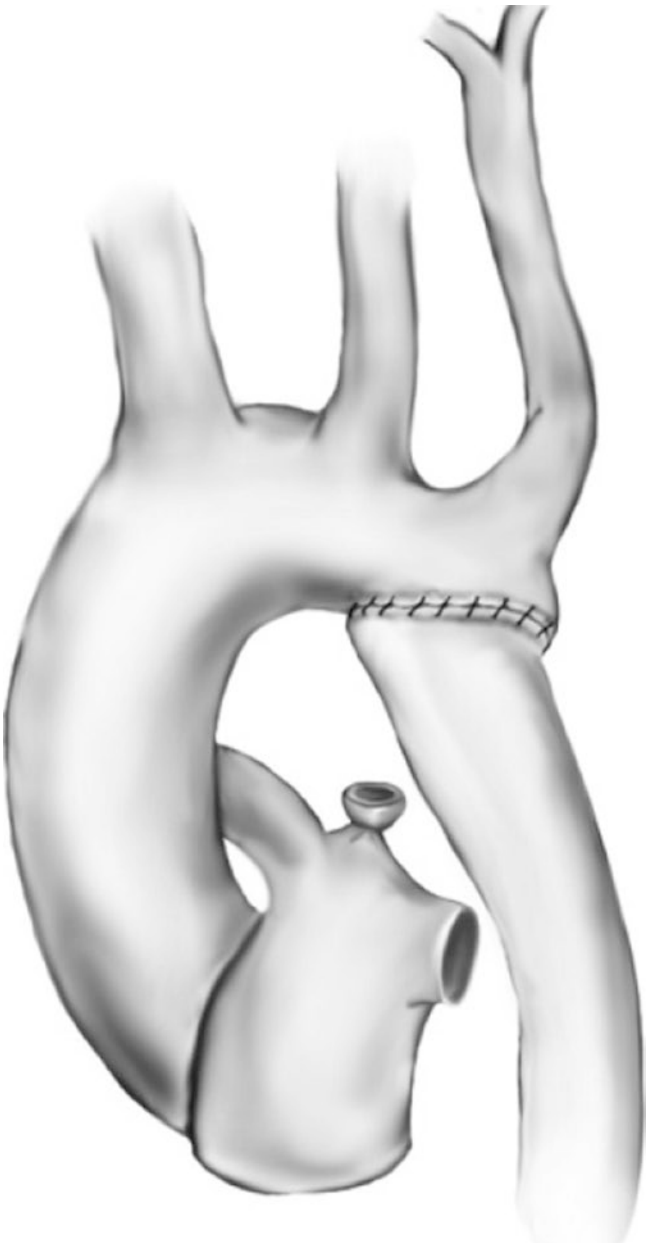

Fig. 24.3 Completed extended end-to-end repair; note the placement of the distal aortic segment to the undersurface of the distal aortic arch

24.5.2.4 Subclavian Flap Aortoplasty

In this repair, the left subclavian artery is ligated and divided distally. A longitudinal arteriotomy is then made along the length of the artery and is extended across the aortic isthmus and the area of coarctation. The opened left subclavian artery is folded down and sutured to the edges of the aortotomy, thus serving as a patch (Fig. 24.5). The major disadvantage of this technique is the possibility of left arm ischemia and/or growth disturbance.

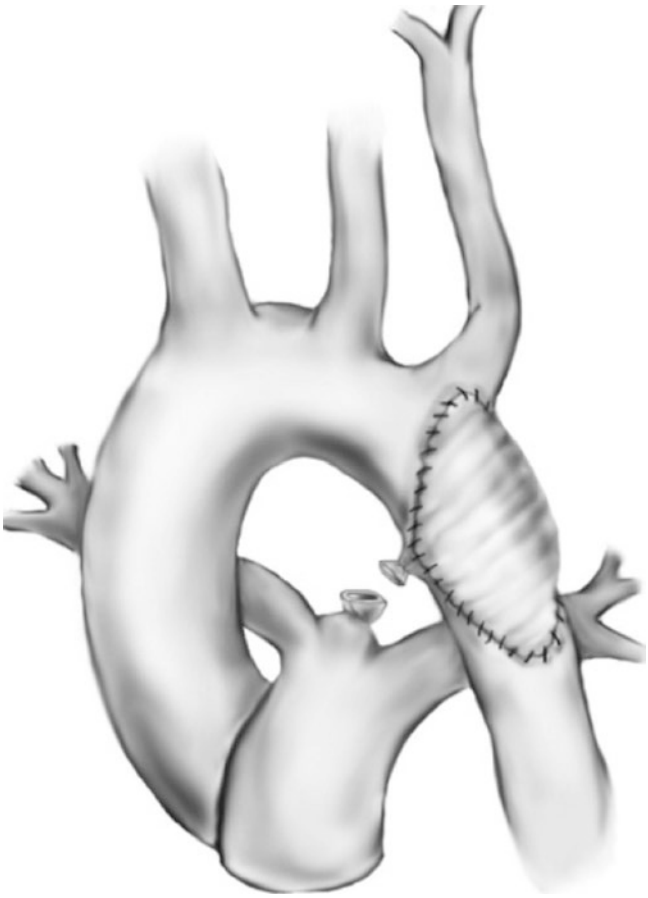

Fig. 24.4 Completed patch aortoplasty

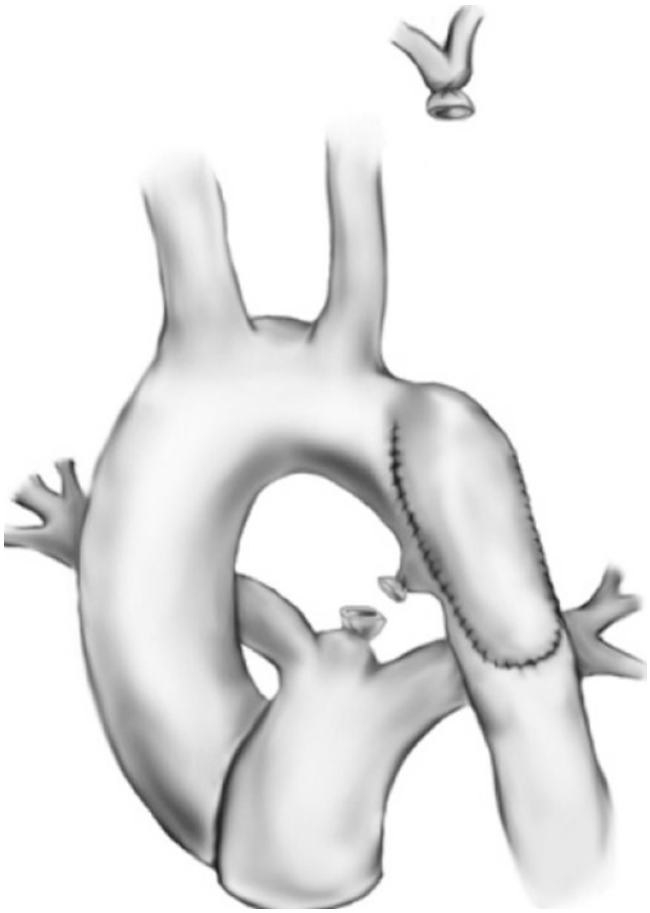

Fig. 24.5 Completed subclavian flap aortoplasty

24.5.3 Transcatheter Interventions

Although balloon dilation with and without stenting has been used as a treatment for CoA since the 1980s, its role in the setting of native CoA continues to be controversial [2, 17]. The interventional approach is appealing, because it avoids surgery and aortic cross-clamping, which is particularly attractive in those with previous surgery and in those with native CoA and minimal collateral arterial formation. In fact, in a native CoA, this approach typically results in acceptable immediate results, yet it carries a risk of acute aortic dissection and results in a higher rate of recoarctation, especially in infants. Patients who undergo angioplasty for native CoA continue to experience a worrisome incidence of aortic aneurysm late after the procedure [18]. Some patient populations, notable patients with Turner Syndrome [19], experience an especially high complication rate.

Nevertheless, primary CoA stenting (not simple ballooning) has become a relatively well-accepted alternative to surgery in the older child, adolescent, and young adult with CoA (Fig. 24.6). If used to treat native CoA, it is applied to patients over 2 years of age with a simple CoA and never to neonates, except for the very rare palliative procedures in those who are not surgical candidates. Modern techniques increase the procedural success rate while limiting the incidence of post-angioplasty complications, which include aortic dissection, stent malposition, femoral arterial damage, and cerebrovascular accidents, to approximately 6%. The procedural mortality is about 0.3% [20–23].

On the other hand, balloon angioplasty (not reoperation) is clearly the approach of choice in the cases of postoperative recoarctation (Fig. 24.7), regardless of the surgical technique used for previous repair. In this setting, it carries a high success rate, low complication rate, and low need for reintervention [18].

From a technical standpoint, CoA is crossed retrograde using the femoral artery approach in most cases. In patients with postoperative CoA after single ventricle palliation, CoA is typically addressed transvenously, to minimize the risk of damage to the femoral artery. Simultaneous pre- and post-CoA pressures are recorded, and the CoA area is imaged by biplane angiography. The angioplasty balloon (diameter no larger than 1.2 times that of the healthy vessel before and after the stenotic area) is positioned across CoA over a wire

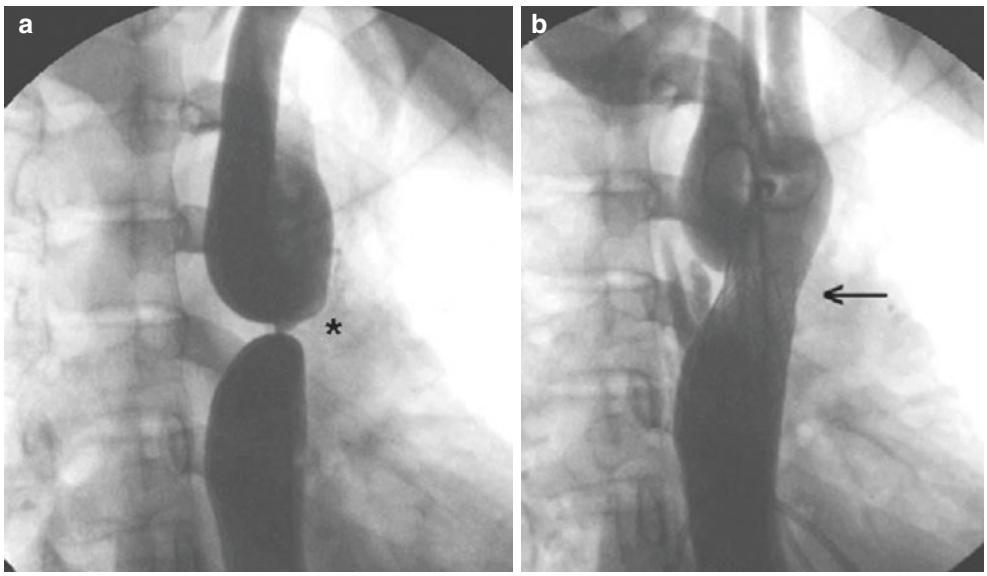

Fig. 24.6 Coarctation stenting. A) Aortogram performed in AP projection demonstrates a severe discrete native coarctation of aorta (∗). Aortogram following stent implantation demonstrates marked angiographic improvement (arrow)

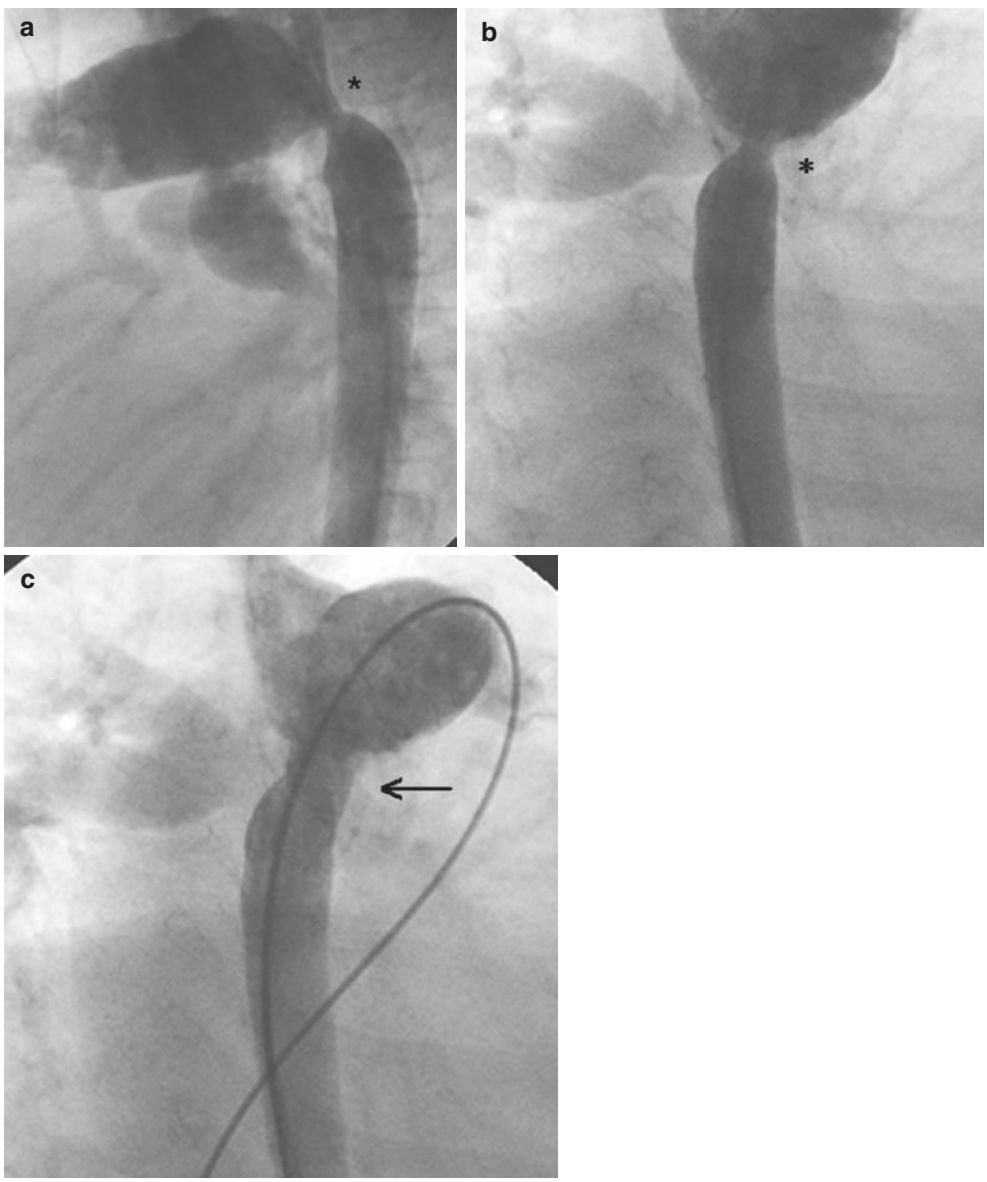

Fig. 24.7 Postoperative coarctation of aorta. Aortogram in the lateral projection (A) and the anterior-posterior projection with caudal angulation (B) demonstrate a severe postoperative coarctation of aorta (∗) following Norwood procedure for hypoplastic left heart syndrome. Immediately after antegrade balloon angioplasty, there is significant angiographic improvement (arrow)

and inflated for a few seconds. Pressures across CoA are then remeasured, and the area is reimaged by repeat angiography.

24.5.4 Surgical Complications

The most dreaded complication associated with CoA repair is spinal cord ischemia leading to paraplegia. The reported incidence of paraplegia is approximately 0.4% in neonates and infants [24, 25] and 2.6% in older children and adults [26]. More common complications include chylothorax, recurrent laryngeal nerve injury, phrenic nerve injury, and recoarctation (15%). The operative mortality is less than 2%.

24.5.5 Postoperative Management

24.5.5.1 Monitoring

Patients should be monitored with an arterial and central venous line in addition to the usual intensive care monitoring of vital signs and EKG. Noninvasive blood pressure measurements in the upper and lower limbs will help identify any residual or recurrent CoA. Near-infrared spectroscopy (NIRS) is useful for the assessment of regional perfusion, particularly in the splanchnic vascular bed.

24.5.5.2 Respiratory Management

Neonates recovering from uncomplicated surgical repair of critical CoA are usually extubated in the operating room or upon admission to the intensive care unit (ICU). Patients who had a complicated preoperative course may require mechanical ventilation for 12–24 hours after CoA repair because of reactive pulmonary vascular bed and a risk of pulmonary hypertension. If clinically significant pulmonary hypertension is present, it should be treated in the standard fashion, including sedation and nitric oxide. Patients after complex arch repair that required circulatory arrest and median sternotomy may also need mechanical ventilation. Once hemodynamically stable, these infants are weaned to extubation. Older infants, children, adolescents, and adults are much easier to care for than infants. They are usually extubated in the operating room.

24.5.5.3 Cardiovascular Management

The hemodynamic management in the ICU is guided by the presence of any residual intracardiac or extracardiac lesions, the postoperative ventricular function, and the volume status. Low-dose epinephrine and/or milrinone (0.5–1 mcg/kg/min) infusion may be started in the operating room and continued for several days in the ICU. Inotropes are usually weaned after the extubation.

24.5.6 Fluid Management and Nutrition

Fluid restriction is unnecessary after CoA repair, unless cardiopulmonary bypass was used to repair associated intracardiac lesions. Feedings are started very slowly when the infant is hemodynamically stable, has bowel sounds, and the abdominal exam is benign. A peculiar morbidity following CoA repair is the post-coarctectomy syndrome, which manifests as abdominal pain, tenderness, hypertension, fever, and leukocytosis 2–3 days after the CoA repair. The etiology of the post-coarctectomy syndrome seems to involve a sudden increase of blood flow to the mesenteric vessels after the coarctectomy, resulting in mesenteric necrotizing arteritis [27].

24.5.7 Complications

In older patients, postoperative systemic hypertension is common after CoA repair. Its etiology is likely multifactorial, involving baroreceptor dysfunction, increase in circulating catecholamines and renin, and the presence of mesenteric arteritis [28]. It is crucial to control hypertension diligently for the first 24–48 postoperative hours to prevent anastomotic leaks and the post-coarctectomy syndrome and to limit bleeding. Esmolol, labetalol, nicardipine, or nitroprusside may be used to keep systolic blood pressure below 80–90 mmHg. However, aggressive afterload reduction is contraindicated in the presence of significant residual aortic stenosis. Once extubated and fed, the infants are transitioned to an angiotensin-converting enzyme (ACE) inhibitor or beta-blocker for long-term treatment, especially in the presence of aortic regurgitation.

Chylothorax (due thoracic duct injury) affects the respiratory effort of the patient, if not adequately drained. It may be addressed by changing the infant's diet to a formula, the entire fat content of which is in the form of medium-chain fatty acids (such as Postagen), since medium-chain fatty acids do not travel through the thoracic duct once absorbed. However, often more drastic measures, such as cessation of all enteral feeding for at least 2 weeks (and institution of parenteral nutrition) followed by Portagen or a similar formula, are required. If the chylothorax persists, thoracic duct ligation should be considered. Of note, lymphocytes, immunoglobulins, and antithrombin III are lost into the chylous effusion and should be closely followed for as long as chylothorax is present.

Injury to the recurrent laryngeal nerve may occur after CoA repair, leading to paralysis of the left vocal cord, which

manifests as stridor and respiratory distress upon extubation. Its net effect is breathing through a partially obstructed airway, which potentiates the negative intrathoracic pressure (and thus LV afterload) on inspiration. Small infants tend not tolerate this well and may require continuous positive airway pressure (CPAP), heliox, or reintubation (especially if their cardiac function is marginal). If the recurrent laryngeal nerve has not been severed, its function usually recovers in about 7 days, at which time CPAP wean or extubation may be attempted. If the infant again develops stridor and respiratory distress, complete transection of the nerve is likely. Such infants need to undergo an airway endoscopy, and, unless another reason for stridor is found, they should be considered for a tracheostomy.

Injury to the phrenic nerve manifests as hemidiaphragmatic paralysis and is often initially seen on the chest X-ray as an elevated hemidiaphragm. The diagnosis (paradoxical movement of the paralyzed hemidiaphragm – up on inspiration and down on expiration) can be made with fluoroscopy or ultrasound [29]. During the diagnostic study, it is important to avoid positive pressure ventilation because it can interfere with the paradoxical movement of the diaphragm. The respiratory status of young infants is especially compromised by hemidiaphragmatic paralysis, and in them prompt surgical intervention is required.

Those undergoing surgical correction of CoA in the post-infancy period may experience more significant bleeding due to more extensive collateral formation. Bleeding should also be vigilantly sought in those who undergo interventional balloon-dilation and stenting of CoA. In this cohort of patients, bleeding can occur either at the site of the aortic intervention or at the point of entry in the groin. In addition, serial neurological exams should be performed in patients recovering from interventional balloon-dilation and stenting of CoA site, because strokes can occur in this subset of patients.

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Chapter 25
Interrupted Aortic Arch

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Abstract It this chapter we will review cardiac anatomy, pathophysiology, and clinical presentation of Interrupted aortic arch to better understand the preoperative and postoperative management of the patients with this pathology. A brief review of surgical techniques and outcomes is also included.

25.1 Anatomy

Interrupted aortic arch (IAA) involves a discontinuity of a segment of the aortic arch [1].

The Celoria and Patton classification is used to describe the anatomic location of the discontinued or atretic segment (Fig. 25.1): type A: distal to the left subclavian artery (1/3 of cases), type B: between the left subclavian artery and the left common carotid artery (most common, nearly 2/3 of cases), type C: between the left carotid artery and the innominate artery (least common, around 1% of cases).

In addition, the classification of IAA can be based on the anatomy of the subclavian arteries, and it is divided into normal subclavian arteries or an aberrant right subclavian artery with retroesophageal course (present in 50% of type B but also may be seen in type A) [2, 3].

Based on embryologic and anatomic findings, type A and type B have been described as having different etiologies, with type A being an interruption late in development after the subclavian artery had migrated from the proximal descending aorta to the distal transverse arch and type B thought to occur because of inappropriate regression of the left fourth aortic arch [1, 4].

IAA rarely happens in isolation and is associated with other heart defects in more than 95% of cases. The most common association is a ventricular septal defect (VSD) in about 70% of cases. Other common associations include left ventricular outflow tract obstruction (LVOTO), bicuspid aortic valve, aberrant right subclavian artery, aortopulmonary window, truncus arteriosus, and/or transposition of the great arteries and some cases of single ventricle [1].

Type B IAA is more commonly associated with an aberrant right subclavian artery and a cono-ventricular VSD with posterior malalignment causing LVOTO. It has been reported that about 50–80% of patients with this type of arch have DiGeorge syndrome (22q11 deletion) [1, 5, 6]. Only in these patients has the rare finding of right aortic arch been described [7].

25.2 Pathophysiology

IAA is a ductal-dependent anomaly as adequate blood supply to the distal arch is dependent on a patent ductus arteriosus (PDA). Within days after birth, with progressive closure of the PDA, the newborn develops cardiogenic shock, metabolic acidosis, multiorgan dysfunction, and eventually a prompt death if left without an appropriate and vigorous resuscitation.

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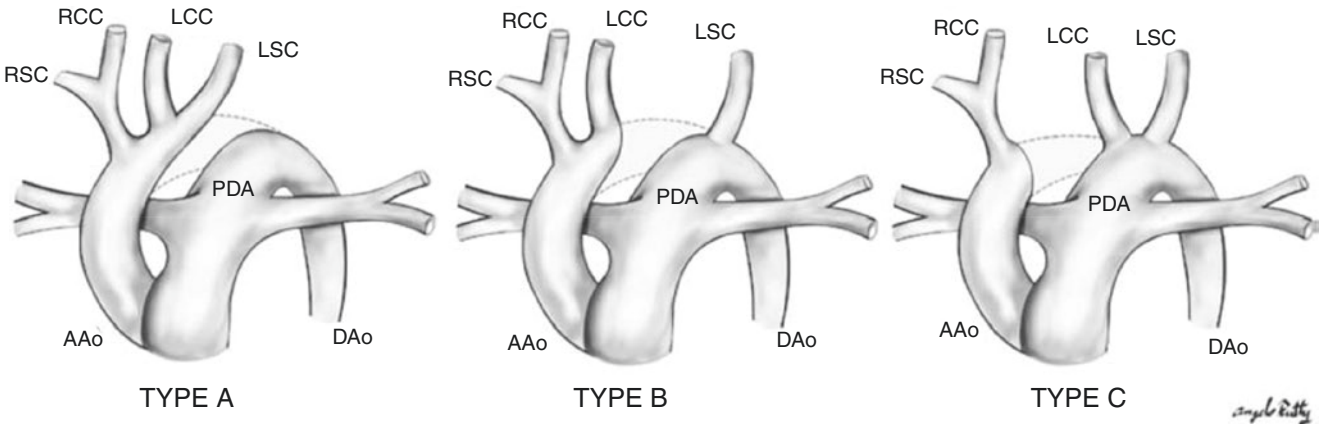

Fig. 25.1 Classification of interrupted aortic arch (Celoria and Patton). The interrupted lines represent the atretic aortic segment. AAo ascending aorta, RSC right subclavian artery, RCC right common carotid artery, LCC left common carotid artery, LSC left subclavian artery, PDA patent ductus arteriosus, Dao descending aorta

In cases where the PDA remains open and in the setting of an intact atrial and ventricular septum, the lower half of the body will be supplied by the PDA with desaturated blood, and differential cyanosis will be present [8].

The shunt across the PDA is dependent of the resistance between the pulmonary and systemic vasculature. In a well-balanced state, the shunt is bidirectional but predominantly right to left. As a result, the patient will have differential cyanosis and diastolic runoff [9].

The pathophysiology of IAA with VSD and/or ASD is different. A left-to-right shunt across ASD or VSD level is present, and the blood that is ejected from the right ventricle and shunted through the PDA to the distal arch is less desaturated than the blood in patients without intracardiac communications. Thus, differential cyanosis may not be clinically appreciated. Nevertheless, assuming normal lung gas exchange and the absence of an aberrant right subclavian artery, the brain and right arm oxygen saturation will be higher than in the lower extremities [10].

Patients with transposition of the great arteries and IAA type B exhibit a distinct physiology that is dependent upon the following factors: (1) intracardiac communications, (2) pulmonary hypertension, and (3) lung pathology. In the absence of intracardiac and extracardiac communications, the neonate has parallel circulation with no effective pulmonary and systemic blood flow [11]. Refractory cardiogenic shock will appear soon after birth, and the only chance of survival is a rapid atrial septostomy coupled with the initiation of prostaglandin E1. If only an insufficient atrial communication exists, a cascade of hypertension from the left atrium through the pulmonary circulation is initiated. At this point, a pulmonary artery to distal arch shunt will occur across the PDA. Because the pulmonary artery carries the more oxygenated blood (as the PA is connected to the left ventricle), the lower half of the body will have higher oxygen saturation compared to the upper part of the body in a condition known as "reverse differential cyanosis." The same physiology applies in any patient with transposition of the great arteries, a PDA, and pulmonary hypertension. In unrepaired surviving infants with significant lung disease and pulmonary hypertension, pulmonary venous desaturation will exist, and reverse differential cyanosis may not be apparent. In the presence of an aberrant right subclavian artery arising after the interruption, the oxygen saturation measured on the right arm may not be different from those measured in the lower extremities [12].

25.3 Clinical Presentation

Prenatal diagnosis of IAA, although improving, remains about 50% of cases [13].

When IAA is not diagnosed during fetal life, the presentation is similar to that in patients with critical coarctation of the aorta. These infants usually remain clinically stable as long as the PDA remains open. Once the PDA becomes smaller, there is not a reliable source of blood supply to the lower body, with a rapid and catastrophic development of cardiogenic shock and multiorgan dysfunction. Physical examination at this point reveals a typically agonal infant with flaccid limbs, tachypnea with moderate-to-severe retractions and weak or absent pulses in lower extremities, blood pressure and saturation differential between upper and lower extremities (depending on site of interruption), decreased urine output, prolonged capillary refill, among other signs of poor perfusion. Indeed, sometimes the patient presents in extremis with agonal breathing and variable grunting. Action must be swift at this point in order to rescue these extremely sick infants.

Careful examination of pulses and four extremities blood pressure is very important in these infants. Weak right

brachial pulses may be present in patients with an aberrant right subclavian artery arising postinterruption. If all pulses are weak, severe LVOTO, ventricular dysfunction, and/or aortic stenosis must be suspected. This finding is accompanied by poor systemic perfusion, loud systolic murmur (VSD and LVOTO), tachypnea, and an increased work of breathing.

In rare cases, IAA can present later in unoperated surviving children or even in adulthood. Patients may present with hypertension, an upper-to-lower extremity blood pressure gradient, or no gradient at all. There may be differential cyanosis with lower oxygen saturation in lower extremities. Again, oxygen saturation may be equal in patients with an aberrant right subclavian artery and varying degrees of cyanosis, clubbing, increased apical impulse, and pulmonary hypertension [1, 14].

25.3.1 Electrocardiogram

The ECG reveals prominent right ventricular forces but is otherwise nonspecific.

25.3.2 Chest Radiography

The chest X-ray demonstrates cardiomegaly, pulmonary edema secondary to overcirculation, and/or ventricular enlargement. Superior mediastinal shadow may be narrow, reflecting an absent thymus in cases with DiGeorge syndrome.

25.3.3 Echocardiography and MRI

Echocardiography and MRI are the gold standard for the diagnosis of IAA. Catheterization is rarely indicated. Goals of imaging include the determination of the location and the length of the aortic arch discontinuity, the origin of brachiocephalic vessels, the size of the arch, and patency of PDA, an evaluation of any intracardiac defect, the dimensions of the left ventricular outflow tract, aortic annulus, and ascending aorta [15].

25.4 Preoperative Management

With fetal diagnosis, the early initiation of PGE1 prevents the progression to cardiogenic shock and usually allows for a semi-elective surgical planning [13].

When an infant presents in cardiogenic shock, PGE1 must be initiated together with volume resuscitation and inotropic support should be started and titrated according to clinical response and echocardiographic findings. If the infant has significant work of breathing, endotracheal intubation should be performed and hyperoxia, hypocarbia, and alkalosis must be avoided to promote right-to-left shunt across the PDA and to increase systemic blood flow. In selected cases, it may be necessary to decrease the systemic vascular resistance with milrinone. Some institutions may try to increase the pulmonary vascular resistance with a hypoxic gas mixture to avoid pulmonary overcirculation.

The goal of therapy is to maintain optimal distal arch perfusion with right-to-left shunting across the PDA. This goal can be monitored by physical examination (peripheral pulses, perfusion, and urine output). A preductal saturation above 90% and a postductal saturation of 70–80% suggest a good gas exchange and an appropriate distribution of the cardiac output. Near-infrared spectroscopy (NIRS) has been used to assess regional tissue perfusion with some reports showing an excellent correlation between splacnic NIRS and mixed venous O2 sat, lactate, and gastric tonometry [16, 17]. Biochemical markers such as lactate levels, arterial and/or venous blood gases, and liver and renal function tests must be closely monitored. Chromosome studies are routinely requested to rule out DiGeorge (22q11 deletion) or CHARGE syndrome (CHD7 mutation on chromosome 8q12.1) [18], as well as other congenital anomalies, and irradiated blood must be administrated until DiGeorge syndrome is eliminated from the differential. In addition, renal and head ultrasounds are routinely obtained to rule out anomalies. If possible, once the patient is stable, enteral trophic feeds at approximately 20 ml/kg/day may be initiated and slowly advanced if tolerated, but a cautious approach may be preferred until repair to avoid NEC, a most dreadful complication. If NEC is suspected, the cardiac repair is delayed until improvement and the patient is treated with broad spectrum antibiotics, no enteral feeding for 10–14 days, and parenteral nutrition. Serial abdominal radiographs should be closely followed in these infants. In the author's practice, if sepsis is suspected, ampicillin and cefotaxime are initiated. They are discontinued if cultures remain negative after 72 h of therapy.

25.4.1 Surgical Management

The surgical repair of IAA consists of anastomosis of the aortic ends and closure of any associated defect (i.e., VSD, AP window). The surgery requires cardiopulmonary bypass, moderate-to-deep hypothermia, and cardioplegic arrest. A

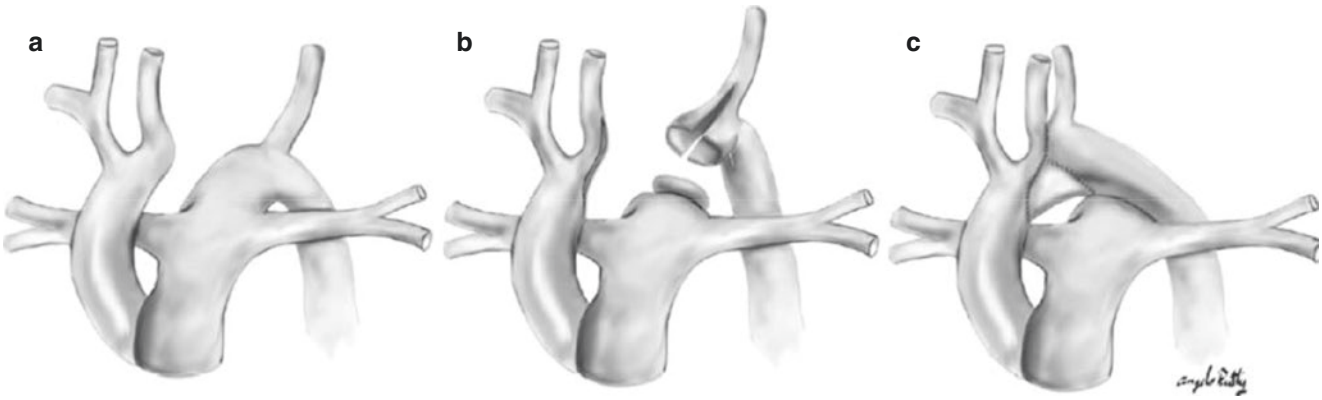

Fig. 25.2 Repair of type B interruption. (**a**) Discontinuity of the aorta between the left common carotid artery and the left subclavian artery; (**b**) the ductus arteriosus is divided, and the distal aortic segment is opened superiorly into the proximal left subclavian artery and inferiorly into the descending aorta, past the area of ductal tissue. The proximal aortic segment is opened into the origin of the left common carotid, (**c**) the two aortic ends are sutured together, and the anastomosis is augmented with a prosthetic patch

period of circulatory arrest and/or low flow is required for the arch repair. A unique aspect of the arterial cannulation is the fact that two cannulas are needed, one for each end of the aorta, to perfuse both the upper body and the lower body [19, 20]. The aortic reconstruction requires extensive mobilization of the distal aortic segment to allow for a stress-free aortic anastomosis (Fig. 25.2). The arch anastomosis is made with homograft or autologous pericardium or in some cases direct anastomosis [21].

We routinely augment the undersurface of the aorta across the area of anastomosis; this technique has been reported to decrease the incidence of recurrent arch obstruction [11, 22] [23]. When present, the ventricular septal defect is closed via a right atriotomy. The mortality rate associated with the repair of an IAA is approximately 8% [24].

The optimal time for surgery is usually during the neonatal period with complete repair as outcomes have improved with improved neonatal operative experience and postoperative management [25].

When IAA is associated with VSD, the surgical approach includes a standard repair with VSD closure and arch anastomosis. In patients with LVOTO, it includes a concomitant conal resection or initial LVOT bypass (Damus-Kaye-Stansel with Sano shunt), followed by the Rastelli procedure at a median age of 8 months. Currently, resection of the conal septum is a strategy no longer in favor due to its high reoperation rates and technical difficulties [26, 27].

For high-risk neonates with IAA, a hybrid approach has been proposed; this includes branch pulmonary artery banding and ductal stent implantation allowing recovery, maturity, and weight gain until complete repair [28].

25.5 Postoperative Management

The postoperative management will depend upon the associated congenital heart disease [29].

There are four main postoperative courses:

1. Isolated IAA
2. IAA with ventricular septal defect (VSD) and left ventricular outflow tract obstruction (LVOTO)
3. IAA with VSD and transposition of the great arteries (TGA)
4. IAA with VSD and truncus arteriosus (TA)

25.5.1 Isolated IAA

Postoperative care of isolated IAA is similar to that after the repair of coarctation of the aorta. Attention should be paid to possible residual arch gradient, and evaluation of the femoral pulses and the blood pressure of the four extremities is mandatory [30].

25.5.1.1 Cardiovascular Management

The inotropic support of choice is milrinone and low-dose epinephrine (if needed). Due to manipulation of the aortic arch and the friable tissues, hypertension should be avoided to prevent bleeding and tension along the sutures lines [9]. Some infants may benefit from the use of an arteriovenodilator such as sodium nitroprusside. In cases without circulatory arrest, milrinone alone is sufficient. Diuretic therapy is initiated within 6–8 h after surgery.

25.5.1.2 Respiratory Management

Extubation should be planned within 48 h of chest closure. Similar to coarctation of the aorta, the caregiver should be aware of the complications related to injury of the structures near the aortic arch, such as left lung atelectasis (left bronchial compression by a reconstructed arch), or damage to the

recurrent laryngeal nerve, thoracic duct, phrenic nerve, and sympathetic ganglia.

25.5.1.3 Metabolic Management

Patients with DiGeorge syndrome may require frequent calcium supplementation. A full endocrine and immunologic evaluation should be completed as a wide spectrum of this syndrome exists with mild-to-severe endocrine and immune deficiencies.

25.5.2 IAA with Ventricular Septal Defect (VSD) and Left Ventricular Outflow Tract Obstruction (LVOTO)

Currently in patients with these anomalies, all defects can be repaired in one surgical stage [31, 32]. Therefore, the postoperative care can be challenging. In addition to the aforementioned management of the arch repair, one needs to be aware of the potential complications of VSD and LVOTO repair [30, 33]. As a rule, the caregiver must always find evidence of an adequate surgical repair [34]. Residual defects may have devastating consequences, especially in infants after cardiopulmonary bypass, cardioplegic arrest, and circulatory arrest. In an infant with a combination of residual arch obstruction and residual VSD, significant LV dysfunction and low cardiac output syndrome will develop due to LV volume (left-to-right shunt across the VSD) and pressure overload (residual arch obstruction). Left ventricular dysfunction will lead to left atrial hypertension, pulmonary venous hypertension, pulmonary edema, pulmonary hypertension, and eventually RV dysfunction. The clinical signs of these residual defects are a VSD murmur, weak pulses in lower extremities, pulmonary edema, and signs of congestive heart failure with potential cardiogenic shock. An echocardiogram and even cardiac catheterization should be promptly done in cases with no clear explanation of a torpid postoperative course in order to decide on surgical reintervention [35]. Surgical patch closure of a VSD also implies the possibility of a conduction system injury with ensuing arrhythmias and atrioventricular block. Depending upon the surgical approach (via right atrium-tricuspid valve, pulmonary valve, or ventriculotomy), the intensivist may see various degrees of tricuspid or pulmonary valve incompetence in addition to ventricular dysfunction. More specific details regarding the postoperative care of VSD and LVOTO are discussed elsewhere in this volume.

25.5.3 IAA with VSD and Transposition of the Great Arteries (TGA)

In patients with these abnormalities, the presence of residual arch obstruction, injury to the extracardiac structures (phrenic nerve, thoracic duct, etc), conduction abnormalities, and a residual VSD must be evaluated. Details of postoperative care of arterial switch will be discussed in the chapter regarding transposition of the great arteries. Some of the potential morbidities of this repair include ventricular dysfunction, mitral regurgitation, arrhythmias secondary to coronary insufficiency, bleeding due to multiple suture lines, supravalvular pulmonic stenosis, and supravalvular aortic stenosis [36]. These patients may need ECMO shortly after surgery until ventricular function improves [37].

25.5.4 IAA with VSD and Truncus Arteriosus (TA)

In patients with these conditions, immediate postoperative complications of truncus arteriosus must be avoided. These include pulmonary hypertension, branch pulmonary artery stenosis, right ventricular dysfunction, conduit stenosis, conduction system abnormalities, arrhythmias, coronary ostium injury, and truncal valve insufficiency and/or stenosis [22].

After direct repair of interrupted aortic arch, the narrow area between the aortic arch, the right pulmonary artery and the left main bronchus may increase the risk of bronchovascular compression. To avoid this, some authors have reported their experience performing anterior translocation of the right pulmonary artery over the aorta [38, 39].

25.6 Long-Term Outcome

Surgical results for the repair of IAA are improving, and short- and long-term outcomes are influenced by the initial surgical approach (single-stage complete repair versus staged palliative repair), coexistence of other associated anomalies, low-birth weight, and experience of the cardiovascular team [40–45]. In the study of Brown, et al., which compiled 20 years of surgical experience in patients with IAA and associated anomalies, it was revealed that regardless of operative technique, there is still a long-term probability of reoperation and/or reintervention. The actuarial survival, including early mortality, was 92% at 1 year, 81% at 5 years, and 76% at 10–15 years [23]. Another study of 472 neonates reported that reintervention was more likely for those who had a diagnosis of truncus arteriosus, IAA repair by a method other than direct anastomosis with patch augmentation, and/or the use of polytetrafluoroethylene as either an interposition graft or a patch [11]. Patients with low birth weight, immediate presentation, type B IAA, and major associated cardiac anomalies remain at high risk for death [46].

Outcomes may vary based on the type of surgical repair. A 2005 Congenital Heart Surgeons' Society (CHSS) study of interruption of the aortic arch found that after repair by direct anastomosis with patch augmentation, at 16-year

follow-up, 18% of patients died, 23% required reintervention, and only 59% survived without reintervention. Those without patch augmentation had only a 47% chance of survival. Among those who had undergone placement of an interposition graft, without arch augmentation, only 16% survived without reintervention at 16-year follow-up and 30% died.

Stenosis at the aortic arch anastomosis site and LVOT obstruction are the most common residual defects [25]. Aortic annulus size has an impact on reoperation rates. Hirata et al. described that almost half of the patients with aortic annulus less than the patients' weight + 1.5 mm required reoperation [46].

More recent studies have proposed a selective management strategy of IAA and VSD to decrease the risk of LVOTO. Alsoufi et al. in 2016 reported their experience with a 4% of operative mortality and 14% of reoperation rate in a 10-year period. This selective strategy considers the degree of aortic valve and subaortic area narrowing, type B interrupted aortic arch, aberrant distal aortic origin of the right subclavian artery, and bicuspid aortic valve [24].

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Chapter 26
Mitral Valve Anomalies and Related Disorders

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Abstract This chapter will discuss mitral disorders with the exception of mitral stenosis to which a specific chapter has been dedicated in this book. It will also provide information about some associated entities such as Marfan syndrome (MFS) and rheumatic disease.

26.1 Mitral Valve Anatomy and Physiology

The normal mitral valve apparatus consists of four components: the annulus, leaflets, tendinous cords, and papillary muscles [1]. The normal mitral valve consists of two leaflets, the anterior leaflet and the posterior leaflet, suspended from the fibrous mitral valve annulus at the level of the atrioventricular junction. The anterior leaflet guards approximately two-thirds of the left atrioventricular orifice, but occupies only one-third of its circumference. The posterior leaflet is subdivided into three sections, or scallops (P1, P2, P3); it guards approximately one-third of the left atrioventricular orifice, but occupies two-thirds of its circumference. The two leaflets coapt at the anterolateral and posteromedial commissures; each scalloped section of the posterior leaflet (P1, P2, P3) coapts with the anterior leaflet in areas designated A1, A2, A3 [2] (Figs. 26.1 and 26.2). Thus, for proper mitral valve function, the mitral valve leaflets require proper functioning of all eight areas of coaptation (two commissures and six leaflet sections). The valve leaflets are normally prevented from prolapsing into the left atrium by the tendinous cords attached to the underside of the valve that insert into the papillary muscles. The papillary muscles are normally symmetric, occupying the anterolateral and posteromedial aspects of the left ventricle, below the anterolateral and posteromedial commissures, and each of them typically has tendinous insertions that support both valve leaflets [2].

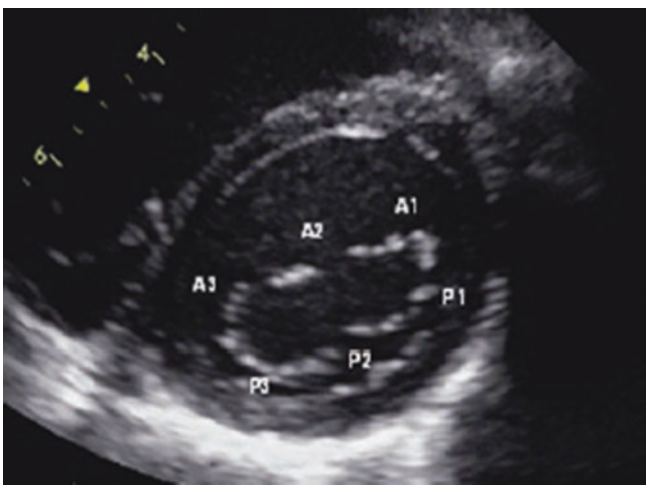

Fig. 26.1 Echocardiography short axis view of the mitral valve, with the scallops of the anterior (A) and posterior (P) leaflets identified: *A1* anterolateral; *A2* middle; *A3* posteromedial; *P1* anterolateral; *P2* middle; *P3* posteromedial

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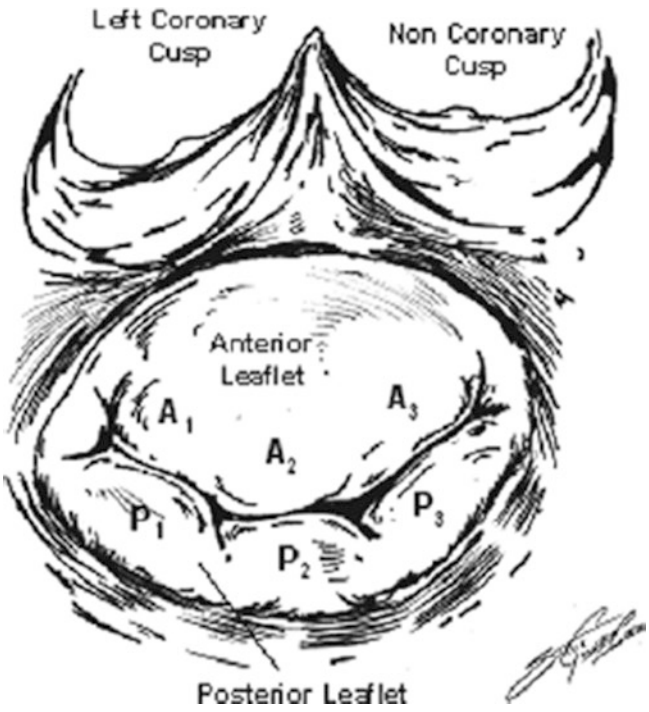


Fig. 26.2 Mitral valve anatomy (drawing from Steven P. Goldberg, MD)

26.2 Etiology and Presentation of Mitral Diseases

26.2.1 Marfan Syndrome

Marfan syndrome (MFS) is a heritable connective tissue disorder which may affect the eyes, cardiovascular system, skeletal system, lungs, spinal cord, skin, kidney, and other systems [3]. The diagnosis is clinical, made predominantly by applying the Ghent criteria (Table 26.1). The Ghent nosology has been revised in 2010 and new diagnostic criteria have superseded the previous agreement (Table 26.2) [4]. Cardiovascular complications in MFS have accounted for more than 90% of premature deaths in the era prior to open-heart surgery [5]. While nearly all Marfan patients continue to exhibit cardiovascular involvement [6], current anticipatory guidance and effective management have allowed patients with MFS to achieve near-normal life expectancies [7]. However, neonatal MFS, with severe mitral and/or tricuspid insufficiency and infantile pulmonary emphysema, continues to carry a very poor prognosis, with a life expectancy of 2 years [8].

The estimated incidence of MFS is 2–3 per 10,000 individuals [9], and the estimated prevalence is 1 in 5000 individuals [10]. MFS exhibits autosomal dominant inheritance with complete penetrance but variable expression in 75% of patients, while sporadic occurrence accounts for the remaining 25% [7]. Preimplantation and prenatal genetic diagnosis is available; however, because variable expression of the syndrome exists even within families, molecular diagnosis of MFS cannot predict disease severity [11]. The birth prevalence of neonatal MFS, the most severe phenotypic expression of MFS, is quite rare; one study reports a prevalence of 1 per 27,000 live births [12].

Table 26.1 Ghent diagnostic criteria: An index case must meet two major criteria in two organ systems and a minor criterion in a third system

System	Major criteria	Minor criteria
Family history	MFS in parent, child, or sibling	
Genetics	Mutation of FBN1	
Cardiovascular	Aortic root dilation	Mitral valve prolapse
	Dissection of ascending aorta	Calcification of the mitral valve (<40 years)
		Dilatation of the pulmonary artery
		Dilatation/dissection of descending aorta
Occular	Ectopia lentis	Flat cornea elongated
		Globe myopia
Skeletal	Pectus excavatum needing surgery	Moderate pectus excavatum
	Pectus carinatum	High arched palate
	Pes planus	Typical facial features
	Positive wrist or thumb sign	Joint hypermobility
	Scoliosis >20[4] or spondylolisthesis	
	Arm span height ratio >1.05	
	Protrusio acetabulae	
	Diminished extension elbows <170[4]	
Pulmonary		Spontaneous pneumothorax
		Apical bulla
		Striae
		Recurrent or incisional hernia
Central system	Nervous lumbosacral dural ectasia	

The most common cardiovascular abnormalities in pediatric MFS are dilation of the aorta (Figs. 26.3 and 26.4) and mitral valve prolapse [13], the morphology of which can be characterized both by histology and by gross pathology. This chapter will concentrate on the description of the mitral anomalies.

26.2.1.1 Mitral Valve in Marfan Syndrome

In MFS, the mitral valve leaflets are most frequently abnormal. The mitral valve in patients with MFS demonstrates progressive histologic and morphologic abnormalities. Fibrillin density is reduced and accompanied by partial fragmentation of the longer fibrillin-coated elastic fibers, with abnormal globular change in the fibrillin coating of remaining portions of elastic fibers [14]. Both the anterior and posterior leaflets tend to become elongated and redundant, with some degree of thickening. Chordal elongation and rupture can occur. Progressive annular dilation and calcification can be demonstrated in 30% of MFS patients

Table 26.2 Revised Ghent diagnostic criteria of Marfan syndrome and related conditions

In absence of family history	
1. Aortic Z-score ≥ 2 AND ectopia lentis = MFS∗	
2. Aortic Z-score ≥ 2 AND FBN1 = MFS	
3. Aortic Z-score ≥ 2 AND systemic score ≥ 7 points (see below) = MFS∗	
4. Ectopia lentis AND FBN1 with known Ao = MFS	
Ectopia lentis with or without systemic score AND with an FBN1 mutation not previously associated with aortic root aneurysm/dissection or no FBN1 = ELS	
Aortic Z-score < 2 AND systemic score ≥ 5 and at least one skeletal feature without ectopia lentis = MASS	
Mitral valve prolapse AND aortic Z-score < 2 AND systemic score < 5 without ectopia lentis = mitral valve prolapse syndrome (MVPS)	
In the presence of family history of MFS (as defined above):	
5. Ectopia lentis = MFS	
6. Systemic score ≥ 7 = MFS	
7. Aortic Z-score ≥ 2 above 20 years old, ≥3 below 20 years = MFS	
∗ Caveat: without discriminating features of Shprintzen-Goldberg syndrome, Loeys-Dietz syndrome or vascular Ehlers-Danlos syndrome after TGFBR1/2, collagen biochemistry, COL3A1 testing if indicated.	
Systemic scoring system	
Wrist AND thumb sign	3
Wrist OR thumb sign	1
Pectus carinatum deformity	2
Pectus excavatum or chest asymmetry	1
Hindfoot deformity	2
Plain flat foot (pes planus)	1
Pneumothorax	2
Dural ectasia	2
Protrusio acetabulae	2
Reduced upper segment/lower segment AND increased arm span/height ratios	1
Scoliosis or thoracolumbar kyphosis	1
Reduced elbow extension	1
3 of 5 facial features	1
Skin striae	1
Myopia	1
Mitral valve prolapse	1

Adapted from Loeys et al. [4]
Ao aortic diameter at the sinuses of Valsalva above indicated Z-score or aortic root dissection, *EL* ectopia lentis, *ELS* ectopia lentis syndrome, *FBN1* fibrillin-1 mutation, *MASS* myopia, mitral valve prolapse, borderline (Z < 2) aortic dilatation, striae, skeletal findings phenotype, *MFS* Marfan syndrome

[15]. Massive calcification of the mitral valve annulus has been reported in adolescence [16].

All phases of mitral regurgitation – acute, chronic compensated, and chronic decompensated – have been described in neonates and children with MFS [17].

As the anterior and posterior leaflets of the mitral valve become elongated, redundant, and somewhat thickened [15], it results in the prolapse of the anterior leaflet or the posterior leaflet or both [18]. Mitral valve prolapse can be demonstrated in 17% of children at age 5 [13]; in 75% of adolescents at age 15 [13]; and in 80% of young adults at 30 years of age [15]. It has been suggested that 100% of children with evolving phenotypic expression of MFS will develop mitral valve dysfunction by 18 years of age, and one half of children with mitral valve dysfunction will develop mitral regurgitation (MR) before 25 years of age [13]. By 30 years of age, 13% would have developed moderate-to-severe MR [15]. In fact, in the pediatric MFS population, mitral valve dysfunction and regurgitation contribute most to morbidity and mortality, and have been suggested to be of prognostic significance [15, 19]. Severe MR in very young children is a feature of the infantile and neonatal expression of MFS [20–22].

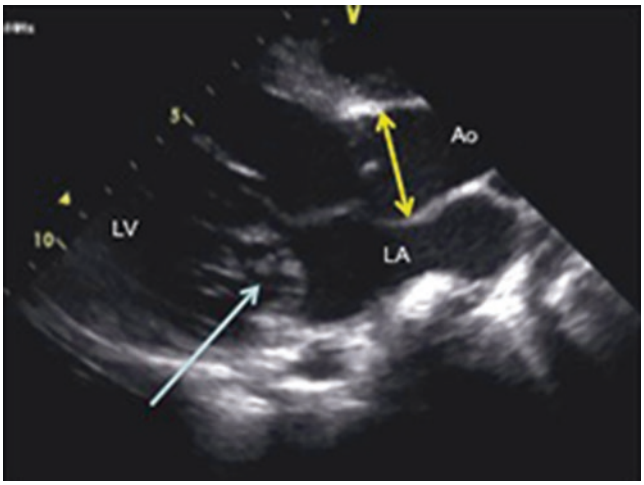


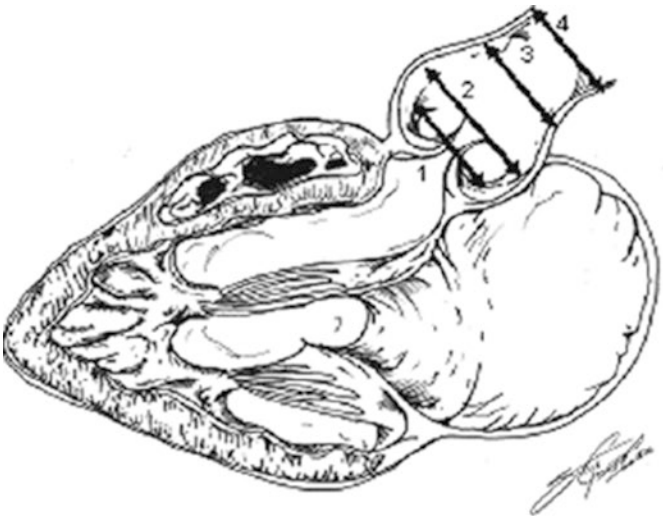
Fig. 26.3 2D echocardiography of a patient with Marfan syndrome demonstrating dilation of the sinuses of Valsalva and abnormal mitral valve

26.2.1.2 Arrhythmias in Marfan Syndrome

Patients with MFS have a greater prevalence of cardiac dysrhythmias when compared to healthy patients without MFS [23]. In children and adults with MFS, ventricular dysrhythmia can occur and progress with or without significant valve disease [24]. Young patients with MFS with stable cardiovascular involvement on medical therapy are more likely to die from dysrhythmia than from aortic dissection [25]. Ventricular tachycardia can occur as a consequence of mitral valve prolapse [26]. Atrial tachydysrhythmia can take place secondary to atrial dilation in the setting of valvar regurgitation.

26.2.1.3 Myocardial Dysfunction in Marfan Syndrome

Symptomatic myocardial dysfunction in MFS rarely occurs in the absence of significant valvar regurgitation. Chronic left ventricular volume overload from aortic regurgitation (AR) or mitral regurgitation (MR) causes ventricular dilation and increased end-diastolic pressure. To maintain cardiac output in accordance with the Frank-Starling mechanism, increased end-diastolic pressure results in increased ventricular performance until the point beyond which compensation cannot be maintained and circulatory failure results. In the setting of valvar regurgitation, the left ventricle is hyperdynamic. A "normal" appearing left ventricle in the setting of



Aorta (End-Diastole)

	N	Mean ± SD	Range
1 Aortic Annulus	68	1.9 ± 0.2	1.4-2.6
2 Sinus of Valsalva	68	2.8 ± 0.3	2.1-3.5
3 Sinotubular Junction	64	2.4 ± 0.4	1.7-3.4
4 Ascending Aorta	44	2.8 ± 0.3	2.1-3.4

Fig. 26.4 Echocardiographic measurements in Marfan syndrome (drawing from Steven P. Goldberg, MD)

significant valvar regurgitation may be a harbinger of progressive left ventricular failure. The clinical features of cardiac failure in MFS can be described by the general features of cardiac failure described elsewhere in this Chapter.

26.2.1.4 Diagnosis of Marfan Syndrome

Clinical Presentation of Marfan Syndrome

Classic MFS

MFS is most often suspected on the basis of skeletal and ophthalmic features that suggest the diagnosis. Due to its variability and tendency towards an evolving phenotype, the diagnosis of MFS is primarily clinical, made by applying the Ghent criteria (Table 26.1). However, when the clinical diagnosis is less clear, a full range of diagnostic studies can be performed, and the objective findings can be assembled to make the diagnosis [3].

Atypically Severe MFS

Though MFS exhibits a significant degree of clinical variability, both within and among families with MFS, no generally accepted clinical grading system exists for MFS. Tiecke et al. have proposed that a reasonable preliminary definition of "atypically severe" MFS be considered for MFS patients who manifest severe cardiovascular disease and require operative intervention for aortic root dilation or severe aortic or mitral valvular dysfunction before 17 years of age [27].

Neonatal Marfan

As a genetic diagnosis, MFS is always present from birth, and therefore symptoms of MFS in the neonatal period are insufficient to support a diagnosis of neonatal MFS [22]. Rather, the diagnosis of neonatal MFS is reserved for neonates with the most severe phenotypic expression of MFS: severe cardiac valvular insufficiency and cardiac failure and congenital pulmonary emphysema [19, 28]. Mortality in infants with neonatal MFS can be as high as 95% in the first year of life from relentlessly progressive, severe mitral, tricuspid, and/or aortic insufficiency [22, 29] that is often complicated by scoliosis, congenital pulmonary emphysema, and pulmonary hypertension [21]. In addition to the cardiac and pulmonary manifestations, neonatal MFS exhibits a distinctive neonatal phenotype [19, 21, 22, 28, 30]:

- Very loose skin, as if "two sizes too big," lending an aged appearance to the face
- Dolichocephaly
- Dislocated lenses, iridodonesis, megalocornea
- Down-slanting palpebral fissures
- Crumpled, low-set ears
- High-arched palate
- Micrognathia
- Anterior chest deformity
- Flexion contractures
- Hyperextensible joints
- Dislocated hips
- Arachnodactyly

26.2.1.5 Presentation of Mitral Complications of Marfan Syndrome

Many of the cardiovascular complications of MFS sufficient to require admission to the intensive care unit are likely to be characterized by general signs and symptoms of cardiac failure. Infants may exhibit symptoms like failure to thrive, tachypnea, coughing, wheezing, diaphoresis, irritability or listlessness, tachycardia, and poor perfusion. Children and adolescents may show dyspnea, orthopnea, reduced exercise tolerance, syncope or presyncope, chest pain, or palpitations. Tachypnea, increased breathing, or hyperpnea may result from pulmonary edema, bronchial compression may result from cardiac enlargement, or metabolic acidemia and hypoxemia may result from the poor peripheral balance of oxygen demand

delivery. Pulmonary hypertension frequently complicates the course of these patients in the intensive care unit. Additionally, if the ventricular function is compromised, the patient may be at risk for thromboembolism.

MFS patients with severe mitral valve regurgitation enter the intensive care unit with decompensated MR. Contractile and ejection functions are impaired; the hemodynamic consequences are reduced forward output and increased pulmonary vascular congestion. The clinical presentation is variable, depending on the degree of hemodynamic compromise, and can be dominated by the typical features of cardiac failure, circulatory shock, and respiratory failure from pulmonary edema.

In all MFS patients with mitral complications, caregivers must be cautious in identifying other compromised potential cardiovascular functions related to the aortic valve, the aorta, and the myocardial function. As a matter of fact, clinical presentation of an aortic aneurysm in children with MFS is typically asymptomatic; it is detected by serial echocardiographic evaluation. Complications of aortic root aneurysms from rupture, dissection, and tamponade can occur in children with MFS [31–33]; however, early aortic dissection is more characteristic of the recently described Loeys-Dietz syndrome.

Lastly, endocarditis should be considered in any patient with MFS who shows acutely progressive valvular disease, recurrent fevers, or persistent constitutional symptoms of anorexia, weight loss, malaise, or personality changes. Perivalvular abscess can be associated with conduction abnormalities, including complete heart block [34].

Other clinical features on physical examination often include:

- A displaced LV apical impulse from chronic aortic insufficiency
- Soft or absent S2 from incomplete aortic valve closure
- An S3, heard immediately after S2, from the rapid, large volume flow into the LV
- An S4, heard immediately before S1, from flow into noncompliant or stiff ventricle during atrial contraction
- A holodiastolic decrescendo murmur at the left sternal border, also at the right sternal border if associated with aortic root dilation
- Austin Flint murmur, a soft mid-diastolic rumble heard at the apex, when severe regurgitant jet renders partial anterior mitral leaflet closure
- Widened pulse pressure with bounding palpable pulses

26.2.1.6 Electrocardiogram in Marfan syndrome

The resting electrocardiogram in MFS may include findings of [23]:

- Atrial fibrillation
- Premature atrial beats
- Long QT interval and decreased QT dispersion
- ST segment depression
- Premature ventricular beats, with occasional R on T configuration
- Prolonged atrioventricular conduction time

Ventricular arrhythmias are associated with increased left ventricular size, mitral valve prolapse, and abnormalities of repolarization; they are an important cause of sudden death in Marfan patients [35]. Complete heart block may be indicative of endocarditis complicated by perivalvular abscess [34].

26.2.1.7 Imaging in Marfan Syndrome

Echocardiography is the cornerstone method to diagnose mitral anomalies in patients with MFS. In grown-up patients, transthoracic echocardiography may be limited and transesophageal approach may be required.

However, other techniques like angio-CT scan and MRI are essential to complement the assessment of the mitral valve and function and to identify aortic compromising, particularly in the context of suspected aortic dissection.

26.2.1.8 Other Type of Connective Tissue Disease: Loeys-Dietz Syndrome

Loeys-Dietz syndrome (LDS) was first described in 2005 by Bart Loeys and Harry Dietz from Johns Hopkins University School of Medicine [36]. It can be distinguished from MFS by the unique presence of hypertelorism, an abnormal uvula or cleft palate, and widespread aortic and arterial aneurysms and tortuosity [37]. Important additional features that distinguish LDS from MFS include craniosynostosis, clubfoot, joint contractures, and cervical spine instability. Importantly, there is no association between LDS and ectopia lentis, a key feature of MFS.

Compared to MFS, cardiovascular manifestations are more severe and aortic aneurysms tend to dissect or rupture at a smaller diameter and at a younger age [37].

LDS has been categorized into six subtypes, based on the underlying genetic mutations (Table 26.3).

The diagnosis of Loeys-Dietz syndrome [38] is established in a person without a known family history of LDS, who has a heterozygous pathogenic variant in SMAD2, SMAD3, TGFB2, TGFB3, TGFBR1, or TGFBR2 and EITHER of the following:

- Aortic root enlargement (z-score $\geq$ 2.0) or type A dissection.

Table 26.3 Loeys-Dietz syndrome subtypes

LDS subtypes	Gene	Proportion
LDS1	TGFBR1	20–25%
LDS2	TGFBR2	55–60%
LDS3	SMAD3	5–10%
LDS4	TGFB2	5–10%
LDS5	TGFB3	1–5%
LDS6	SMAD2	1–5%

Adapted from Meester et al. [37]
LDS Loeys-Dietz syndrome

- Compatible systemic features including characteristic craniofacial, skeletal, cutaneous, and/or vascular manifestations found in combination, with special emphasis on arterial tortuosity (head and neck vessels), and to aneurysms or dissections involving medium-to-large muscular arteries throughout the arterial tree.

Mitral valve prolapse with mitral regurgitation has been observed in individuals with LDS, although less frequently than in MFS [38].

26.2.2 Rheumatic Fever

Rheumatic fever is a delayed nonsuppurative sequela of group A beta-hemolytic streptococcal (GABHS) pharyngitis in children. The disease has a delayed onset after the initial infection and presents with various other manifestations including arthritis, carditis, chorea, subcutenous nodules, or erythema marginatum.

The incidence of rheumatic heart disease has decreased dramatically in industrialized countries over the past several years related to the introduction of penicillin and a change in the virulence of the Streptococci. A dramatic decline in both the severity and mortality from acute rheumatic fever has occurred in the past 30 years in these countries. The prevalence of rheumatic heart disease in the US is now less than 0.05 per 1000, with rare regional outbreaks [39–42].

In contrast, rheumatic fever and rheumatic heart disease have not decreased in developing countries. Around 5–30 million children and young adults are estimated to have chronic rheumatic heart disease worldwide [43, 44].

Race and sex do not influence the disease incidence. However, aboriginal populations in Australia and natives from Hawaii, Maori, and New Zealand have a higher incidence of rheumatic fever even with antibiotic prophylaxis of streptococcal pharyngitis [45, 46]. Rheumatic disease in females is usually worse with a higher incidence of chorea and a worse prognosis of carditis.

Rheumatic fever is principally a disease of childhood, occurring between 5 and 15 years, with a median age of 10 years at diagnosis. It is still the major cause of acquired valve disease in the World [47, 48].

Though the exact pathogenesis of rheumatic fever remains unclear, it is believed to result from an autoimmune response. It develops following GABHS pharyngitis and almost only infections of the pharynx initiate or reactivate rheumatic fever [49]. Rheumatic fever has also been described in aboriginal populations from Australia following GABHS skin infection [45, 50, 51].

The initial infection consists of sore throat, fever, malaise, and headache in a small percent of patients for several weeks before leading to rheumatic fever.

Penicillin treatment shortens the clinical course of streptococcal pharyngitis and more importantly prevents the major sequelae [52].

Acute rheumatic heart disease produces a pancarditis involving the pericardium, epicardium, myocardium, and endocardium. Endocarditis is manifested as mitral and aortic valve insufficiency [53]. The most commonly affected valve is the mitral valve (65–70% of patients), followed by the aortic (25%) and the tricuspid (10%) valves. The pulmonary valve is rarely affected. Whether myocardial dysfunction during acute rheumatic fever is related primarily to myocarditis or is secondary to severe valve insufficiency is not known [54, 55]. When pericarditis is present, it is usually self-limiting and rarely results in constrictive pericarditis.

Congestive heart failure secondary to severe valve insufficiency is a complication of acute and chronic rheumatic fever. Recurrent episodes of rheumatic fever may cause progressive damage to the valves. Severe scarring of the valves develops months to years after the initial episode of rheumatic fever and is responsible for most cases of mitral valve stenosis in adults.

Patients with a history of rheumatic fever are at a high risk of recurrence. The risk of recurrence is high within 5 years of the initial episode and if the patient is of younger age at the time of the initial episode. The risk of carditis and severity of valve damage increases with each attack.

26.2.2.1 Clinical Presentation of Rheumatic Fever

Acute rheumatic disease is a systemic disease with a large variety of symptoms.

A history of a sore throat 2–5 weeks prior to onset of symptoms is present in 70% of patients. Systemic complaints are frequent including fever, fatigue, weight loss, headache, malaise, and pallor. Abdominal pain is common.

Major clinical manifestations are as follows:

- Fever: is usually greater than 39° C at the onset of symptoms. The fever decreases spontaneously in 1 week, but low-grade fever can persist for 2–3 weeks.
- Arthritis: Polyarthritis is the most common symptom and frequently is the earliest manifestation (70–75%). The arthritis involves usually in the large joints, beginning in the lower extremities (knees, ankles) and migrating to other large joints in the upper extremities (elbows, wrists). Affected joints are painful, erythematous, swollen, and warm. The pain is out of proportion to clinical findings. The arthritis persists for about 1 week, is migratory, and responds dramatically to aspirin [56]. Polyarthritis is more common and more severe in teenagers and young adults than in younger children.
- Carditis: Pancarditis is the second most common complication of rheumatic fever (50%). The classical clinical presentation is a new or changing murmur and tachycardia that is out of proportion to the fever. The murmurs of acute rheumatic fever are from valve regurgitation (most

commonly mitral or aortic) and the murmurs of chronic rheumatic fever from stenosis, most commonly mitral. Dyspnea, edema, cough, orthopnea, and edema are signs of congestive heart failure. Chest discomfort, chest pain, and a pericardial friction rub are signs of pericarditis. All degrees of heart block can be seen, including atrioventricular dissociation [57].

– Sydenham chorea: is a late manifestation of acute rheumatic fever, occurring 1–6 months after the initial sore throat [58, 59]. Patients with chorea often do not demonstrate other Jones criteria, and this criterion alone is sufficient for the diagnosis. Complete resolution of the symptoms typically occurs in 3 months, but some patients can have wax and wane symptoms for several years.
– Pediatric autoimmune neuropsychiatric disorder (PANDAS): is characterized by obsessive-compulsive personality disorder [60]. Patients tend to show aggressive and compulsive comportment. They may also show emotional liability, separation anxiety, and oppositional behaviors.
– Erythema marginatum: begins as pink nonpruritic macules or papules located on the trunk and proximal limbs but never on the face [61]. The lesions form a serpiginous ring with erythematous raised margins and central clearing. The rash is classically exacerbated by heat. The rash occurs early in the course of the disease and remains for long after the resolution of other symptoms.
– Subcutaneous nodules: are firm, nontender, and mobile and are located over the extensor surfaces of the elbows, knees, ankles, knuckles, scalp, and spinous processes of the lumbar and thoracic vertebrae. They are rare but strongly associated with severe rheumatic carditis [62].
– Arthralgias: may be reported upon presentation. Arthralgia cannot be considered a minor criteria if arthritis is present.

26.2.2.2 Diagnosis of Rheumatic Fever: Jones Criteria

The modified Jones criteria [63, 64], revised by the American Heart Association in 1992 [65] and reviewed in 2002 [66], provide guidelines for the diagnosis of rheumatic fever. The diagnosis of rheumatic fever requires evidence of a previous GABHS pharyngitis as well as the presence of two major or one major and two minor criteria (Table 26.4). These criteria are not absolute, and the diagnosis can be made in patients with only confirmed streptococcal pharyngitis and chorea.

Three settings may be identified without strict adherence to the Jones criteria:

- Chorea: may occur late and be the only manifestation of the disease.
- Indolent carditis as the only manifestation in patients who have received medical attention months after the onset of rheumatic fever.

Table 26.4 Jones criteria

Jones criteria:	
Preceding streptococcal infection	Positive throat culture
	Rapid streptococcal antigen test
	Elevated or rising streptococcal antibody titer
Major diagnostic criteria	Carditis
	Polyarthritis
	Chorea
	Subcutaneous nodules
	Erythema marginatum (erythema annulare)
Minor diagnostic criteria	Fever
	Arthralgia
	Prolonged PR interval
	Elevated acute-phase reactants (ESR, CRP)

- Recurrent rheumatic fever: a patient with a history of rheumatic fever, especially rheumatic heart disease, with evidence of a recent GABHS infection with either a single major, or two minor criteria.

The AHA guideline 2002 update [66] concluded that the role of echocardiography in the diagnosis of rheumatic fever was controversial in patients without cardiac findings on clinical exam. It was concluded that echocardiographic Doppler evidence of mitral or aortic regurgitation alone should not be either a major or a minor criterion in the diagnosis of rheumatic fever.

26.2.2.3 Laboratory Examinations in Rheumatic Fever

- Throat culture for GABHS: negative in about 75% of patients by the time rheumatic fever appears [45]. Isolation of the organism prior to the initiation of antibiotic therapy is important to help confirm the diagnosis of streptococcal pharyngitis and to allow typing of the organism.
- Rapid antigen detection test: Allows rapid detection of GABHS antigen with specificity >95% but a sensitivity of only 60–90%. Thus, a throat culture should be obtained [67].
- Antistreptococcal antibodies: are at their peak at initial presentation and are useful for confirming previous GABHS infection [68]. Antibody titers should be performed 2 weeks apart to detect a rising titer. Most patients with acute rheumatic fever have elevated antibodies titers to at least one of the antistreptococcal antibodies [69, 70]. The most common antibodies tested include:
  - Antistreptolysin O (ASLO)
  - Anti-DNase B
  - Antihyaluronidase
  - Antistreptokinase
  - Antistreptococcal esterase
  - Anti-nicotinamide adenine dinucleotide (anti-NAD)

- ▶ Antistreptococcal polysaccharide
- ▶ Anti-teichoic acid
- ▶ Anti-M protein

- Acute-phase reactants: C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are elevated and have high sensitivity but low specificity [71, 72].
- Mild normochromic normocytic anemia: Anemia secondary to acute inflammation may be seen during acute rheumatic fever.
- Heart reactive antibodies: Rapid-detection test for B cell marker D8/17 by immunofluorescence is positive in 90% of patients with rheumatic fever and may be useful for identifying patients who are at risk [73, 74].

26.2.2.4 Other Studies in Rheumatic Fever

- Chest X-ray

Chest X-ray may display cardiomegaly and pulmonary congestion, and other findings consistent with heart failure may be observed.

- ECG

Sinus tachycardia is a common finding. Alternatively, some children present sinus bradycardia from increased vagal tone. First-degree atrioventricular block (prolongation of PR interval), probably related to localized myocardial inflammation of the atrioventricular node, is a common finding and is one of the Jones criteria. Second- and third-degree atrioventricular have been described. In patients with acute pericarditis, ST segment elevation may be present.

- Echocardiography

In individuals with acute rheumatic heart disease, echocardiography identifies and quantitates valve insufficiency and ventricular dysfunction. In patients with mild carditis, Doppler evidence of MR may be present during the acute phase of disease and usually resolves in some weeks or months. In contrast, patients with moderate-to-severe carditis have persistent mitral or aortic regurgitation [75]. According to the revised Jones criteria, evidence of new MR from Doppler echocardiography, in the absence of accompanying auscultatory findings, is not sufficient for making the diagnosis of carditis [76, 77].

Three mechanisms of mitral insufficiency have been described with rheumatic fever (Fig. 26.5): prolapse of the aortic leaflet, rupture of the tendinous chords, and noncoapting retracted immobile mural leaflet [78, 79]. The aortic valve usually shows improper central coaptation of the leaflets. Echocardiographic features of MR from acute rheumatic valvulitis are annular dilatation, elongation of the chordae to the anterior leaflet, and a posterolaterally directed MR jet. A distinctive feature of acute rheumatic valvular disease is focal nodular thickening of the tips and bodies of the leaflets [80]. Left ventricular dilation is frequently seen and contributes to MR.

In individuals with chronic rheumatic heart disease, echocardiography assesses the progression of valve stenosis. The leaflets of affected valves become thickened diffusely, with fusion of the commissures and chordae tendineae (Fig. 26.6). Increased echodensity of the mitral valve is often seen.

26.2.2.5 Complications of Rheumatic Disease

- Congestive heart failure from valve insufficiency (acute rheumatic fever), stenosis (chronic rheumatic fever) or both
- Thrombus formation, pulmonary emboli, and systemic emboli
- Infective endocarditis

- Atrial flutter, multifocal atrial tachycardia, or atrial fibrillation from chronic mitral valve disease and atrial dilation

26.2.3 Congenital Mitral Valve Anomalies

Isolated congenital mitral valve diseases are uncommon in children, occurring in 0.5% of patients with congenital heart defects. More frequently, mitral valve anomalies are seen in association with other lesions in the context of hypoplastic left ventricle syndrome variant or Shone's complex. Shone's

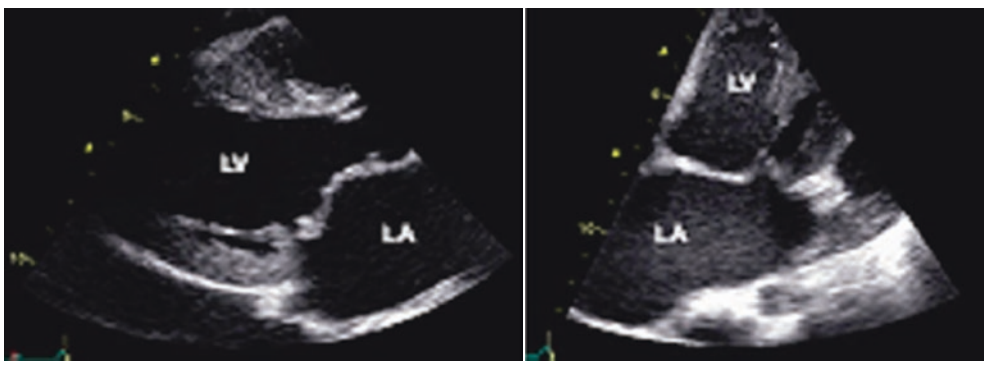


Fig. 26.5 2D Color Doppler echocardiography long axis and four chamber view demonstrating a rheumatic mitral valve with thickened leaflet, absence of central coaptation and marked left atrial dilation secondary to severe regurgitation. LA left atrium; LV left ventricle

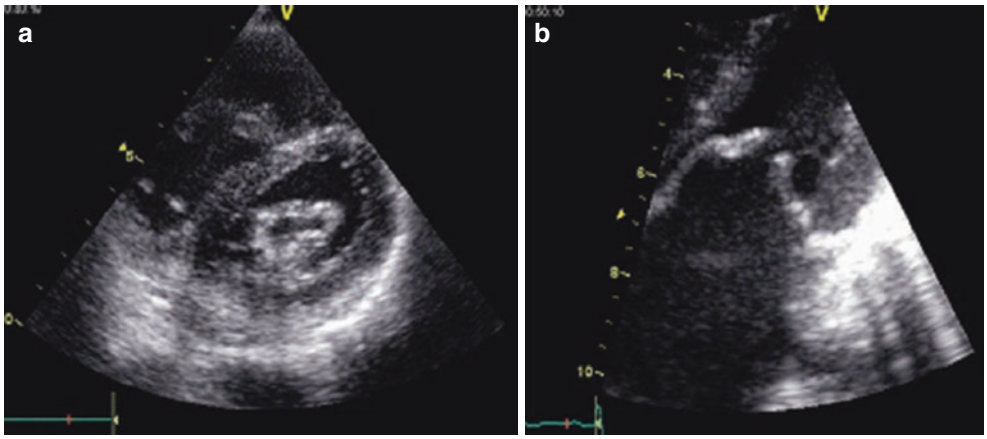


Fig. 26.6 (**a**) 2D echocardiography with severe rheumatic mitral stenosis: short-axis view (left) demonstrating thickened leaflets and limited mitral orifice area, four chamber view (*right*) demonstrating limited leaflet excursion. (**b**) 2D echocardiography in four-chamber view, showing a severe rheumatic mitral stenosis with limited leaflet excursion

complex is characterized by a constellation of left heart obstructive lesions: supravalvar stenosing mitral ring, parachute mitral valve, left ventricular subaortic obstruction, and coarctation of the aorta [81].

26.2.3.1 Annular or Mitral Valve Hypoplasia

In annular or mitral valve hypoplasia, all components of the valve apparatus are morphologically normal but relatively small in relation to the size of the tricuspid valve. Some degree of hypoplasia of the left ventricle and left ventricular outflow tract obstruction are universally present, creating a variant of hypoplastic left ventricle syndrome [82]. Occasionally, annular hypoplasia may result from a dilated coronary sinus and left-sided vena cava. The dilated coronary sinus may cause left ventricular inflow obstruction, which can be demonstrated by abnormal Doppler inflow patterns and increased left atrial "a" waves during cardiac catheterization [83].

26.2.3.2 Congenital Mitral Valve Stenosis

Congenital mitral stenoses, including supravalvar mitral ring, parachute mitral valve, and anomalous arcade or hammock mitral valve, are extensively discussed elsewhere in this book.

26.2.3.3 Congenital Mitral Valve Regurgitation

Congenital MR is uncommon; however, malformations of each of the major components of the mitral valve apparatus have been described in the etiology of MR:

- Annular dilation secondary to anterior or posterior leaflet prolapse
- Leaflet abnormalities, including leaflet dysplasia [2], abnormal leaflet morphology [84], posterior leaflet hypoplasia with chordal shortening [85], isolated cleft of the anterior or posterior leaflet [86] or of both mitral valve leaflets [87], and anterior leaflet fenestrations.
- Commissural abnormalities
- Chordal abnormalities, including chordal length, organization, and insertion
- Papillary muscle abnormalities, including alterations in papillary muscle number, positioning, and chordal attachments

26.2.3.4 Isolated Mitral Cleft

Isolated cleft of the anterior mitral leaflet is a rare cause of MR (Figs. 26.7 and 26.8). This defect is very different from the cleft atrioventricular valve found in the patient with atrioventricular septal defect [88]. The anomaly is characterized by a cleft dividing the anterior leaflet of the mitral valve into two portions with a normally positioned mitral annulus and intact atrioventricular muscular and membranous septum.

26.2.3.5 Double Orifice Mitral Valve

This defect is characterized by two complete mitral orifices supported by their own tension apparatus [89]. Three types have been described:

1. Eccentric or hole type is the most common, and is characterized by a small accessory orifice at the anterolateral or posteromedial commissures.
2. Central type is the next most common and is characterized by excessive leaflet tissue which bridges the central zones of the anterior and posterior leaflets, thereby dividing the mitral orifice into two. The resulting two orifices may be equal or unequal, and they are usually supported by separate tendinous chords that insert into separate papillary muscles.
3. Duplicate mitral valve is an exceptionally rare entity, and is characterized by two mitral valve annuli and valves, each with its own set of leaflets, commissures, chordae, and papillary muscles.

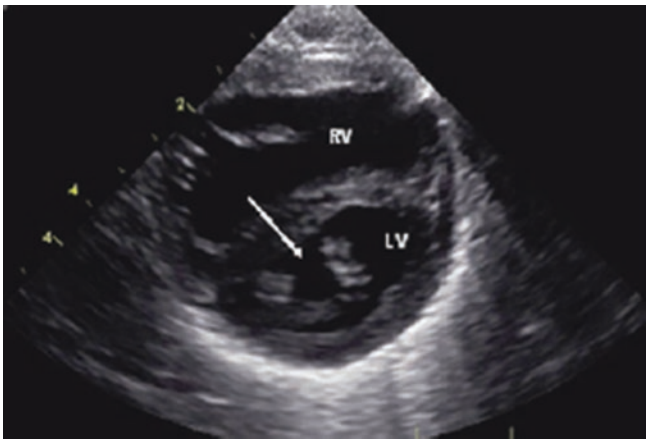


Fig. 26.7 Echocardiography short axis view demonstrating the cleft mitral valve (arrow)

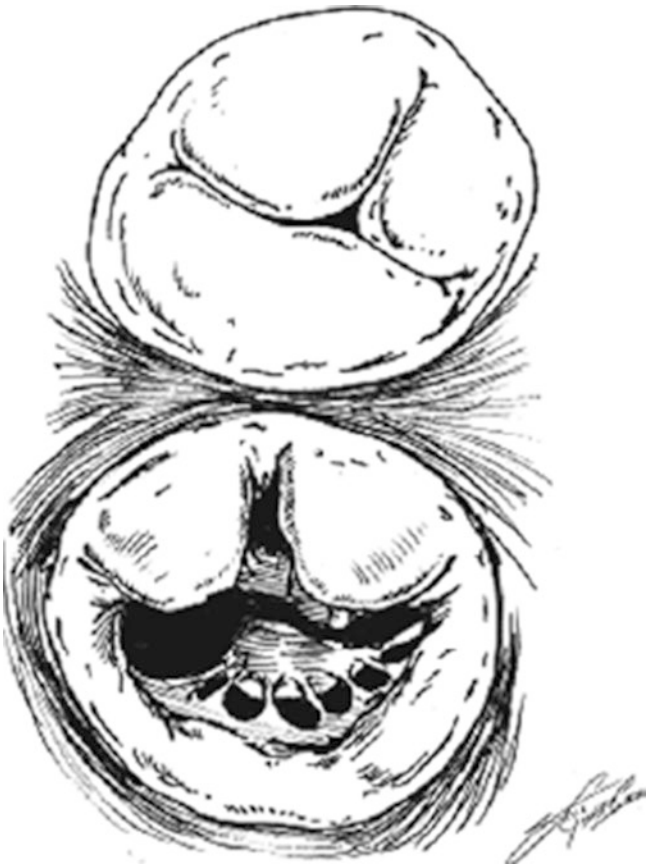


Fig. 26.8 Mitral cleft (drawing from Steven P. Goldberg, MD)

Double orifice mitral valve may occur in isolation or in association with atrioventricular septal defect, and though this condition can be associated with mitral stenosis or insufficiency, it can be asymptomatic, occurring only as an incidental echocardiographic finding (Figs. 26.9 and 26.10).

26.2.3.6 Mitral Valve Prolapse

The etiology of this common condition is not clear and is probably multifactorial. It can be seen in individuals with a wide range of congenital heart malformations including MFS, ischemic heart disease, hypertrophic cardiomyopathy, and pectus excavatum, as well as in thin patients (Fig. 26.11). It is usually diagnosed on the clinical basis of a mid-systolic click and a late systolic murmur of MR.

26.3 Pathophysiology of Mitral Regurgitation

Mitral regurgitation (MR) can be described in three phases: acute, chronic compensated, and chronic decompensated. In all phases of MR, blood is ejected into both the aorta and the low pressure left atrium. Left ventricular wall stress (afterload) is reduced secondary to the significantly decreased outflow resistance. However, increased left atrial volume leads to increased left atrial pressure, both of which are transmitted to the left ventricle, increasing both left ventricular end-diastolic volume and pressure. The stroke volume and left ventricular work increase, yet aortic flow decreases [90, 91]. Both acute and chronic dilation of the left atrium from MR lead to elevated left atrial pressure and reduced pulmonary venous return to the left atrium, with consequent increased pulmonary venous pressure and reflex pulmonary arteriolar vasoconstriction. This further results in right ventricular hypertension and right ventricular dysfunction. Annular dilation occurs secondarily to left atrial and left ventricular dilation, which further exacerbates MR. Severe left atrial dilation increases the risk of atrial arrhythmias and of respiratory compromise from left mainstem bronchial compression, reduced lung capacity, and pulmonary edema from elevated pulmonary capillary hydrostatic pressure.

26.3.1 Acute Severe Mitral Regurgitation

In acute severe MR, the sudden volume overload imposed on the left atrium increases LV preload, which modifies the inotropic state and results in a modest increase in left ventricular stroke volume. As compensatory hypertrophy has not occurred, the ability of the left ventricle to continue to make adjustments in inotropic state is limited; forward stroke volume and cardiac output are soon reduced [90, 91].

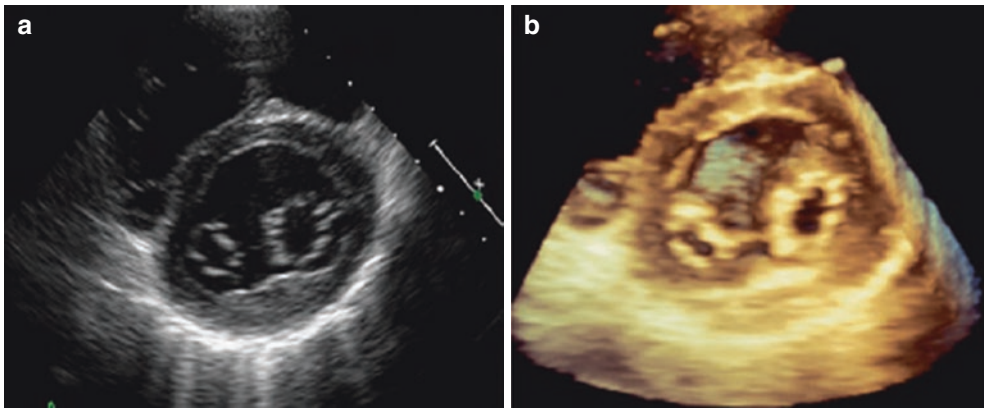


Fig. 26.9 (**a**) 2D echocardiography short axis view demonstrating a double orifice mitral valve (3D reconstruction by Shawn Popylisen). (**b**) 3D echocardiography in short axis view demonstrating a double orifice mitral valve (3D reconstruction by Shawn Popylisen)

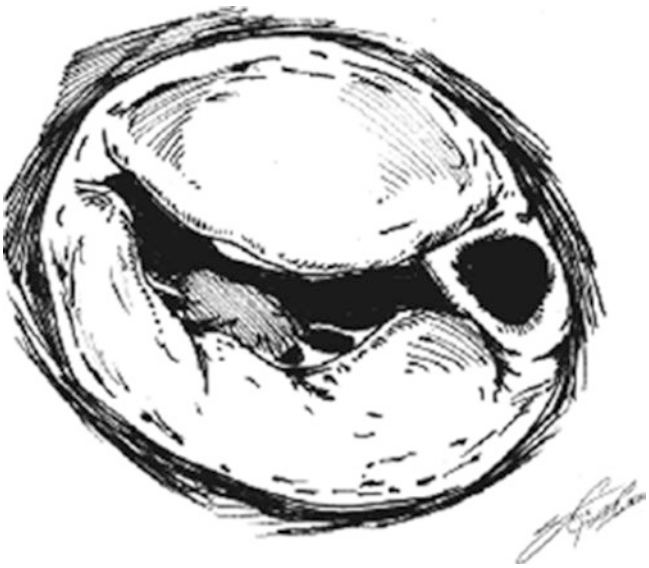


Fig. 26.10 Double orifice mitral valve (drawing from Steven P. Goldberg, MD)

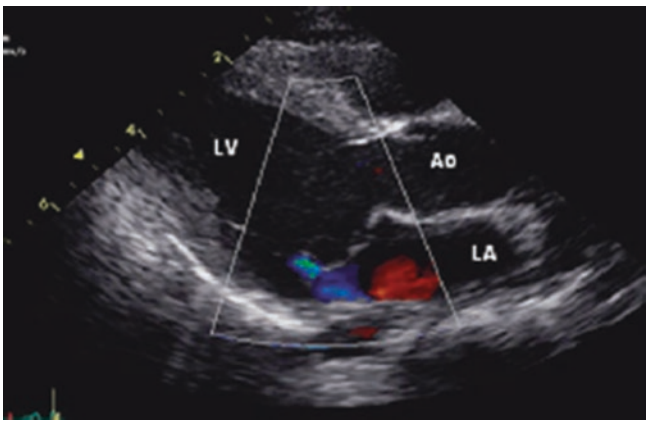


Fig. 26.11 Echocardiography long axis view of a patient with Marfan syndrome, demonstrating mitral valve prolapse and dilation of the sinuses of Valsalva

26.3.2 Chronic Compensated Mitral Regurgitation

In chronic compensated MR, a series of new sarcomeres are added to existing myocytes, thereby increasing individual myocardial fiber length and adjusting the length-tension relationship to allow the left ventricle to bear the volume load, increase performance, and maintain forward cardiac output [90, 91].

26.3.3 Chronic Decompensated Mitral Regurgitation

In chronic decompensated MR, chronic left atrial volume and pressure overload are transmitted to the left ventricle, resulting in impaired contractile function and ejection such that ejection fraction decreases, end-systolic volume increases, and cardiac failure ensures. A normal ejection fraction can be a sign that heralds left ventricular dysfunction. Indeed, intervention for MR should be considered prior to the onset of left ventricular dysfunction, as left ventricular dysfunction may not be reversible even with mitral valve surgery [90, 91].

26.3.4 Physical Examination in Mitral Regurgitation

The physical exam of a patient with MR is characterized by a pansystolic murmur loudest at the apex and radiating to the left axilla and to the back. The first heart sound is usually diminished and the second heart sound is split.

Other clinical features on physical examination often include:

- A displaced LV apical impulse from chronic severe MR
- An apical thrill, though significantly impaired LV function may attenuate this finding
- A loud P2, in the setting of severe pulmonary hypertension
- An S3, heard immediately after S2, from the rapid, large volume flow into the LV
- An S4, heard immediately before S1, from flow into noncompliant or stiff ventricle during atrial contraction
- Small volume peripheral pulses with sharp upstroke

26.3.5 Mitral Valve Prolapse

The physical exam is characterized by a systolic click that varies with postural changes. The systolic click moves towards S1 with upright position and new click may appear. The systolic murmur of MR becomes louder and longer in duration (holosystolic). A MR murmur may be present only with the patient in the upright position. Rarely, a systolic precordial "honk" may be heard. Prompt squatting results in a movement of the systolic click away from S1 and the systolic murmur of MR moves back to late systole. These postural changes are related primarily to change in left ventricular volume, myocardial contractility and heart rate (Fig. 26.12). Left ventricular volume is decreased in the upright position compared to the supine position, and reflex tachycardia occurs in the supine position [92].

26.4 Preoperative Management

Several diagnostic studies are likely to be valuable in guiding clinical management of patients who come to the ICU with decompensated cardiac failure secondary to mitral valve disease, regardless of whether the etiology of mitral valve disease is MFS, rheumatic fever, or congenital malformation:

- Electrocardiogram: to establish heart rhythm, and to detect signs of ischemia, strain, and chamber enlargement.
  - Ventricular strain can often be demonstrated with ventricular failure from decompensated valvar insufficiency.
    Signs of left ventricular strain
    - ST depression with upward convexity in left precordial leads
    - T-wave inversion in left precordial leads
    - ST elevation in right precordial leads
    - Tall T waves in right precordial leads

    Signs of right ventricular strain
    - ST segment depression in right precordial leads
    - Wide QRS-T angle >90°
  - Chamber enlargement and pulmonary hypertension associated with chronic mitral valve disease may be demonstrated.
    Signs of left atrial enlargement:
    - Left axis deviation
    - First-degree atrioventricular block
    - Broad notched P waves in leads I, II, aVF
    - Biphasic P wave in lead V1 with deep portion of negative deflection

    Signs of left ventricular enlargement:
    - Tall R wave in V6
    - Deep S wave in V1
    - Deep Q waves in lead III (≥4 mm) or V6 (≥5 mm)

    Signs of right ventricular hypertrophy suggestive of pulmonary hypertension:
    - Tall R wave in V1
    - Deep S wave in V6
    - qR pattern in V1
- Chest X-ray: to establish heart size and evaluate pulmonary edema. Left atrial enlargement is seen as elevation of the left main stem bronchus with opening of the carina's angle on the anteroposterior projection.
- Echocardiography: to quantify severity of valvar regurgitation and LV dysfunction; to delineate the mechanism of valvar regurgitation, including assessment of:
  - Aortic root dimensions: annulus, sinus of Valsalva, sinotubular junction, ascending aorta (Fig. 26.4)
  - Pattern of aortic root dilation: loss of sinotubular junction contour associated with increased risk of dissection [93].
  - Mitral annulus size and shape
  - Valvular function
    - Leaflet anatomy: number, size, location, and location of commissures to predict
    - Location and spacing of papillary muscles
    - Leaflet morphology: elongated, thickened, calcified, myxomatous, vegetations
    - Leaflet motion: normal, flail, prolapsed, restricted
    - Leaflet function: mechanism and adequacy of leaflet coaptation

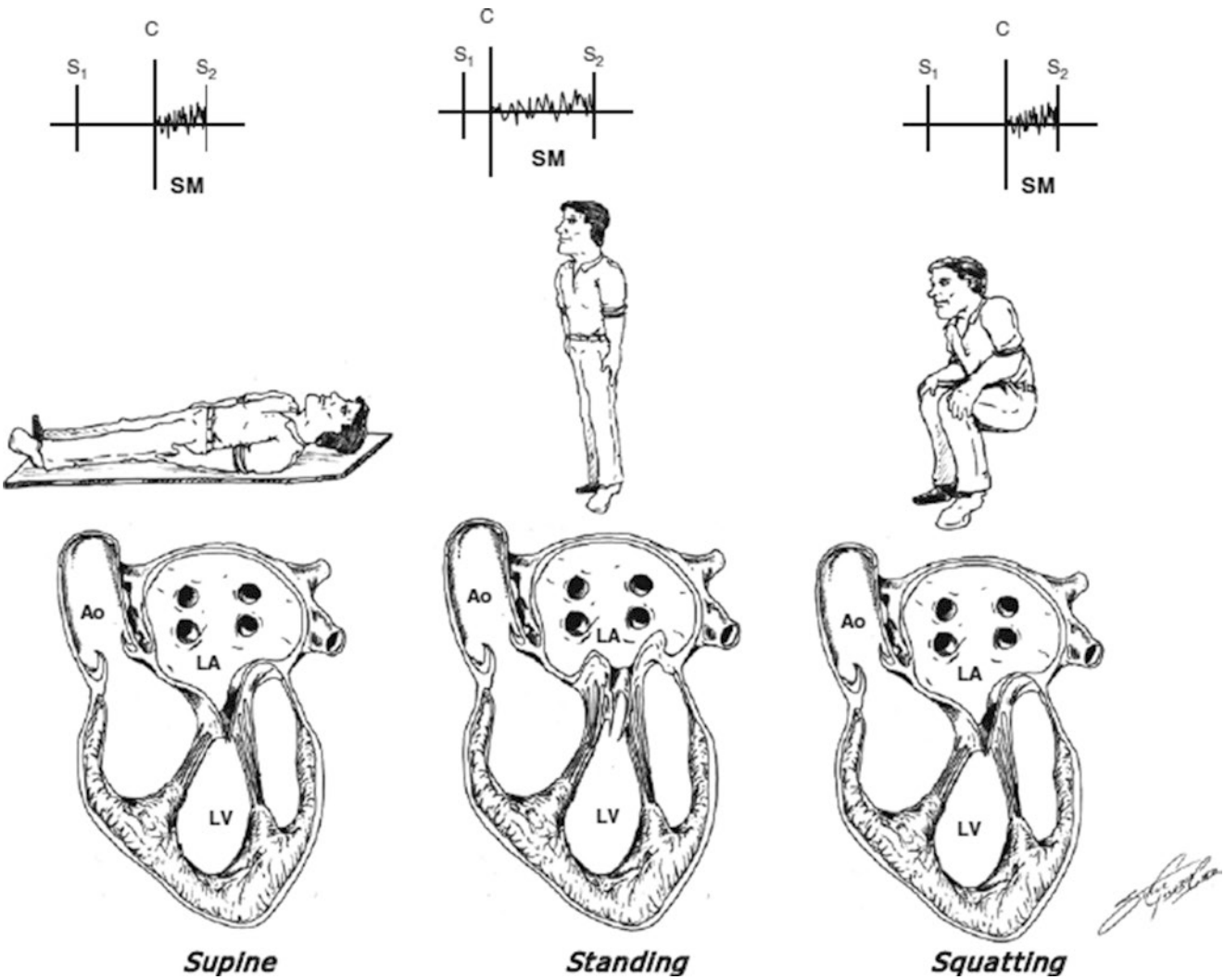


Fig. 26.12 Postural changes and auscultatory phenomena in patients with mitral valve prolapse, with alteration of systolic click (C) and systolic murmur (SM). As the LV volume decreases (upright position), the systolic click moves towards the first heart sound (S1) and the murmur becomes more holosystolic [91] (drawing from Steven P. Goldberg, MD)

- Subvalvular apparatus
  - Papillary muscle architecture, number, symmetry, and positioning, particularly relative to the commissures
  - Presence of endocardiofibroelastosis as a marker of the adequacy of subendocardial perfusion
  - Chordae structure and function
- Left atrial size
- Size and direction of regurgitant jets to ascertain mechanism of valvar pathology
- Atrial septal geometry; septal bowing
- Left ventricular size (end-systolic volume and dimension) and function, including wall motion abnormalities
- Estimation of left atrial pressure
- Estimation of regurgitant fraction (mitral or aortic regurgitation)
- Estimation of mean mitral gradient (mitral stenosis)
- Estimation of right ventricular and pulmonary artery pressures

- Transesophageal echocardiography can be a valuable tool for preoperative assessment, particularly if the transthoracic echocardiogram is compromised by poor acoustic windows.
- 3D echocardiography is an emerging tool that may provide useful imaging of abnormal valves.
- Cardiac catheterization: indications include assessment of pulmonary vascular reactivity in pulmonary hypertension, or investigation of mitral stenosis, in which case there is a pressure gradient between the "a" pressure wave

of the left atrium and the left ventricular end-diastolic pressure. The left atrial pressure is elevated in either mitral stenosis or MR.
- Cardiac MRI: can be used to generate cardiac volumetric data; to delineate ventricular function; and to demonstrate a panoramic view of the thoracic aorta.
- Laboratory data: such as BNP, CKMB, troponin I, lactate, BUN, creatinine, hepatic function tests, and blood gases are often useful to establish biochemical evidence of circulatory shock. Serologic markers for inflammation, such as CRP, ESR, and procalcitonin [25], are useful when rheumatic fever or endocarditis is suspected.
- Blood culture (3 mL in infants; 10 mL adolescents): may be considered if bacterial endocarditis is suspected as the etiology for decompensation.

26.4.1 Clinical Monitoring

The clinical management of patients who are admitted to the ICU with heart failure from mitral valve dysfunction secondary to MFS, RF, or congenital mitral valve malformations begins with airway, respiratory, cardiac, and circulatory stabilization.

26.4.2 Monitoring

Patients with hemodynamic compromise often require routine continuous cardiovascular monitoring, which includes:

- Continuous cardiorespiratory monitoring with telemetry
- Central venous pressure monitoring
- Continuous arterial pressure monitoring, with attention to the pulse wave contour
- Occasional pulmonary artery pressure monitoring
- Continuous or intermittent central venous saturation to monitor adequacy of global tissue oxygen delivery; progression of cardiac failure; response to therapeutic interventions
- NIRS (near-infrared spectroscopy) may be a useful noninvasive tool to monitor changes in regional oxyhemoglobin saturation, particularly of the frontal lobes of the brain, and also of the kidney and gut
- Continuous urine output monitoring via Foley catheter
- Serial echocardiographic assessment, especially in the setting of severely compromised left ventricular function, to monitor for clot and embolism risk, progression of cardiac failure, response to therapeutic interventions
- Serial laboratory monitoring for biochemical evidence for adequacy of global oxygen delivery

26.5 Medical Management

26.5.1 Medical Management of Marfan Syndrome

The medical management of each cardiovascular lesion focuses on the hemodynamic consequence of the lesion, irrespective of its etiology.

Decompensated cardiac failure is treated with preload reduction through diuresis, afterload reduction through systemic vasodilation, and ventricular performance augmentation with inotropes and inodilators. The recommended drug of choice for this purpose is milrinone.

Many patients with MFS are on chronic beta-blockade therapy to decrease inotropy, chronotropy, ectopy, and aortic wall stress [94]. Chronic beta-blockade therapy may complicate the treatment of acute decompensated heart failure by rendering the myocardium less responsive to catecholamine infusion. For this reason, phosphodiesterase inhibitors, such as milrinone, and calcium sensitizers, such as levosimendan, may be preferable, as they increase contractility through increasing cAMP and improving the calcium-troponin C interaction, respectively, without specifically requiring adrenergic receptor stimulation.

In MFS patients with acute decompensated heart failure complicated by ventricular dysrhythmias and fibrillation, catecholamine infusion may decrease the defibrillation threshold, possibly by increasing coronary artery perfusion [95].

26.5.2 Medical management of Rheumatic Fever

The goal of treatment for patients with rheumatic fever consists of:

- Symptomatic relief of acute inflammation
- Eradication of GABHS
- Prophylaxis against future infection to prevent recurrent cardiac disease
- Supportive treatment of heart failure

26.5.3 Anti-inflammatory Treatment

Treatment of the inflammatory manifestations of acute rheumatic fever uses salicylates and steroids. Aspirin at anti-inflammatory doses (80–100 mg/kg/day in children and 4–8 g/day in adults) effectively reduces all manifestations of the disease except chorea, and the response typi-

cally is dramatic [96]. Target salicylate blood level is 20–30 mg/dL. Aspirin should be maintained at anti-inflammatory doses until the signs and symptoms of acute rheumatic fever are resolved or residing (6–8 weeks) and the acute phase reactants (CRP, ESR) have returned to normal. When discontinuing therapy, aspirin should be withdrawn gradually over weeks while monitoring the CRP and ESR for rebound.

In patients with moderate-to-severe carditis, oral prednisone (2 mg/kg/day) is usually used for 2–4 weeks, but studies on the effect of corticosteroids in the treatment of rheumatic carditis have shown conflicting results [97–101]. Prednisone should then be tapered over 2 weeks, while maintaining salicylates for an additional 2–4 weeks.

Chorea is most frequently self-limited, but may be alleviated with phenobarbital or diazepam.

26.5.4 Eradication of GABHS (Primary Prophylaxis)

Antibiotic therapy with oral penicillin V (250 mg tid for children and 500 mg tid for adults) should be started and maintained for 10 days regardless of the presence or absence of pharyngitis at the time of diagnosis [102]. A single dose of intramuscular benzathine penicillin G (600,000 Units for children <27 kg and 1.2 million units in children >27 kg and adults) is an alternative if compliance is an issue (Table 26.5). For patients who are allergic to penicillin, erythromycin can be used. Other options include clarithromycin, azithromycin, or a first-generation cephalosporin.

For recurrent GABHS pharyngitis, a second 10-day course of the same antibiotic may be repeated. GABHS carriage is difficult to eradicate with conventional penicillin therapy. Thus, oral clindamycin (20 mg/kg/day for 10 days) is recommended.

26.5.5 Prophylaxis of Recurrence (Secondary Prophylaxis)

Prophylactic therapy is indicated after rheumatic fever to prevent recurrent streptococcal infection and further damage to the valves [103, 104]. Antibiotic prophylaxis should be started immediately after resolution of the acute episode [105, 106].

– An injection of benzathine penicillin G intramuscularly (600,000 Units for children <27 kg and 1.2 million units in children >27 kg and adults) every 4 weeks is the recommended regimen for most patients. In areas where rheumatic fever is endemic, in patients with residual carditis and in high-risk patients, the administration should be made every 3 weeks [107].
– In patients with valve prosthesis under anticoagulation, oral penicillin V (250 mg twice daily for children and adults) prophylaxis should be used (Table 26.6). Data from the World Health Organization indicate that the recurrence risk of GABHS pharyngitis is lower when penicillin is administered parenterally.

The duration of antibiotic prophylaxis is controversial. The American Heart Association currently recommends [106, 108] that patients with rheumatic fever without carditis receive prophylactic antibiotics for 5 years or until aged 21 years, whichever is longer, and that patients with carditis but no valve disease receive prophylactic antibiotics for 10 years or until they are well into adulthood, and finally that patients with carditis and valve disease receive antibiotics at least 10 years or until aged 40 years (Table 26.7) [109].

26.5.6 Medical Management of Congestive Heart Failure

Treatment of congestive heart failure includes inotropic support, diuretics, afterload reduction, supplemental oxygen, bed rest, and sodium and fluid restriction.

Patients with congestive heart failure from acute valve insufficiency will probably require continuous intravenous inotropic support. The beneficial role of digoxin in cardiac failure is controversial [110–112]. Digoxin should be started

Table 26.5 Primary prophylaxis of rheumatic fever

Agent	Dose	Mode	Duration
Benzathine Penicilline	≤27 kg: 600,000 U	Intramuscular	Once
	>27 kg: 1,200,000 U	Intramuscular	Once
Penicillin V	Children: 250 mg 2–3 times daily	Oral	10 days
	Adolescents/Adults: 500 mg 2–3 times daily	Oral	10 days
Allergy to Penicillin:			
Erythromycin	20–40 mg/kg/day 2–4 times daily (maximum 1 g/day)	Oral	10 days

Table 26.6 Secondary prophylaxis of rheumatic fever

Agent	Dose	Mode
Benzathine Penicillin	1,200,000 U every 4 weeks (every 3 weeks for high-risk patients)	Intramuscular
Penicillin V	250 mg twice daily	Oral
Allergy to Penicillin:		
Erythromycin	250 mg twice daily	Oral

Table 26.7 Duration of secondary prophylaxis of rheumatic fever

Category	Duration
RF with carditis and residual heart disease	10 years or greater since last episode and at least until age 40, sometimes life-long prophylaxis
RF with carditis but no residual heart disease	10 years or well into adulthood, whichever is longer
RF without carditis	5 years or until age 21, whichever is longer

only after checking serum electrolytes due to the increased toxicity of digoxin with hypokalemia.

Diuretics frequently are used in conjunction with inotropic agents. Furosemide is usually the first choice. Spironolactone is often added in conjunction with furosemide as a potassium-sparing diuretic.

Afterload reduction with angiotensin converting enzyme inhibitors (ACE inhibitor) may be effective in improving cardiac output, particularly in the presence of mitral and aortic insufficiency [113]. Captopril is used in infant <6 months, while enalapril is usually preferred in older children, due to its longer half-life. ACE inhibitors should be started carefully with a small, initial test dose, because some patients have an abnormally large response to these agents with hypotension. ACE inhibitors should be administered only after correcting hypovolemia.

Potassium supplementation may be necessary because of the mineralocorticoid effect of corticosteroid and the salt wasting effect of the diuretics. Potassium level should be maintained in the normal range, particularly in patients on digoxin.

When heart failure persists or worsens during the acute phase after aggressive medical therapy, surgery is indicated to decrease valve insufficiency.

26.5.7 Prophylaxis of Endocarditis

Patients with rheumatic heart disease and valve damage require a single dose of antibiotics 1 hour prior to surgical and dental procedures to help prevent bacterial endocarditis [108, 114]. Patients who had rheumatic fever without valve damage do not need endocarditis prophylaxis. Penicillin, ampicillin, or amoxicillin should not be used for endocarditis prophylaxis in patients already receiving penicillin for secondary prophylaxis due to an increased relative resistance of oral streptococci to penicillin and aminopenicillins. Alternate drugs recommended by the American Heart Association for these patients include oral clindamycin (children: 20 mg/kg; adults: 600 mg), azithromycin or clarithromycin (children: 15 mg/kg; adults: 500 mg).

26.6 Interventional Catheterization

26.6.1 Percutaneous Balloon Mitral Valvuloplasty

Approximately 40% of patients with acute rheumatic fever subsequently develop mitral stenosis later in life. For patients with mitral stenosis who require relief of obstruction, percutaneous balloon mitral valvuloplasty is the preferred treatment and gives results comparable to surgical commissurotomy [115]. 2D-echocardiographic assessment of mitral valve morphology is the most important predictor of outcome. An echocardiographic score can be determined according to the valvar and subvalvar mitral anatomy, with a score < 8 predicting good immediate and long-term results [116, 117]. More details are discussed in the chapter dedicated to mitral stenosis.

26.6.2 Percutaneous Mitral Valve Repair

Percutaneous MR repair is an emerging area of interventional cardiology. Direct percutaneous repair of the mitral valve is undergoing trials using the Abbott MitraClip, Edwards Cardioband (transcatheter annuloplasty device) and other devices [118–120]. The EVEREST trial showed that the MitraClip device could be effective at reducing the grade of mitral regurgitation in selected poor surgical candidates; however, results were poor compared to surgical valve repair: procedural success was just 74%, 36% of patients were discharged with MR >1+, and 30% had a mitral valve repair within 3.2 years of follow-up [121]. The EVEREST II trial compared MitraClip to surgical mitral valve repair, and again showed poor results, with a primary endpoint for efficacy (freedom from death, from surgery for mitral-valve dysfunction, and from grade 3+ or 4+ mitral regurgitation at 12 months) of just 55%, compared to 73% in surgical patients ($P = 0.007$). Additional data is needed to evaluate the long-term outcome of these techniques. Furthermore, none of these devices have been designed for use in the pediatric population, and none of these trials have included children. These devices require a transeptal approach, are large, and require a minimum distance between the atrial septal puncture site and the mitral valve to allow angulation and navigation of the device from the right atrium to the left atrium and finally the mitral valve, making current devices unsuitable for some adult-sized patients, and even more unsuitable most pediatric patients. A transapical approach avoids these limitations, at the expense of making the procedure much more invasive.

26.6.3 Percutaneous Mitral Valve Replacement

As with percutaneous MR repair, transcatheter mitral valve replacement (TMVR) is an emerging field of interventional cardiology, following the phenomenal development and results of percutaneous transcatheter aortic valve implantation or replacement [122, 123]. Many devices for TMVR are in development or initial clinical trials, including the Medtronic Intrepid device in the APOLLO trial, the Edwards CardiAQ and Fortis, and the Abbott Tendyne [124]. The complexity of the mitral annulus and structures surrounding it (aorto-mitral continuity, left ventricular outflow tract, conduction system, and circumflex coronary artery) makes this a much more difficult valve to replace using transcatheter techniques than the aortic valve, and initial trials have shown excessive early mortality, although results are improving. All devices currently in clinical evaluation are delivered through a transapical approach, as the devices are too large to deliver through a transeptal approach. As with transcatheter mitral valve repair, no devices have been evaluated for pediatric patients.

26.7 Surgical Management of Mitral Valve Diseases

26.7.1 Surgical Considerations

Optimal surgical management for MR remains controversial (Table 26.8). Surgical options consist of mitral annuloplasty, commissuroplasty, valvuloplasty, splitting of papillary muscles with resection of subvalvular apparatus, chordal substitution, chordal shortening, or mitral valve replacement [125].

In MFS, the underlying connective tissue disorder is a risk factor for compromise of repair durability. In the majority of cases, MR is caused by leaflet prolapse, and in the remaining minority, by annulus dilatation. Marfan patients have more bileaflet and anterior mitral leaflet prolapse and present earlier for surgery when compared to patients with mitral myxomatous disease. Mitral valve repair feasibility is lower in MFS than in myxomatous valve disease. Nonetheless, despite the important elastic fiber alterations in leaflet tissue and the multisystem involvement, mitral valve repair in MFS gives satisfactory long-term results in terms of freedom from reoperation in children and even in adults presenting with advanced valve pathology.

In rheumatic fever, surgery to decrease valve insufficiency may be lifesaving when heart failure persists or worsens after aggressive medical therapy. Valve replacement appears to be the preferred surgical option for patients with high rates of recurrent symptoms after annuloplasty or other repair procedures. In children, mitral valvuloplasty is preferred [126].

Table 26.8 Indication for surgery for chronic mitral regurgitation (MR) (From [145])

Symptoms	LV EF	LVESD
NYHA II–IV	>60%	<45 mm
Asymptomatic or symptomatic	50–60%	≥45 mm
Asymptomatic or symptomatic	<50% or	≥45 mm
Pulmonary artery systolic pressure	≥50 mmHg	

26.7.2 Mitral Valve Repair

Many techniques for mitral valve repair have been described. Mitral valve repair without the use of prosthetic materials is feasible for the majority of patients and carries an appropriate growth pattern of the mitral valve annulus after surgery [127].

For repair of MR, valvuloplasty techniques are available to repair all four major components of the mitral valve apparatus: annulus, leaflets, chordae, and papillary muscles.

The annulus can be remodeled via commissuroplasties (to reduce the annulus close to the commissures) or annuloplasty using a modified Panneth suture (a running suture along the posterior annulus), a Carpentier ring (metallic ring) or using a Kalangos or biodegradable ring [128]. The leaflets can be repaired, patched, or extended with autologous pericardium, detached and reconstructed, or resected; the chordae can be shortened, transferred, fenestrated, or artificially implanted; the papillary muscles can be elongated, shortened, or split.

For repair of mitral stenosis, fused mitral valve commissures can be directly incised; mitral valve tissue tags can be excised or shaved; leaflets thickened with fibro-elastosis can be shaved; fused tendinous chords can be split; and supravalvar mitral rings can be directly excised. For repair of parachute mitral valve, splitting of a solitary papillary muscle and fenestration of the interchordal spaces can be performed.

Intraoperative assessment of the valve competency and motion is made by "floating" the mitral valve, or injecting and filling the left ventricle with iced saline solution to lift the valve leaflets and expose the valve function. A Hegar dilator is used to measure the mitral valve diameter to ensure normal orifice size for body weight. Transesophageal echocardiography following separation from cardiopulmonary bypass is imperative for the assessment of mitral valve function. Results for operative interventions in MR are generally more favorable than those for mitral stenosis.

26.7.3 Mitral Valve Replacement

Mechanical valves are indicated when reconstructive procedures have failed in young children. Tissue valves are available but are disadvantageous, as they calcify and degenerate at an accelerated rate in small children [129]. The respective sizes of the patient and the prosthetic valve are the greatest considerations in selecting an artificial mitral valve.

Limited mechanical prosthetic valves are available for use in pediatrics, particularly in small children [130]. The bileaflet mechanical valve is the most commonly used in children. It can be sutured in the supra-annular position when the annulus is too small to admit the smallest prosthesis size, i.e., within the left atrium, although this is associated with the risk of pulmonary venous obstruction and higher mortality at subsequent reoperations [131, 138]. A special design with a supra-annular sewing cuff is available for small children, which allows an effective valvar orifice situated at the annular level. Anticoagulation is compulsory; coumadin is used most commonly, with a target INR between 2.5–3.5. Unfortunately, complications are not uncommon. Indeed, mitral valve replacement in young children is fraught with substantially increased risk of morbidity and mortality [123].

The ideal mitral valve replacement would be a device that grows with the child, particularly when the first valve replacement is in a young child, too small for current valves, where the smallest size aortic prosthesis (17 or 19 mm) is inverted to be placed in the mitral position. The Melody valve has been used off-label as a balloon-expandable valve, for mitral valve replacement in infants and children [139–142]. Although this has allowed mitral replacement in small children, the longest reported follow-up is a median of 14 months (range, 0.2 to 42 months) [141], with significant one death, one transplantation, and four valve re-replacements during this short follow-up and no reported transcatheter balloon diltation or upsizing of the valve.

Complications following mitral valve replacement include:

- Complete atrioventricular block
- Atrial fibrillation
- Left ventricular outflow tract obstruction
- Bleeding
- Thromboembolism
- Severe intravascular hemolysis
- Prosthetic valve dysfunction
- Prosthetic valve endocarditis

26.7.4 Minimally Invasive Surgery

Minimally invasive approaches have been increasingly described in adults and involve various modifications of the surgical approach, as in a partial lower sternotomy or sub-mammary right minithoracotomy, or axillary thoracotomy. Cardiopulmonary bypass is provided via the femoral vessels. In children, central cannulation can most often be performed through the same incision (mini-sternotomy or thoracotomy), due to the lesser distance from the incision to the cardiac structures. Robotic-assisted mitral valve surgery, using the Da Vinci system, has shown promising results, although with a steep learning curve even in the largest adult cardiac surgical centers and adapted techniques and implants [143–147]. Advantages of these approaches are diminished pain and discomfort, fewer blood transfusions, and earlier hospital discharge. There are little data available on minimally invasive mitral valve operations in children, and none using robotic assistance.

26.8 Postoperative Management

26.8.1 Postoperative Monitoring

The postoperative monitoring of patients following mitral valve surgery is an extension of the monitoring and vigilance required in the preoperative period, including anticipation of common postoperative complications following mitral valve surgery. As with preoperative monitoring, postoperative monitoring should include:

- Continuous cardiorespiratory monitoring with telemetry that includes data recording and storage, which allows waveform review and analysis, as risk of atrial dysrhythmias is great in the patient with a dilated left atrium, and risk of ventricular dysrhythmias is increased in the patient with a dilated, poorly functioning left ventricle
- Central venous pressure monitoring
- Continuous arterial pressure monitoring, with attention to the pulse wave contour
- Pulmonary artery pressure monitoring, particularly in patients at risk for pulmonary vascular reactivity as in those with mitral valve stenosis
- Continuous or intermittent central venous saturation to monitor adequacy of global tissue oxygen delivery; progression of cardiac failure; response to therapeutic interventions

- NIRS may be a useful tool to monitor changes in regional oxyhemoglobin saturation, particularly of the frontal lobes of the brain, but also of the kidney and gut
- Continuous urine output monitoring via indwelling catheter
- Serial echocardiographic assessment, especially in the setting of severely compromised left ventricular function, to monitor for clot and embolism risk, progression of cardiac failure, response to therapeutic interventions
- Serial laboratory monitoring for biochemical evidence for adequacy of global oxygen delivery

Additionally, postoperative monitoring, following mitral valve surgery may also include:

- Left atrial pressure monitoring, utilizing equipment with enough fidelity to appreciate differences and alterations in the "a" and "v" pressure waveforms
- Epicardial atrial and ventricular pacing wires, which allow epicardial electrocardiogram recordings that can be useful in the analysis of postoperative dysrhythmias

26.8.2 Postoperative Occurrences and Complications

Regardless of the etiology of mitral valve disease, whether by MFS, RF, or congenital malformation, mitral valve surgery requires excellent technical surgical results if significant postoperative complications are to be averted. Transesophageal echocardiography should be performed in the operating room following separation from cardiopulmonary bypass so that the surgical result can be assessed and immediately addressed with reoperation, if persistent regurgitation or stenosis is identified, particularly with associated left atrial hypertension. Consideration of the intravascular volume at the time of echocardiographic study is important, as hypovolemia leads to underestimation of the severity and hemodynamic consequence of residual lesions.

26.8.2.1 Left Atrial Hypertension

Causes of elevated left atrial pressure after mitral valve surgery are:

- Residual mitral valve regurgitation, which may be suggested by giant "v" waves on the left atrial pressure tracing
- Residual mitral valve stenosis, which may be suggested by large "a" waves on the left atrial pressure tracing
- Prosthetic mitral valve leaflet immobility, dysfunction, or thrombosis, which may also be suggested by large "a" waves on the left atrial pressure tracing
- Loss of atrioventricular synchrony, which may be suggested by canon "a" waves on the left atrial pressure tracing
- Left ventricular dysfunction
- Pericardial effusion
- Tension pneumothorax with cardiac tamponade

26.8.2.2 Pulmonary Hypertension

In patients with long-standing mitral valve stenosis or regurgitation, the pulmonary vascular changes of medial thickening and intimal fibrosis associated with progressive pulmonary vascular disease may complicate the postoperative course. Standard therapy for pulmonary hypertension should be administered, as pulmonary hypertensive crises are common. In small children with valve replacement in supra-annular position, the relatively large prosthesis can impede pulmonary venous outflow or left ventricular inflow, thereby promoting pulmonary hypertensive crises. In patients with pulmonary hypertension and postoperative left ventricular dysfunction, or residual mitral valve dysfunction, cautious use of nitric oxide therapy is indicated, as the increased pulmonary venous return may worsen pulmonary hypertension or left ventricular dysfunction.

26.8.2.3 Low Cardiac Output

Low cardiac output syndrome can complicate any bypass surgery. After mitral stenosis repair, decreased left ventricular compliance can lead to low cardiac output in the initial postoperative period. After MR repair, adaptation of the left ventricular volume overload can lead to low cardiac output. Additionally, left ventricular function may be compromised by the significantly increased afterload associated with a newly competent valve. Therapy consists of maintenance of optimal heart rate either with atrial pacing or isoproterenol as the cardiac output is highly rate-dependent. Adequate preload should be maintained, but volume should be replaced slowly as excessive fluid infusion can lead to rapid left atrial pressure elevation and subsequent pulmonary hypertension crisis.

Adequate left ventricular filling pressure should be maintained to accommodate for diastolic dysfunction. Afterload reduction with milrinone infusion is beneficial to increase cardiac output, especially in patients with left ventricular dysfunction. Afterload reduction may also be useful for reducing the hemodynamic consequences of residual MR. When poor cardiac output does not respond to conventional medical therapy, mechanical circulatory support may be necessary.

26.8.2.4 Arrhythmia

Atrial flutter, atrial fibrillation, multifocal atrial tachycardia secondary to chronic mitral valve disease, and atrial dilation can complicate the postoperative period. Atrial arrhythmias are not well tolerated, especially when left ventricular compliance is impaired. Management of such arrhythmias is essential in the early postoperative period to restore atrioventricular synchrony and optimize cardiac output.

26.8.2.5 Anticoagulation

Heparin infusion should be started when bleeding through the chest tubes have ceased and when the coagulation profile has normalized. A heparin bolus is initially administered followed by an infusion rate targeting a PTT of 50–70 s or an anti-Xa inhibition test of 0.5–0.7 U/mL. When the intracardiac lines, the chest tubes and the pacing wires have been removed, transition to coumadin can be initiated.

26.8.2.6 Prosthetic Valve Malfunction

Proper function of the prosthetic valve should be carefully monitored, especially in small children with the prosthesis in a supra-annular position. Leaflet malfunction may be suspected on the basis of serial chest X-rays, in which leaflet position is fixed (Fig. 26.13), or dynamically with fluoroscopy. When thrombosis is suspected, as in acute prosthetic valve dysfunction, streptokinase or tissue plasminogen activator therapy may be attempted. Chronic valve malfunction may be secondary to tissue entrapment of the valve leaflets. The surgical appearance is that of a pannus of tissue, which encroaches upon the valve leaflets. The usual presentation is intermittent left atrial hypertension and absence of a valve click.

26.8.3 Special Considerations of the Marfan Patient in the ICU

26.8.3.1 Respiratory

Patients with MFS and associated severe pectus deformity with kyphoscoliosis often have reduced lung volumes and can be anticipated to demonstrate varying degrees of respiratory insufficiency, pulmonary hypertension, and right heart dysfunction when hospitalized in the intensive care unit for management of either decompensated cardiac failure or postoperative intervention. Additionally, patients with MFS are at increased risk for spontaneous pneumothoraces and should be considered in the differential diagnosis in the MFS patient with sudden decompensation.

26.8.3.2 Abdominal

Patients with MFS and associated aortic dilation are at risk for dissection of the abdominal aorta, which can cause mesenteric ischemia and bowel perforation. Heightened awareness of this complication should accompany assessment of abdominal pain in the patient with MFS.

26.8.4 Orthopedic

Consideration of cardiac position should be made in the MFS patient with kyphoscoliosis and significant pectus deformities with or without repair, as standard cardiac compression techniques may be ineffective in this population. Nuss bar surgical correction of severe pectus deformities may also complicate resuscitative procedures in the intensive care unit.

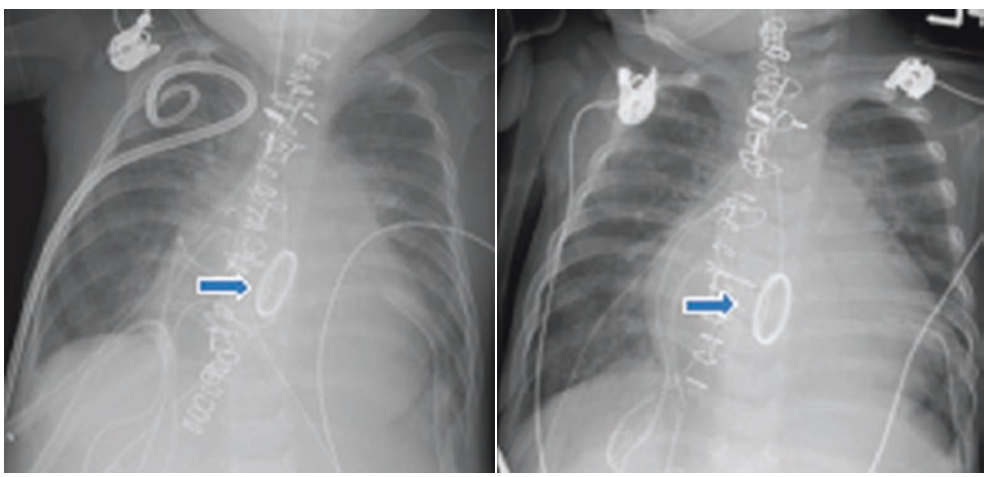


Fig. 26.13 Serial chest X-rays on a patient with a #16 ATS prosthesis turned upside down in the mitral position. A malfunctioning posterior leaflet (arrows) is fixed in position, contributing to the patient's failure to progress from continuous positive airway pressure

26.8.5 Sudden Death

MFS patients are at increased risk of ventricular arrhythmia and sudden death.

26.8.6 Long Term Outcome

26.8.6.1 Prognosis of Marfan Syndrome

Long term outcome in MFS patients is determined by the severity of cardiovascular manifestations. Neonates with phenotypic expression of MFS and cardiovascular involvement are most severely affected, and often do not survive past 2 years of age without multiple valve replacements or heart transplantation. Children with MFS and mitral valve involvement can also have significantly limited lifespans, particularly if valve dysfunction is rapidly progressive and accompanied by compromised ventricular function. Perisurgical complications related to mitral valve replacement denote the greatest risk of mortality in young patients with MFS. Alternatively, mitral valve disease can often be slowly progressive, with increased risk to female patients in the second and third decades of life.

Aortic root dilation and dissection often occurs in the third and fourth decades, such that by age 40, the risk of fatal aortic dissection is considerable without surgical intervention. Since the association between aortic aneurysm diameter and risk for dissection and rupture is clearly established, echocardiographic aortic root surveillance is the gold standard (Fig. 26.2). Aortic root replacement surgery is recommended for aortic diameter greater than or equal to 5.0 cm; rapid growth of aortic diameter (>1 cm/year); a family history of premature aortic dissection at <5 cm; and the presence of greater than mild aortic regurgitation. Compared with urgent and emergency replacement of the aortic root, prophylactic aortic root replacement is associated with excellent results in the modern surgical era: 93.5% survival at 5 years; 91% survival at 10 years; 59% survival at 20 years [124, 125].

26.8.6.2 Prognosis of Rheumatic Fever

The manifestations of acute rheumatic fever resolve during a period of 3–4 months in the majority of patients. Rheumatic heart disease is the major cause of morbidity after rheumatic fever, and it is the major cause of mitral insufficiency and stenosis in the world. Variables that correlate with severity of valve disease are the number of previous attacks, the length of time between the onset of disease and beginning of treatment, and sex, the prognosis being worse for females. Without recurrent attacks, valve insufficiency resolves in 70–80% of patients. In patients with carditis and valve insufficiency, numerous factors (severity of initial carditis, presence of recurrences, time elapsed since rheumatic fever) affect the likelihood that valve abnormalities and the murmur will disappear.

Following the development of antibiotics, the mortality rate in developed countries has decreased to nearly 0%, but has remained 1–10% in developing countries. Prior to penicillin, 60–70% of patients developed valve disease after acute rheumatic fever as opposed to 9–39% nowadays.

26.8.6.3 Prognosis After Mitral Valve Repair

Prognosis after mitral valve repair is good, with an event-free rate at 15 years of about 73% [126]. The current risk of mitral valve reoperation in the pediatric age group is low, and the long-term results are satisfactory, irrespective of severe deformation of the mitral valve apparatus and associated complex cardiac anomalies [117]. Patients with significant associated congenital cardiac abnormalities are at a higher risk of early death after mitral reconstructive surgery. Mitral repair with a technique that allows annular growth is possible in most children with good long-term functional results [127].

26.8.6.4 Prognosis After Mitral Valve Replacement

Mitral valve replacement is an accepted alternative when the valve cannot be repaired, with a reported freedom from reoperation of 66–86% [126, 128]. A multi-institutional study reported a 1-year survival of 79%, a 5-year survival of 75%, and a 10-year survival of 74% for children <5 years of age [128]. The majority of deaths occur early after initial replacement, with little late attrition despite repeated MVR and chronic anticoagulation. Adverse outcome is common, particularly in the young child undergoing palliative surgery or requiring additional surgical procedures [129]. Complications include heart block requiring pacemaker, endocarditis, thrombosis, and stroke [128]. Complete atrioventricular canal, Shone's syndrome, and increased ratio of prosthetic valve size to patient weight increase the risk of adverse outcome. Reasons for second mitral valve replacement are prosthetic valve stenosis in the majority of cases, thrombosis, or endocarditis [129]. Younger patients (<2 years), low weight, smaller prostheses (<20 mm), and greater ratio of prosthesis size to body size were risk factors for second mitral valve replacement [129].

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Chapter 27
Mitral Stenosis

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Abstract Congenital mitral stenosis is a spectrum of disease with specific anatomic characteristics. In this chapter we will review the anatomic variants of congenital mitral stenosis with particular attention to clinical presentation and management.

27.1 Introduction

Isolated congenital mitral valve malformations resulting in stenosis are rare, and it is considered more a spectrum of defects. Reported prevalence is 0–0.5% of congenital heart defects [1–3].

The etiology of congenital mitral stenosis is not yet well elucidated. A theory involves a developmental arrest or malformation of the mitral valve apparatus occurring during the earliest phase of formation of the endocardial cushion [4, 5].

Acquired mitral stenosis is primarily related to rheumatic heart disease and, though uncommon in the United States, remains a considerable problem for children worldwide and will be reviewed in another chapter.

27.2 Anatomy

The mitral valve apparatus is formed by the annulus, the leaflets, the chordae tendineae, and the papillary muscles.

The mitral valve annulus is formed by the fibrous skeleton of the heart. It can be divided into anterior and posterior areas. The anterior portion, which is 2/3 of the annulus, is next to the aorta and corresponds to the mitral-aortic curtain and continuity; it is made of collagenous fibers and provides good support to the valve.

The shape of the annulus also plays an important role. It is described as saddle shape, with the superior aspect being the anterior portion and the inferior aspect the lateral portion of the annulus. This specific shape provides the benefit of decreasing the stress on the leaflets during systole.

The leaflets are made by mucoid myxomatous tissue. In a normally formed mitral valve apparatus, there are two leaflets. The anterior leaflet attaches to the anteromedial one-third of the annulus and inserts into the anterolateral papillary muscle. It is sail-shaped and is in direct continuity with half of the non-coronary cusp and most of the left coronary cusp of the aortic valve.

The posterior leaflet attaches to the posterolateral two-thirds of the annulus and inserts into the posteromedial papillary muscle [3]. It is C-shaped and is often subdivided by medial and lateral clefts.

Each leaflet attaches to both papillary muscles. They are separated at the anterolateral and posteromedial commissures, where they attached to the fibrous trigone. Both leaflets despite having different shapes have about the same area, which is about 20% more of the actual mitral orifice, which helps to overlap the tissue with systolic closure.

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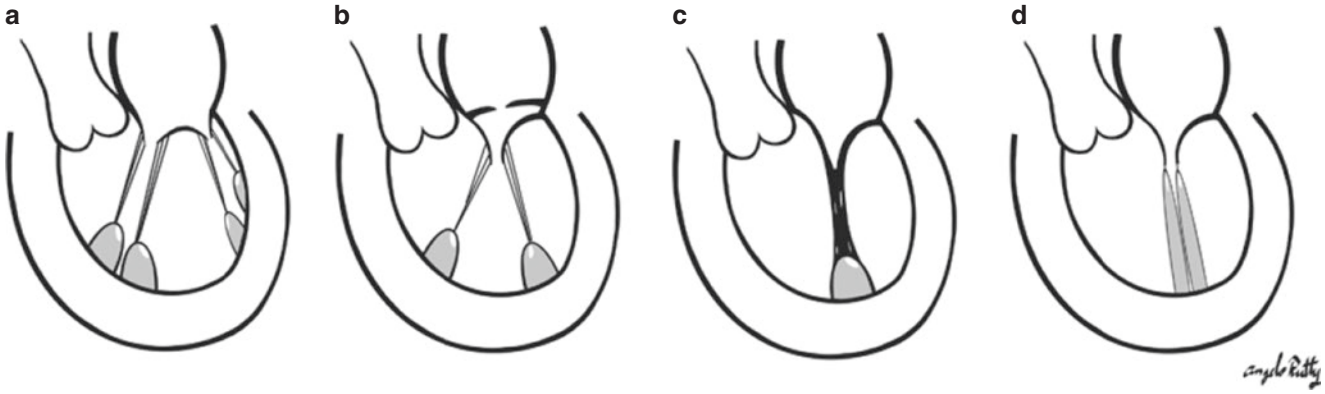

Fig. 27.1 Types of congenital mitral stenosis. (**a**) Double orifice mitral valve, (**b**) supravalvar mitral ring, (**c**) "parachute" mitral valve, (**d**) "hammock" mitral valve

The chordae tendineae, which are made by collagen, attach the undersurface of the mitral valve leaflets to the papillary muscles. These divide into primary, secondary, and tertiary chordae starting from the papillary muscles with progressive branching to insertion into the leaflets [2].

The papillary muscles are located strategically in the anterolateral and posteromedial position. They secure the chordae and leaflets during ventricular systole. The anterolateral papillary muscle has dual coronary supply by the left anterior descending and the circumflex coronary arteries, compared with the posteromedial papillary with variable blood supply, which increases the ischemia risk.

Congenital mitral stenosis results from anatomic deformity of one or multiple portions of the mitral valve apparatus (Fig. 27.1). Isolated or combined abnormalities of the annulus, leaflets, chordae tendineae, and papillary muscles can result in stenosis at the valvar, subvalvar, and supravalvar levels.

Malformations resulting in the reduction of the effective mitral valve orifice include hypoplasia of the valve annulus, fusion of the commissures, and thickened valve leaflets with rolled, dysplastic edges. Shortened, fused, thickened chordae tendineae may limit mitral valve mobility and reduce the secondary orifice area, normally created by the intercordal spaces [6]. The papillary muscles may be normal, underdeveloped, fused, or abnormally positioned resulting in a decreased intrapapillary distance and affecting the mobility of the mitral valve [2]. The lesions responsible for congenital mitral stenosis include typical (symmetric) mitral stenosis, parachute mitral valve, parachute-like asymmetric mitral valve, mitral arcade, double orifice mitral valve, and supravalvar mitral ring. Cor triatriatum is similar in terms of clinical presentation and pathophysiology to mitral stenosis but results from the lack of involution of an accessory membrane related to abnormal pulmonary venous incorporation into the wall of the left atrium during embryologic development.

Van Praagh et al. classified abnormalities of the mitral valve based on pathology specimens from autopsies as follows [7]:

- Typical mitral stenosis
- Hypoplastic congenital mitral stenosis
- Supramitral ring
- Parachute mitral valve

Later, Carpentier and Chauvaud described a functional classification based on the location of the major lesion [8]:

- Normal papillary muscles (Type A)
  - Supravalvular ring
  - Leaflet fusion (intraleaflet ring)
- Abnormal papillary muscle (Type B)
  - Parachute deformity
  - Primary papillary muscle abnormality

Despite these proposed systems, classification remains difficult as multiple pathologies can be present in the same valve and not entirely reflect the mechanism responsible for obstruction [4].

Congenital mitral stenosis anatomic abnormalities that will be reviewed in this chapter include:

- Mitral valve dysplasia and hypoplasia
- Dysplasia of the posterior or mural leaflet
- Supravalvar mitral stenosis
- Mitral arcade
- Parachute mitral valve

Typical (symmetric) congenital mitral valve stenosis. In this lesion, the valve is globally hypoplastic and can involve abnormalities of several portions of the apparatus. The annulus is small, the leaflets are thick, and the edges are rolled

together. Also, the space in between the chordal is obliterated, and the chordae are short [3, 9]. There is deformation of the papillary muscles; they can be underdeveloped or may be closely spaced. When there is equal distribution of chordae to each papillary muscle and equal papillary muscle size, it is defined as symmetric [10].

The combination of these lesions results in restriction of diastolic filling and tethering and deficient zones of coaptation [10]. Despite the thicker characteristics of the leaflets, they are usually pliable in younger children and don't represent a significant restriction of flow. If there is a band of connective tissue along the entire edge of the leaflets and extending to each papillary muscle, this restricts the motion of the leaflets, with the ensuing severe obstruction [4].

The etiology of these lesions is challenging as it is usually associated with other complex heart anomalies, especially small left-sided structures [9]. Some of the more frequent associations include pulmonary vein stenosis, supravalvar and valvar aortic stenosis, subaortic membrane, and coarctation of aorta. Shone's complex, described in 1963 by Shone, Sellers, and Anderson [11], refers to the combination of four lesions including supravalvar mitral ring, parachute mitral valve, subaortic stenosis, and coarctation of the aorta. The term is generally used whenever there is mitral valve disease associated with left ventricular outflow tract obstruction and aortic arch obstruction.

Asymmetric congenital mitral valve stenosis, reported in about 30% in a large cross-sectional study, includes asymmetric papillary muscle location, size, and distribution of chordal attachment. It can even result in a true parachute mitral valve, with all chordae inserting into a single papillary muscle (described below) [12].

It has also been described as dysplasia of the posterior or mural leaflet. This lesion results in a regurgitant jet that extends along the total length of the valve orifice and may respond to leaflet extension during surgical repair [3].

A supravalvar mitral ring is created by a circumferential shelf-like ridge of connective tissue attached to the atrial surface of the mitral valves [2, 6]. There have been described two types: intramitral ring, which consists of a thin membrane adherent to the atrial surface of the valve leaflets and is more commonly associated with Shone complex. The other type is the supramitral ring, which is a shelf-like membrane at or just above the mitral annulus; this lesion is usually associated with a normal subvalvular apparatus [10].

The ring can be partial or complete and becomes obstructive if it interferes with the primary mitral valve orifice [6, 13]. The supravalvar mitral ring can be differentiated from cor triatriatum by its position below the left atrial appendage and patent foramen ovale [13]. These lesions result in a variable degree of stenosis and can be progressive. It is usually a challenging lesion to image and requires a high index of suspicion [10].

Although a supravalvar mitral ring can rarely occur as an isolated lesion, the majority are associated with other mitral valve defects [2]. Therefore, a close evaluation of the entire mitral valve apparatus is required when a supravalvar mitral ring is identified. Likewise, careful echocardiographic evaluation for the presence of a supravalvar mitral ring should be undertaken when other mitral valve anomalies are present, particularly when there is increasing degree of stenosis in a patient with a known congenital mitral defect [10].

This is a type of lesion that can be repaired surgically with overall good results [3].

Parachute mitral valve refers to an abnormality resulting from shortened thickened chordae tendinea from both mitral valve leaflets inserting into a single papillary muscle limiting leaflet mobility [6, 14]. Most patients with parachute mitral valve have additional cardiac lesions. Commonly associated defects include coarctation of the aorta, bicuspid aortic valve, subvalvar aortic stenosis, left ventricular hypoplasia, valvar aortic stenosis, and supravalvar mitral stenosis as well as atrial septal defect, ventricular septal defect, patent ductus arteriosus, and other more complex cardiac lesions [14]. Patients with parachute mitral valve and atrial septal defect often have other severe left heart lesions and are more likely to be selected for univentricular palliation than patients without an atrial septal defect. This is likely reflective of the fetal physiology associated with the underdevelopment of the left-sided structures.

Parachute-like asymmetric mitral valve involves a lesion with two asymmetric papillary muscles. The dominant papillary muscle is elongated, displaced toward the mitral valve annulus, positioned higher in the left ventricle, and attached along its base and lateral side to the left ventricular wall. The chordae tendinae attach predominantly to one papillary muscle, limiting mitral valve mobility and reducing the effective mitral valve orifice [14, 15].

Mitral arcade or hammock mitral valve is a rare and severe lesion, occurring when the papillary muscles continue as a muscular structure to the free edge of the leaflets, with absence or near absence of the chordae tendinae. With this lesion, it is difficult to differentiate between the leaflets, chordae, and their supporting papillary muscles.

This lesion results in obstruction to left ventricular inflow [2, 6] but can also produce regurgitation due to tethered valve with deficient zones of leaflet coaptation. Usually it presents early on in life and invariably results in poor outcome when left untreated [3].

Double orifice mitral valve can be complete or incomplete, symmetric or asymmetric. The two openings can be created by an adhesion between the two leaflets [13], by a hole-type lesion creating a secondary orifice in the lateral commissure [16], or by the presence of redundant leaflet tissue forming a bridge between the anterior and posterior leaflets [17]. This lesion can present with mitral regurgitation, mitral stenosis, or a combination of both. It can be associated with both partial and complete atrioventricular septal defects and obstructive left-sided lesions, as well as with more complex congenital heart disease [18].

Acquired mitral stenosis is most frequently secondary to rheumatic carditis and results from thickening, calcification, fibrosis, and eventual fusion of the mitral valve leaflets, commissures, and chordae tendinae, forming a funnel-shaped valve [19–21]. In the pediatric population in the United States, acquired mitral stenosis from rheumatic carditis is uncommon.

Other conditions can also cause abnormalities in the mitral valve and should be considered in the differential diagnosis for mitral stenosis. These include systemic lupus erythematosus, malignant carcinoid, rheumatoid arthritis, polyvalvar mucoid congenital disease, and mucopolysaccharidosis of the Hunter–Hurler phenotype, Fabry disease, and Whipple disease [19, 22]. Lutembacher syndrome refers to the combination of mitral stenosis with an atrial septal defect [19, 21].

27.3 Pathophysiology

Abnormalities of the mitral valve apparatus result in a reduced effective valve orifice area and obstruction to left ventricular filling. A diastolic gradient is generated between the left atrium and left ventricle due to the reduced size of the effective mitral valve orifice. The mitral valve gradient is determined by the size of the opening and by the amount of diastolic inflow and therefore depends on cardiac output and the length of time for diastole filling [21]. As the area of the valve decreases, a higher transmitral gradient and an increased left atrial pressure are required to maintain cardiac output [19]. An elevated left atrial pressure is then transmitted to the pulmonary venous system, raising the pulmonary venous and pulmonary capillary pressures. Pulmonary edema develops when the hydrostatic pressure of the pulmonary vascular bed exceeds the plasmatic oncotic pressure [3, 22]. Long-standing pulmonary venous hypertension and pulmonary congestion result in an elevated pulmonary arterial pressure, pulmonary alveolar fibrosis, and the thickening of the pulmonary arteriolar bed with reduced pulmonary compliance [19, 20, 23]. Changes and congestion in the pulmonary vascular bed affect ventilation by compressing small bronchiolar airways and alter the mechanics of gas exchange [3]. Respiratory symptoms are therefore often the first manifestation of disease in patients with significant mitral valve stenosis. The relationship between mitral valve area, diastolic filling time, heart rate, and cardiac output is explained by the Gorlin formula, as follows [24]:

Where diastolic flow = (C.O.) × (RR interval)/(60 × diastolic filling time)

Patients develop symptoms with exercise or in other situations with tachycardia and demand for an increased cardiac output. Because in the fixed area of the mitral valve orifice there is less diastolic filling time with increasing heart rate, a higher transvalvar gradient and a higher left atrial pressure are required to maintain or increase cardiac output [19]. This is also manifest when previously asymptomatic women with mitral stenosis develop symptoms during pregnancy due to the requisite increase in cardiac output. Likewise, patients with atrial arrhythmias who have a rapid ventricular response develop exacerbation of symptoms due to tachycardia and to a decrease in the degree of ventricular filling that normally occurs with atrial systole [19].

With prolonged pulmonary venous hypertension and pulmonary edema, changes occur in the pulmonary arteriole bed and eventually result in pulmonary hypertension. With the development of pulmonary hypertension, there is pulmonary insufficiency, right ventricular dilation, dilation of the tricuspid valve annulus, and functional tricuspid valve regurgitation, which ultimately manifest as right heart failure. Mitral stenosis can also be exacerbated by coexistent mitral regurgitation, decreased left ventricular systolic or diastolic function, elevation of the left ventricular end diastolic pressure, and other left-sided obstructive lesions. The degree of mitral valve stenosis may be underestimated when there is a significant atrial septal defect as part of the cardiac output is diverted through the atrial septum, and these patients can have symptoms related to low cardiac output.

27.4 Clinical Presentation

The symptoms with mitral stenosis are related to the degree of stenosis and reflect an elevated left atrial pressure, pulmonary venous congestion, and low cardiac output, as well as the development of pulmonary hypertension and right heart failure or the presence of an atrial arrhythmia.

Patients with mild mitral stenosis are usually asymptomatic. Those with moderate stenosis develop symptoms with exertion, and those with severe stenosis often have symptoms at rest.

In adults, moderate mitral stenosis correlates with a mitral valve area of 1–2.5 cm^2, and severe mitral stenosis correlates to a mitral valve area of less than 1 cm^2. The initial presentation is most commonly due to symptoms with exertion described as decreased exercise tolerance in older children and feeding difficulty in infants. Infants may present with an increased work of breathing, fatigue or diaphoresis with feeds, recurrent respiratory infections, tachypnea, and failure to thrive [22, 25]. Older patients may complain of dyspnea with exertion, orthopnea, nocturnal paroxysmal dyspnea, chronic cough or wheezing, hemoptysis, and palpitations. Hemoptysis occurs due to rupture of dilated thin-walled bronchial vessels in the setting of long-standing pulmonary venous hypertension [13, 14], and atrial flutter and fibrillation are not uncommon in long-standing mitral stenosis. Patients with mitral stenosis should also be assessed for symptoms of

hoarseness, which can occur if an enlarged left atrium causes compression of the recurrent laryngeal nerve [19, 22]. Patients who have pulmonary hypertension secondary to mitral stenosis will have fewer symptoms of lung congestion and more complaints reflective of low cardiac output.

Physical findings are related to the degree of mitral stenosis and to the presence or absence of pulmonary hypertension and right heart failure. The murmur of mitral stenosis is a low-pitched diastolic rumble with presystolic accentuation, heard best at the apex and in the left lateral decubitus position [20–22]. The length of the diastolic murmur is directly related to the degree of mitral stenosis [21]. In patients with congenital mitral stenosis, S1 is either normal or of decreased intensity and P2 is accentuated if pulmonary hypertension is present. With the development of pulmonary hypertension, a right ventricular lift is present, and there may be a Graham Steel murmur of pulmonary insufficiency, which is an early diastolic, high-pitched murmur at the left upper sternal border [21]. Signs of right heart failure include hepatomegaly, ascites, peripheral edema, and jugular venous distension. With rheumatic mitral stenosis, there is a loud opening snap after the second heart sound that is not present with congenital mitral stenosis [3, 22].

27.4.1 Chest X-Ray

A chest film may demonstrate pulmonary congestion with redistribution of pulmonary blood flow to the upper lobes [20, 23], left atrial enlargement with elevation of the left mainstem bronchus [2, 22], prominent pulmonary arteries, and right ventricular enlargement [20, 25].

27.4.2 ECG

The electrocardiogram may show a wide and notched P wave in lead II due to left atrial enlargement and right ventricular hypertrophy with right atrial enlargement once pulmonary hypertension develops. Atrial flutter and fibrillation are not uncommon in association with mitral stenosis.

27.4.3 Echocardiography

Transthoracic echocardiography is imperative for definition of mitral valve anatomy with careful attention to the morphology of the annulus, leaflets, chordae tendinae, papillary muscles, and supravalvar area.

An evaluation of the left atrial size, mitral regurgitation, and presence of an atrial septal defect and other associated cardiac anomalies is also important. Any patient with abnormalities of the mitral valve apparatus must carefully be evaluated for the presence of an associated supravalvar mitral ring that may contribute to stenosis and affect the management plan [26]. The number, position, and relationship of the papillary muscles should be assessed. Right and left ventricular functions are evaluated for signs of pulmonary hypertension and degree of tricuspid regurgitation. Doppler measurements are made of the peak and mean mitral valve gradients. The mean transmitral valve pressure gradient has a fair correlation with the transmitral gradient measured by cardiac catheterization.

Left atrial pressure can be estimated if a patent foramen ovale is present and if the patient has an accurate central venous pressure available. 2D imaging allows linear measurements of the valve annulus, and assuming that the annulus is oval, corresponding equations can be applied to calculate the mitral valve area. Despite the annulus becoming more circular in diseased states, linear singular diameters can provide an approximation of annular size referenced to Z-score values [27].

Measurement of the pressure halftime of mitral valve inflow reflects the time needed for the peak diastolic inflow velocity to decrease by 50% and is inversely proportional to the mitral valve area [21, 26]. As the severity of mitral stenosis increases, the pressure halftime lengthens. In children, the mitral valve area can be calculated at the time of cardiac catheterization by the Gorlin and Gorlin equation. In adults, the mitral valve area can be estimated by echocardiography using an empirically derived constant [22] divided by the pressure halftime, with fair correlation to the area obtained with the Gorlin and Gorlin formula. The accuracy of this method has not been reliable in children when compared with mitral valve area obtained by calculation by the Gorlin formula and is usually not used for pediatric patients [26, 28]. There are several other echocardiographic formulas for estimating mitral valve area in children, including the continuity equation and the PISA (proximal isovelocity surface area) technique. Both are well described in standard echocardiography textbooks [26].

In the presence of an atrial septal defect, the severity of mitral valve stenosis may be underestimated; this should be considered during the interpretation of the study. In adults, mitral stenosis is categorized as mild if the mean gradient is less than 5 mmHg, moderate when the mean gradient is 5–10 mmHg, and severe when the mean gradient is greater than 10 mmHg [29]. In children, mild mitral stenosis has been defined as a mean gradient of less than 5 mmHg, moderate stenosis falls between 6 and 12 mmHg, and severe stenosis is described when the mean gradient is greater than 13 mmHg [25]. Transesophageal echocardiography may be indicated when transthoracic images are inadequate or for

evaluation for thrombus in patients with atrial flutter or fibrillation.

Some noninvasive imaging laboratories are now combining three-dimensional imaging. Three dimensional imaging of the mitral valve provides several advantages which includes simultaneous evaluation of the entire mitral valve from the supraannular region to the insertion of the papillary muscles to the myocardium; evaluation from unique imaging planes and projections to assess the synchronous motion and spatial arrangement of the valve proving an on-face view of the valve from the left atrium; and allowing for area measurement regardless of area size or shape in a more precise delineation, not only for annular area but also for the vena contracta regurgitation orifice and the smallest effective orifice area. 3D imaging must be used in combination with 2D imaging due to the limited frame rates and the need to further characterize leaflet motion and coaptation [27, 30, 31].

Exercise testing can be helpful for objective evaluation of functional capacity and to monitor for deterioration or improvement with time or intervention [23].

27.4.4 Cardiac Catheterization

Cardiac catheterization is performed when additional diagnostic data are necessary or when interventional balloon mitral valvuloplasty is indicated. Data obtained at cardiac catheterization include standard right heart hemodynamic measurements, thermodilution cardiac output, and simultaneous left atrial and left ventricular pressure for direct assessment of the transmitral gradient (Fig. 27.2). The transmitral gradient is the diastolic gradient from the left atrial a wave to the left ventricular end diastolic pressure [22]. If no intervention is planned and no atrial septal defect is present for access to the left atrium, the transmitral gradient can be estimated by recording simultaneous pulmonary capillary wedge and left ventricular end diastolic pressures. Patients with mild-to-moderate stenosis may have normal or mildly elevated pulmonary artery pressure. Those with severe mitral stenosis often have elevated pulmonary artery pressure and elevated pulmonary vascular resistance [19]. Angiography of the left ventricle, left atrium, and other locations is indicated by severity of the disease and the presence of associated lesions (Fig. 27.3).

Hemodynamic assessment with supplemental oxygen and nitric oxide may be indicated as related to the severity of pulmonary hypertension. Balloon dilation of the mitral valve may be considered in patients with severe congenital mitral stenosis in the absence of a supravalvar mitral ring and in those with significant rheumatic mitral valve stenosis.

Surgical resection is the preferred intervention for stenosis related to a supravalvar mitral ring. Balloon mitral valvuloplasty in children is performed with a standard low-pressure angiography balloon (Fig. 27.4) or the specialized Inoue balloon. A double balloon technique may be necessary due to the relatively large mitral valve annulus size. Access to the mitral valve may require transseptal puncture with or without balloon dilation of the atrial septum [32]. Successful results from balloon valvuloplasty in adults and children with rheumatic mitral stenosis are comparable to surgical intervention [32], with an average reduction in the mitral

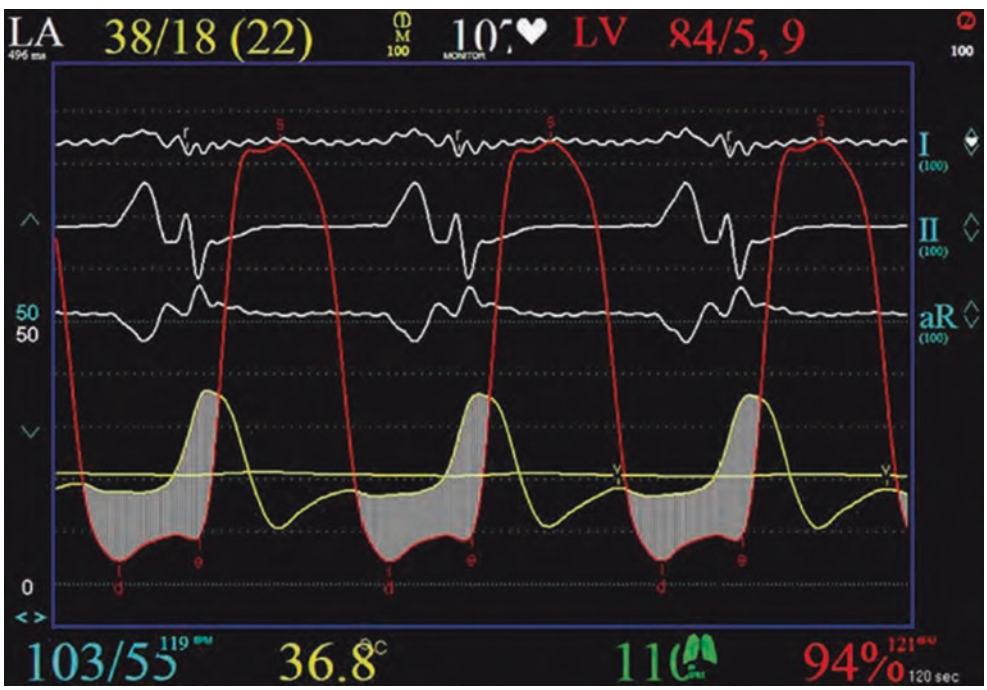

Fig. 27.2 Hemodynamic trace of simultaneous left atrial and left ventricular pressure measurements with the mean mitral valve gradient represented by the shaded area between the left atrial and left ventricular waveforms

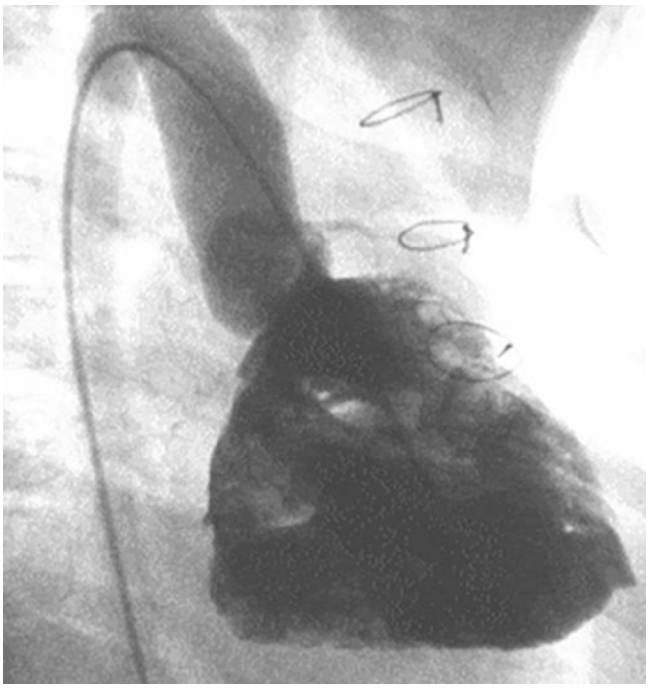

Fig. 27.3 Left ventricular angiography showing double orifice mitral valve

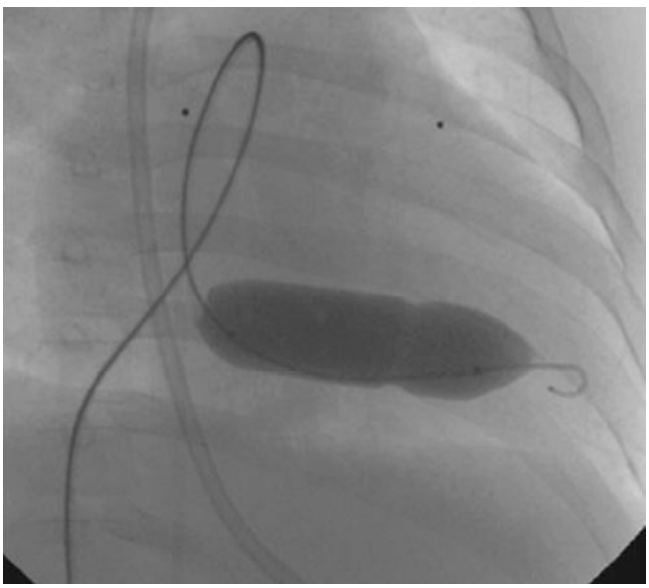

Fig. 27.4 Spot cine of inflation of a standard low-pressure angioplasty balloon across the mitral valve

valve gradient from 17 to 5.2 mmHg and improvement in mitral valve area from 0.84 to 2 cm^2 [33]. Mitral balloon valvuloplasty in children with rheumatic mitral stenosis has a 14.3% incidence of restenosis and a 93% event free survival at 5 years and a 79% event free survival at 10 years [33]. Complication rates for balloon mitral valvuloplasty in children with rheumatic disease are similar to those in adults. Dilation of congenital mitral stenosis carries a higher risk of morbidity and mortality [32] and is often complicated by associated cardiac lesions. Despite the complexity of balloon valvuloplasty for congenital mitral valve stenosis, with increasing experience, results are improving. Lock reports 90% 5-year survival in patients with typical congenital mitral stenosis who require balloon mitral valvuloplasty, with less than 2% of procedural mortality and an average delay of 4 years to surgical intervention [34].

27.5 Preoperative Management

Observation is often all that is required in asymptomatic patients with mild mitral stenosis as it is not usually progressive. In patients with more significant disease, medical management is used to reduce symptoms and delay the need for intervention. Patients with mitral stenosis may be admitted to the intensive care unit with respiratory failure, low cardiac output syndrome, atrial arrhythmias, infectious endocarditis, or a combination thereof. In addition, these patients can be admitted after balloon valvuloplasty for observation or the treatment of complications related to the procedure. Respiratory failure can be secondary to multiple factors, including left atrial hypertension, pulmonary edema, pulmonary hypertension, and pneumonia, especially viral pneumonia secondary to respiratory syncytial virus. Patients have limited ability to augment cardiac output to compensate for any increase in metabolic demand as inflow of blood across the mitral valve is obstructed. Prompt intervention with positive pressure ventilation will improve the ventilation perfusion mismatch.

With mechanical ventilation, moderately high ventilatory settings are usually required, including peak inspiratory and end expiratory pressures with pressure mode ventilation and tidal volume with volume mode ventilation. In the subset of patients with true elevation of pulmonary vascular resistance, inhaled nitric oxide is useful as a selective pulmonary vasodilator, though it can lead to an increase in left atrial pressure and pulmonary edema.

When the mitral valve area is small, the left atrial pressure should be kept appropriately high to maintain a sufficient transmitral gradient to sustain adequate cardiac output. The relationship between the diastolic filling time, cardiac output, and the transvalvar gradient is also important to consider. The gradient across the mitral valve increases markedly with increased heart rate and cardiac output. It is always preferable to avoid tachycardia to allow appropriate time for left ventricular filling. Medical management should target slowing the heart rate.

Immediate goals in an intensive care setting include (1) normalization of temperature; (2) when necessary, use of

inotropic agents and doses that cause the least tachycardia; (3) use of beta blockers and calcium channel blockers for rate control in older children, though these agents are contraindicated in neonates and infants; and (4) diuretics are added judiciously to decrease symptoms attributed to pulmonary venous congestion with attention to the prevention of hypovolemia [2].

Right ventricular dysfunction may be present secondary to pulmonary artery hypertension. Diuretics, inotropic support, and optimization of the ventilation perfusion mismatch with a decrease of pulmonary vascular resistance are the key elements of therapy.

In infants and children, it is important to ensure adequate nutrition and higher calorie formula, or tube feeds may be indicated. In patients with chronic atrial arrhythmias, selective treatment of the specific arrhythmia and appropriate anticoagulation is required.

Patients who remain symptomatic despite maximal medical management should be considered for percutaneous intervention if the anatomy of their lesion is amenable to balloon valvuloplasty. This is true particularly in patients with rheumatic mitral stenosis and symmetric congenital mitral valve stenosis. Patients with supravalvar mitral ring should not routinely be referred to for balloon valvuloplasty as their outcome is better with surgical intervention. Patients with parachute mitral valve tend to have less successful results with balloon valvotomy due to the asymmetric anatomy of the valve [14]. Balloon mitral valvuloplasty is generally not considered if there is more than mild mitral regurgitation at baseline. Balloon mitral valvuloplasty may delay or obviate the need for surgical intervention, which is particularly crucial in infants and small children [34]. Patients who have failed medical management and/or balloon mitral valvuloplasty, those with anatomy unfavorable to percutaneous intervention, and those with significant regurgitation should be referred to for surgical repair [25].

27.6 Surgical Management

The main indication of surgical intervention is the presence of symptoms or severe pulmonary hypertension. Operative management is intended to relieve the obstruction across the mitral valve, but not infrequently patients are left with residual gradients. Therefore, a detailed preoperative echocardiographic assessment of the valve is vital in determining the anatomy of the valve lesion and the chances of a successful repair.

The surgical approach requires cardiopulmonary bypass with bicaval cannulation, mild to moderate hypothermia, and cardioplegic arrest. The valve is usually exposed via a standard left atrial, incision at the level of the interatrial groove but, a transseptal approached could also be used.

Left atrial enlargement is usually present facilitating the surgical exposure. It is important during repair to have an optimal angle and to ensure adequate identification of the entire valvar apparatus including the subvalvular structures [4].

Repair of a supravalvar ring requires complete excision of the fibrous membrane (Fig. 27.5); commissurotomies are utilized to enlarge the effective valve orifice (Fig. 27.6). Surgical

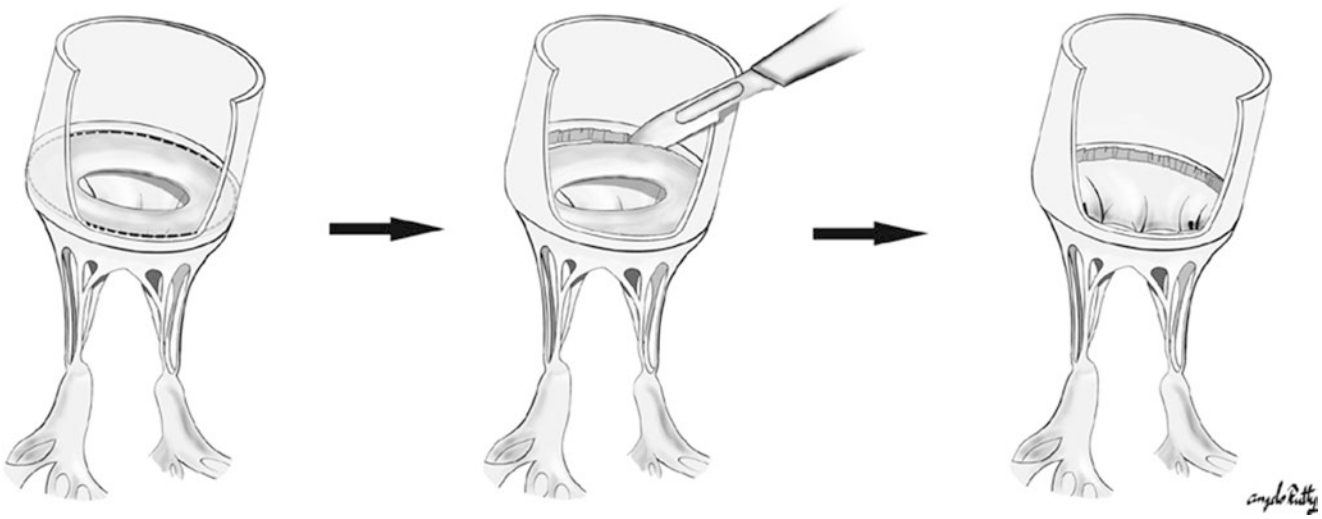

Fig. 27.5 Repair of supravalvar mitral ring. The valve is exposed via a left atriotomy and the fibrous ridge sharply excised. Care is taken not to injure the underlying mitral valve leaflets

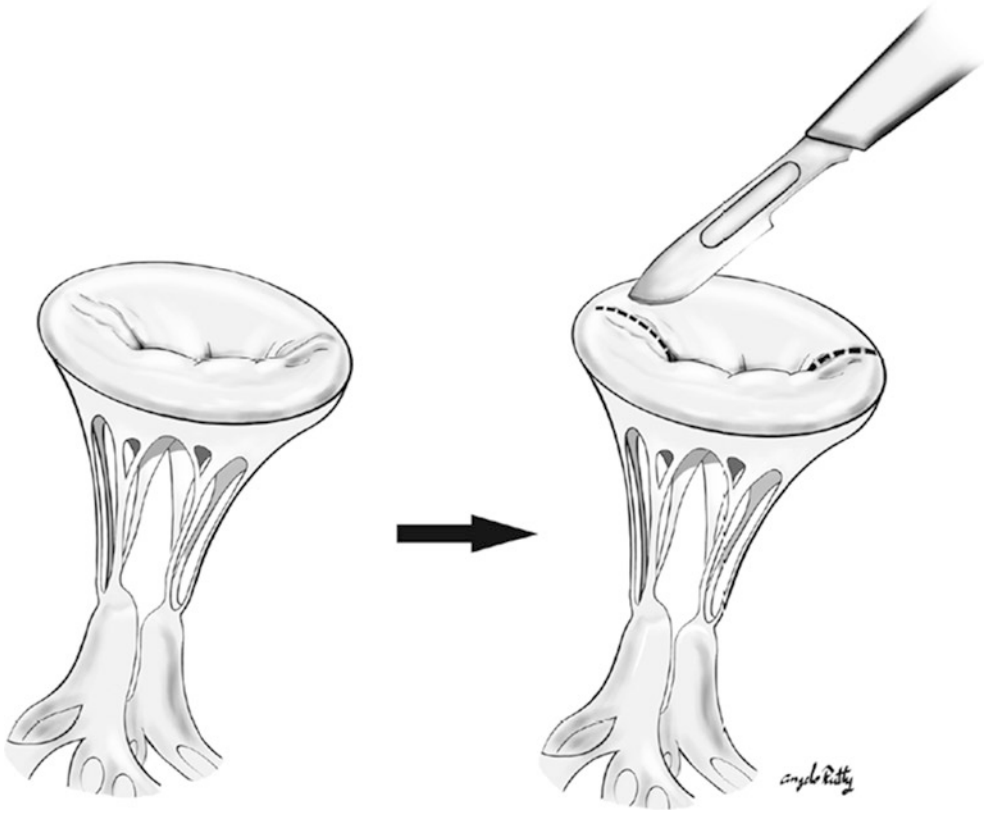

Fig. 27.6 Mitral valve commissurotomy. The effective valve orifice is enlarged by sharply opening areas of commissural fusion

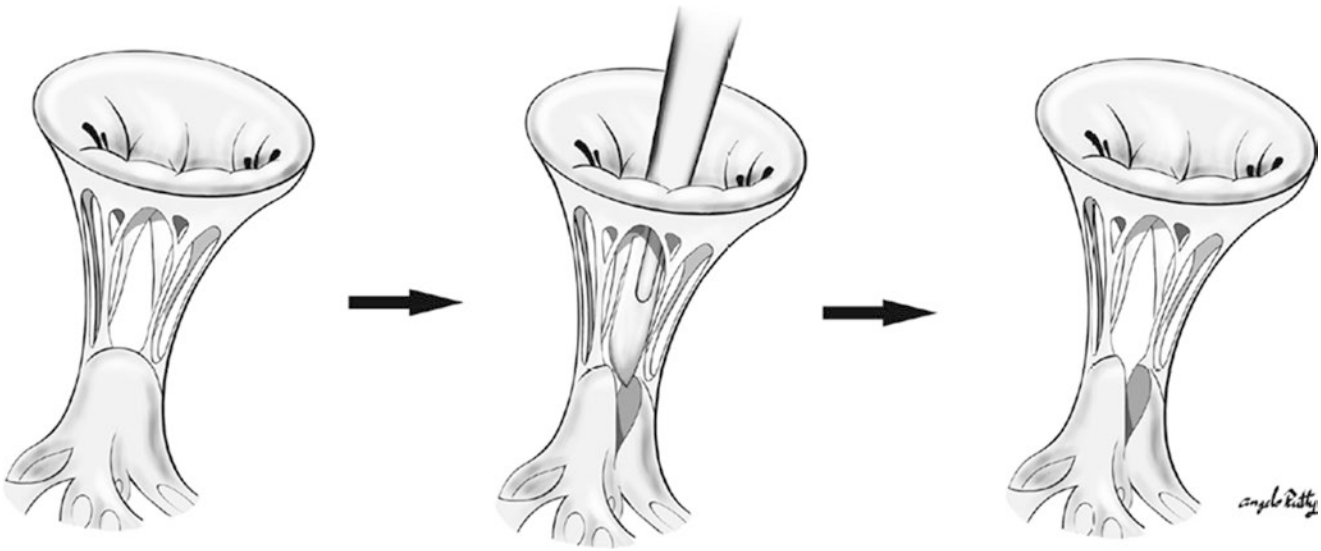

Fig. 27.7 Splitting of single papillary muscle

techniques utilized for the management of an abnormal subvalvar apparatus (i.e., single papillary muscle) include fenestration of the intercordal spaces and splitting of the papillary muscles (Figs. 27.7 and 27.8).

If the repair is unsuccessful or if the valve is deemed as not reparable, then mitral valve replacement is required. In infants and small children with a small mitral valve annulus, the prosthetic valve might need placement in a supraannular position (Fig. 27.9). The operative morbidity and mortality associated with the surgical management of mitral stenosis is not insignificant, as high as 20% [25, 35, 36].

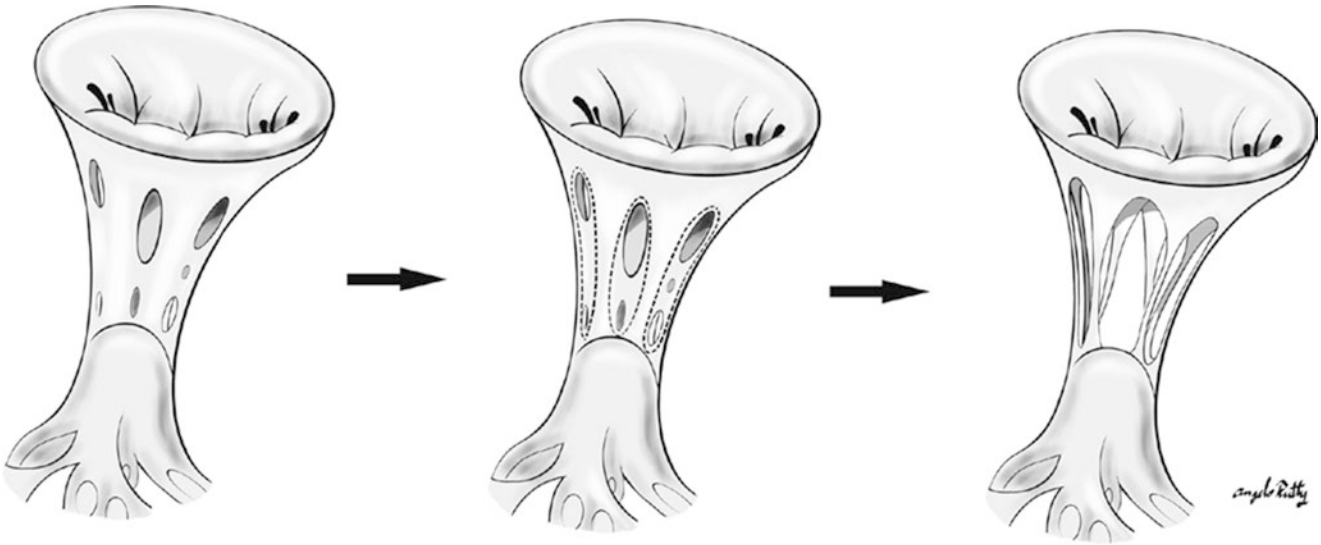

Fig. 27.8 Fenestration of the intercordal spaces

Fig. 27.9 Mitral valve replacement in the supraannular position. The prosthetic valve is sewn circumferentially to the left atrial tissue between the pulmonary veins and the mitral valve annulus

27.7 Postoperative Management

The principles of postoperative care are similar to those of preoperative management. Specific therapy is tailored to the results of surgical repair. Morbidity is related to residual mitral stenosis, pulmonary hypertension, low cardiac output syndrome, right ventricular failure, arrhythmias, atrioventricular block as a complication of prosthetic valve replacement, and presence of coexistent lesions such as left ventricular hypoplasia, subaortic stenosis, aortic stenosis, and arch hypoplasia. Maintenance of sinus rhythm is of critical importance in this subset of patients to maintain adequate cardiac output.

In general, primary valvuloplasty is the procedure of choice, and mitral valve replacement is avoided when possible. Prosthetic valves in young children are problematic due to the need for chronic anticoagulation and because the prosthetic valve often needs to be placed in supraannular position due to small annular size. Left atrial, pulmonary venous, and pulmonary arterial hypertension may result from the relatively large size of the prosthetic valve in comparison with the left atrial size. This is a more significant issue for small infants [35].

Transesophageal or transthoracic echocardiogram must be routinely obtained to assess right ventricular function, left ventricular function and filling, and the gradient across the prosthetic valve. Furthermore, it is important to evaluate for evidence of perivalvar leak.

The approach and therapy of the postoperative complications are described in the section on preoperative management. If inotropic support is needed after surgery, the agent that causes the least tachycardia while augmenting contractility is the drug of choice. Normal temperature must be maintained at all times during the immediate postoperative period. Afterload-reducing agents can be used cautiously. Patients with intravascular depletion who develop tachycardia and hypotension may have decreased coronary perfusion. Systolic systemic hypertension ought to be avoided to reduce the strain on the mitral valve after a surgical plasty. After surgical repair, patients would require 24–48 h of mechanical

ventilation, especially if the chest is left open. An open chest improves ventricular compliance and minimizes the effect of positive pressure ventilation on pulmonary vascular resistance. While the chest is opened, sedation, analgesia, and neuromuscular blockade are required. The chest is normally closed 24–48 h after surgical intervention. In addition, sedation, neuromuscular blockade, and inhaled nitric oxide are required in patients with pulmonary hypertension [37]. A pulmonary artery catheter and left atrial line may be helpful in guiding the medical management in discerning the etiology of postoperative pulmonary hypertension.

27.8 Long-Term Outcomes

Outcome related to mitral valve stenosis is variable dependent upon age at presentation, severity of stenosis, presence of associated cardiac defects, and valve morphology. Children with mild stenosis often remain asymptomatic and have no progression in the degree of stenosis with somatic growth. Infants with symptomatic congenital mitral stenosis and associated left-sided obstructive heart lesions continue to have a higher incidence of morbidity and mortality. Despite improved results with percutaneous balloon mitral valvuloplasty and with primary surgical valvuloplasty, children with congenital mitral valve stenosis remain at risk for development of restenosis, need for reoperation, placement of a prosthetic valve, and life-long anticoagulant therapy.

Fortunately, many patients with valvar mitral stenosis who have developed pulmonary hypertension and right ventricular failure show reversal of pulmonary hypertension over time after an intervention is performed to increase the effective mitral valve area. In a retrospective review reported by Moore et al. in 1994, in a population of 85 infants with congenital mitral stenosis, 36% required intervention, 18 underwent balloon dilation of the mitral valve, and 13 underwent surgery. Freedom from mortality at 2 years was 70% in the group of patients who had balloon valvuloplasty and 60% in those who had surgical intervention. In the group of infants who underwent balloon dilation, symptomatic improvement persisted in only 40% of patients. Procedural mortality was related to the need for repeat balloon dilation and degree of left ventricular hypoplasia [9]. In patients with parachute mitral valve and parachute-like asymmetric mitral valve, in 2004 Schaverien et al. reported 82% survival at 1 year and 77% at 10 years in a study population of 84 patients.

Presence of an atrial septal defect and left ventricular hypoplasia were identified as independent risk factors for death [14].

As reported by del Nido et al., operative mortality was relatively low. Operative survival was 96%, and there were no late deaths after 60 months of follow-up period. In this report, the major risk factor was the age at presentation with most of the deaths occurring in the newborn group. The freedom from reoperation was also good, with 86% at 5 years [4].

McElhinney et al. reported a retrospective review of outcomes for 108 patients with severe congenital mitral stenosis who underwent balloon mitral valvuloplasty or surgical mitral valve intervention. In those patients who underwent balloon mitral valvuloplasty, there was a decrease in peak and mean mitral valve gradients by a median of 33% and 38%, respectively. Balloon valvuloplasty was complicated by the development of significant mitral regurgitation in 28% of patients. Overall survival was 84% at 1 year and 77% at 5 years with an overall trend toward improved survival during the second decade of the study. Younger age and the need for initial mitral valve replacement were associated with worse survival [36]. Rheumatic mitral stenosis is not commonly encountered in the pediatric population in the United States, but results for percutaneous intervention with balloon mitral valvuloplasty are encouraging [33]. Due to the variety of mitral valve pathology, the rarity of the disease, and the frequent presence of associated defects, congenital mitral stenosis remains a challenging defect to study and in which to predict a long-term outcome. Patient and family counseling related to outcome should be individualized dependent upon the severity of disease and the presence of associated cardiac defects.

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Chapter 28
Prosthetic Valves

Peter D. Wearden

Abstract Many challenges are faced by pediatric patients and their surgeons in finding acceptable replacement heart valves for diseased, diminutive, or absent native valves. First of the challenges is valve size. Many prosthetic valves available in the market today are applicable only to the largest of pediatric patients. Even the smallest of commercially available valves can have unacceptable gradients. This can, at times, be circumvented by various surgical techniques, annular enlargement, or valve positioning. Other obstacles faced in this patient population include the issues of somatic growth, valve calcification, structural deterioration, thromboembolism, and the need for anticoagulation and its associated monitoring requirements. This chapter reviews the currently available prosthetic valves, valve choice for various locations and indications in the pediatric patient, and, lastly, management and complications of prosthetic valve placement in children. (Figures 28.1 and 28.2 demonstrate currently available prosthetic and tissue valves.)

Many challenges are faced by pediatric patients and their surgeons in finding acceptable replacement heart valves for diseased, diminutive, or absent native valves. First of the challenges is valve size. Many prosthetic valves available in the market today are applicable only to the largest of pediatric patients. Even the smallest of commercially available valves can have unacceptable gradients. This can, at times, be circumvented by various surgical techniques, annular enlargement, or valve positioning. Other obstacles faced in this patient population include the issues of somatic growth, valve calcification, structural deterioration, thromboembolism, and the need for anticoagulation and its associated monitoring requirements. This chapter reviews the currently available prosthetic valves, valve choice for various locations and indications in the pediatric patient, and, lastly, management and complications of prosthetic valve placement in children. (Figures 28.1 and 28.2 demonstrate currently available prosthetic and tissue valves.)

28.1 Currently Available Prosthetic Valves

The currently available choices of prosthetic valves can be broadly divided into *mechanical* or *biologic* valves. Each of these categories can be further divided by valve design, construction, and tissue of origin or processing of biologic materials. There are certain nuances of valve design of mechanical valves, or preservation of bioprosthetic valves, which are generally proprietary and are not the subject of this chapter.

28.1.1 Mechanical Valves

The design types of mechanical prosthesis include the *caged ball design* (Starr–Edwards Silastic Ball Valve, Edwards Lifesciences, Inc., Irvine, CA) and the *tilting disk* prosthesis.

Tilting disk prostheses includes both *single-disk* and *bileaflet* prostheses. The single-disk prostheses are the Medtronic–Hall (Medtronic Inc, Minneapolis, MN), the Omicarbon valve prosthesis (Medical CV, Inc., Inver Grove Heights, MN), and the Monostrut cardiac valve prosthesis (Alliance Medical Technologies, Inc., Irvine, CA). Bileaflet prostheses include the most commonly used valves today, the St. Jude Medical (SJM) valve (St. Jude Medical, Inc., Minneapolis, MN), the On-X prosthetic valve (Medical Carbon Research Institute, Austin, TX), the ATS Medical Open Pivot mechanical heart valves (ATS Medical, Inc., Minneapolis, MN), and also the CarboMedics prosthetic heart valves (Sulzer CarboMedics, Inc., Austin, TX).

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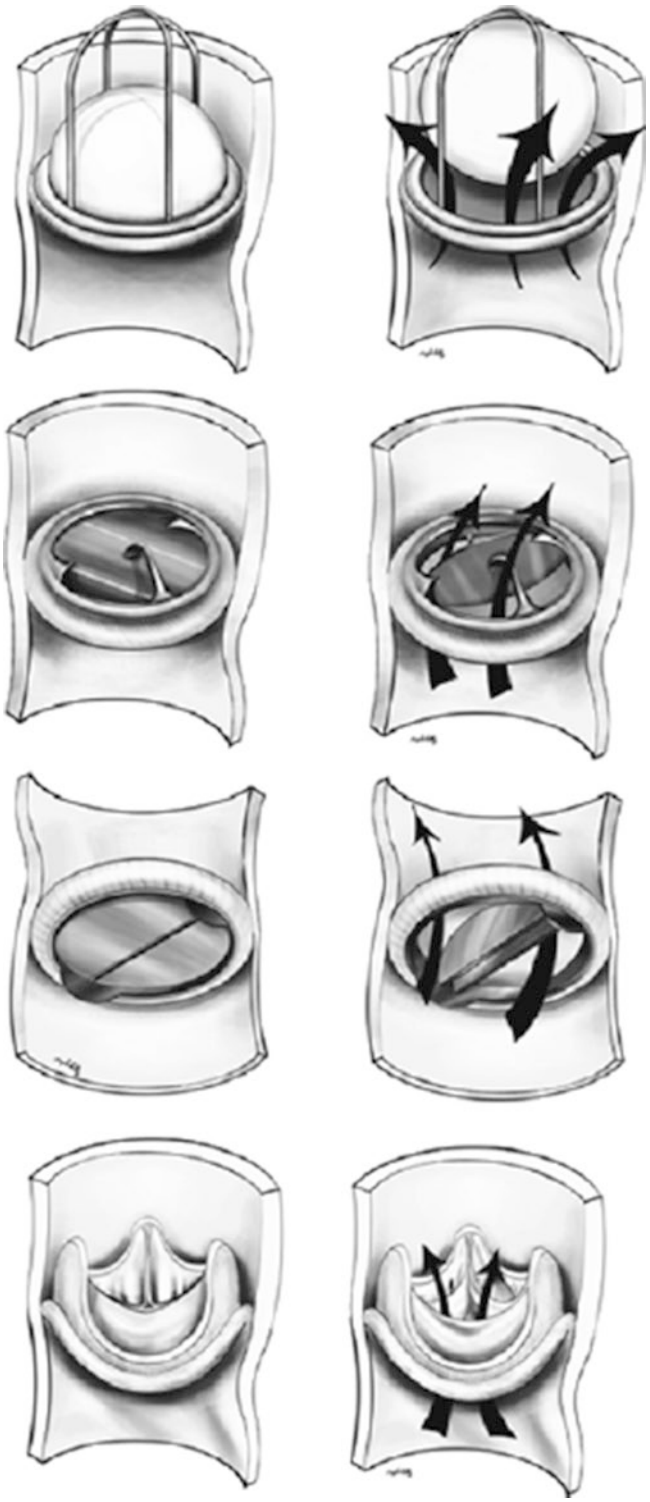

Fig. 28.1 This figure illustrates the most commonly used prosthetic valves. From top to bottom: caged ball valve design which is no longer commonly used, a single tilting disk valve, a bileaflet tilting disk valve, and a stented porcine prosthesis

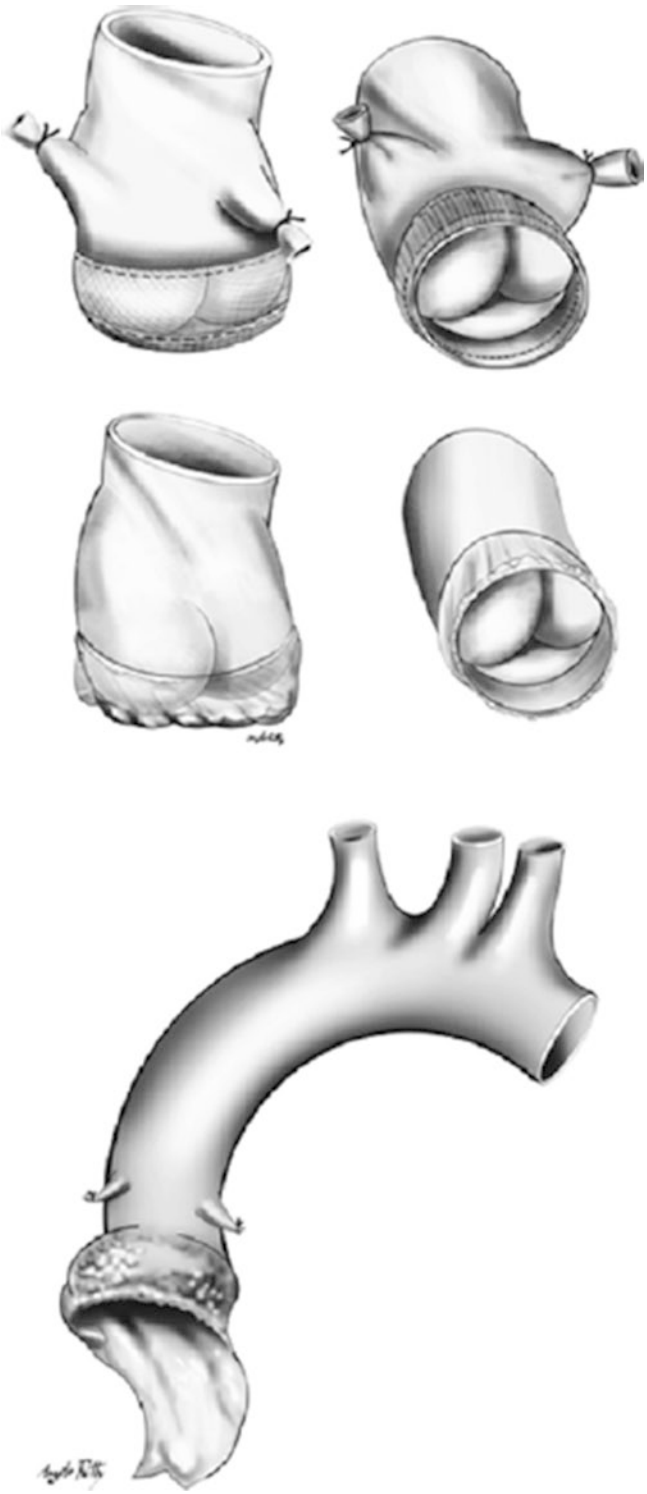

Fig. 28.2 Common biologic valves. From top to bottom: stentless porcine aortic prosthesis, pulmonary homograft (note the attached right ventricular muscle), and an aortic homograft with arch vessels (note the attached anterior leaflet of the mitral valve and ligated coronary arteries)

The caged ball design was the first mechanical heart valve widely available. However, it is generally no longer used. Its usefulness in the pediatric population was somewhat limited by its high-profile design.

Differences in the other valve designs include not only whether there are one or two leaflets but also the material which they are manufactured from, including titanium alloys, tungsten graphite, cobalt-based alloys, and pyrolytic carbons.

Opening and valve washing patterns vary from valve to valve and may affect, among other things, appropriate valve orientation, the ability of retained valvular tissue or sutures to obstruct the valve, and the washing of the valve by blood. Some diastolic regurgitation has been noted to improve continuous washing of the valve with blood and to decrease the incidence of thromboembolism [1, 2]. The type of valve can often be determined from its radiographic appearance. Also, each valve has distinctive flow patterns during both systole and diastole, and they are referred to as "signature jets" on echocardiography.

Depending upon the manufacturer, valves are generally available in odd sizes from 15 to 31 mm for the aortic (semilunar) position and from 19 to 33 mm for the mitral (atrioventricular) position. Several valve manufacturers have designed valves for "supra-annular" positioning. These valves sit above the annulus, or sewing ring which is still secured to the annulus, without obstructing the coronary arteries. This allows for a valve with a larger effective orifice area (EOA) to be placed thereby decreasing the gradient. The most common of these valves are the SJM high performance (HP) and Regent valves, the CarboMedics Top Hat valve, and the ATS Open Pivot AP series of valves. Valves smaller than 19 mm, as would often be required in the smallest of children, include the 17 mm Monostrut valve, 17 mm SJM HP and Regent valves, and 16 mm ATS Medical Open Pivot AP valves.

28.1.2 Bioprosthetic Valves

Bioprosthetic valves have the distinct advantage of not needing lifelong anticoagulation. The trade-off, however, is durability. Xenograft valves calcify when placed into the human circulation ultimately leading to their failure. This calcification process appears to occur more rapidly in younger patients. Various treatments including glutaraldehyde, amino-oleic acid, and polysorbate 80 have been employed to fix the tissue and decrease mineralization. There has also been a trend to move from high pressure fixation to low pressure fixation in an attempt to preserve normal tissue architecture. The bioprosthetic valves include both stented (or supported) and stentless prostheses. The tissue of origin is generally porcine with the exception of a bovine pericardial valve manufactured from fixed bovine pericardium.

The stented valves include the Hancock and Mosaic valves (Medtronic, Inc.). The Mosaic valve is the latest generation valve and differs from the Hancock series in having a different antimineralization treatment, zero pressure fixation, and predilation to increase EOA. The Mosaic valve also has a semiflexible stent. These valves are generally available in sizes from 21 to 35 mm. The other currently available stented porcine prosthesis is the Carpentier-Edwards standard valve (Edwards Life Sciences, Inc.). The Carpentier-Edwards PERIMOUNT valve (Edwards Life Sciences, Inc.) is a stented prosthesis made from bovine pericardium. This valve is manufactured from pericardium, as opposed to the porcine valves which are simply stented. The leaflets are manufactured with low pressure fixation and mounted in a support frame. This valve is available in sizes from 19 to 29 mm. A PERIMOUNT Plus valve is also available for the mitral position and is available in sizes from 27 to 33 mm.

Non-allograft stentless bioprosthesis lacks a rigid metal stent and therefore should have little inherent gradient across the valve. When implanted, these valves may be supported by the aortic root of the patient using, what is known as, the subcoronary or inclusion cylinder technique. They may also be implanted by fully replacing the aortic root in a manner similar to root replacement with an aortic homograft. Because of the diminished gradient, these valves are felt to be less likely to result in patient-prosthesis mismatch, a condition in which the EOA of an inserted prosthetic valve is too small in relation to the body size of the patient and cardiac output. This results in higher gradients than would be expected from a normally functioning prosthesis. This lack of inherent gradient in stentless valves is thought to result in better ventricular remodeling, or regression of ventricular hypertrophy. The technique of insertion is, however, significantly more complicated than that of stented valves. The currently available stentless valves are all porcine and include the Toronto SPV valve (St. Jude Medical, Inc.), the Medtronic Freestyle stentless aortic bioprosthesis (Medtronic, Inc.), and the Edwards Prima Plus stentless bioprosthesis (Edwards Life Sciences, Inc.). These valves are available in sizes from 19 to 29 mm depending upon the manufacturer.

28.1.3 Bioprosthetic Conduits

28.1.3.1 Xenograft Conduits

The Contegra bioprosthesis (Medtronic, Inc.) consists of bovine jugular vein with an integral, natural, trileaflet venous

valve and a natural sinus slightly larger than its lumen. It is preserved in buffered glutaraldehyde solution and has surgical handling characteristics similar to allograft material. It is available for implantation in the right ventricular outflow tract (RVOT) in patients less than 18 years of age and is available in diameters from 12 to 22 mm. Shelhigh pulmonic (Shelhigh, Inc., Union, NJ) valved conduits are also available in the United States with a Humanitarian Device Exemption (HDE) from the Food and Drug Administration. Both bovine and porcine tissue are available for use in the RVOT and have been treated with a proprietary anticalcification treatment.

28.1.4 Allograft Valves

Allograft valves have now been used for over 40 years and are frequently the only valves appropriate for the smallest of patients. Both cadaveric aortic and pulmonary valves are currently widely used. Sufficient supply of donors may, at times, affect valve availability. Liquid nitrogen cryopreservation has replaced antibiotic storage techniques. Depending upon donor size, all sizes of allografts are available.

28.2 Valve Choice and Outcomes by Location

28.2.1 Tricuspid Valve Replacement (TVR)

Compared with other valves, the tricuspid valve is the least commonly replaced in both adults and children with the most common indications being irreparable Ebstein's type valves or valves destroyed by endocarditis. In general, bioprosthetic valves are preferred for TVR, with most surgeons avoiding mechanical valves in this location because of the very low velocity of flow across the valve. Kiziltan examined the Mayo Clinic's experience with TVR for Ebstein's anomaly and in 149 patients with a mean follow-up of 4.5 years (17.8 years longest) found the survival to be 92.5% at both 10 and 15 years. Freedom from replacement was 97.5% and 60.6% at 10 and 15 years, respectively. Interestingly, the authors found that the reoperation rate for bioprostheses in this location was significantly less than for all other cardiac positions [3]. Husain and Brown in their review of the topic make several recommendations with regard to surgical technique including (1) placing the valve cephalad to the coronary sinus, atrioventricular node, and right coronary artery to avoid compression of these structures; (2) ensuring that the struts of the bioprosthesis straddle the area of the membranous septum and conduction tissue; (3) seating the valve with the heart beating to observe for conduction disturbances; and (4) performance of a right atrial maze at the time of TVR if indicated [4].

28.2.2 Mitral Valve Replacement (MVR)

With the evolution of mitral valve repair techniques, MVR in children is generally only undertaken with the failure of medical management and/or mitral valve repair. The most common indications for MVR in a child are rheumatic disease, endocarditis, mitral stenosis (i.e., Shone's complex), and after failed AV canal repair. Replacement of the mitral valve in children less than 1 year of age should be delayed as long as possible because of the significant morbidity and mortality associated with replacement [5, 6]. MVR carries the highest mortality of any pediatric valve procedure and has a much worse long-term prognosis. The reported operative mortality has ranged from 10 to 30% with 5 and 10 year survival between 50 and 80% [7, 8]. Alexiou observed 14% mortality but further observed that the operative mortality at their institution had decreased to 3.6% in the past decade [9]. It has also been fairly well demonstrated that older children generally do better with MVR [9, 10], whereas others have observed only a 33% survival in 5 and 10 year children, undergoing MVR at an age less than 2 [11]. Many of the issues regarding poor outcomes in younger children are related to considerable risk associated with an increased ratio of prosthetic valve size relative to body weight [12]. Much of the short- and long-term mortality in small annulus sizes is associated with implantation in the supra-annular position. Other risks when attempting to oversize the prosthesis include *subaortic obstruction, prosthetic leaflet entrapment, and conduction block*. Low profile bileaflet valves have become the valve of choice for this location. Bioprosthetic xenografts have been found to have limited durability at the mitral position in children and are currently rarely used. Lower profile or supra-annular aortic valves can be particularly useful for smaller patients. When these valves are used in this location, they are removed from their holder and are "reversed" for implantation. Caldarone's paper developed from the pediatric care consortium examined 139 patients less than age five with a median follow-up of 6.2 years. The median longevity they observed for a mitral valve implanted in a child less than age five was 12.7 years. They found survival to be 79%, 75%, and 74% at 1, 5, and 10 years, respectively. This suggests that most of the mortality occurs in the early period following valve placement [12]. This is confirmed by Alexiou's findings of a 5- and 10-year survival for hospital survivors of 90.3%, again pointing to most of the mortality being incurred in the early postoperative period

[9]. Another group reviewed their experience in patients less than 5 years of age, requiring MVR. In 35 children, they observed an actuarial survival of 51% at 20 years, a surgical mortality of 17%, and a freedom from reoperation of 50% at 10 years [5]. When examining the linearized rate of reoperation following mechanical MVR in children, the incidence has been found to be 3.8% per patient-year with a freedom for reoperation of 85.7% at 10 years, which is similar to that observed by others [9, 13].

Brief mention should be made of the Ross II technique. This technique uses a pulmonary autograft placed in the mitral position. The technique was originally introduced by Donald Ross in 1967. The pulmonary autograft is generally placed within a Dacron graft. Kabbani recently reported on 88 patients aged 4–64 years utilizing this technique. At an average follow-up of 5 years, he reported a freedom from degeneration of 93.4%, freedom from reoperation of 94.2%, and freedom from all death of 86.0% [14].

28.2.3 Pulmonary Valve Replacement (PVR)

Valve replacement, or conduit placement, between the right ventricle and pulmonary arteries is one of the more common operations required for congenital heart disease. The list of indicated operations includes tetralogy of Fallot, pulmonary atresia, d- or l-transposition of the great arteries with pulmonary stenosis, truncus arteriosus, and the Ross procedure. Valved conduits constructed of many of the previously mentioned mechanical or bioprosthetic valves can be obtained commercially or manufactured. More recently, the Contegra bovine jugular vein has seen greater usage in smaller children. This valved vein is also the basis for the "percutaneous" pulmonary valves to be placed endovascularly currently in development. Most commonly used, however, is the pulmonary valve allograft. Implantation of a bioprosthetic valve in the older (adult) patient with tetralogy of Fallot previously treated with a transannular patch has become one of the most common adult congenital heart procedures.

Historically, allografts are the most commonly utilized valves in this location because of size and space limitations, as well as the ease in implantation. With regard to these homografts, the reported results of longevity vary from study to study depending upon age and indication. Some of the more favorable results demonstrate an actuarial freedom from reoperation of 89% at 10 years and 80% at 20 years [15]. Others have reported a substantially lower freedom from reoperation of 81% at 5 years and 70% at 7 years [16]. Allograft freedom from reoperation has, however, been reported to be as high as 85% and 69% at 5 and 10 years postimplantation in pediatric patients [17]. The reasons for potential valve failure include valvular calcification resulting in stenosis and insufficiency as well as patient somatic growth. Endovascular stents can prolong the period of time required for valve reoperation in both the instances by reducing the valve gradient, but always render the valve incompetent. Pulmonary vascular resistance has been found to effect pulmonary homograft longevity in patients with congenital heart disease and may reflect much of the variability seen in homograft longevity. When examining the Ross Registry, or implantation of pulmonary homografts in patients with an otherwise normal pulmonary vasculature, homograft survival to 80% at 25 years has been observed [18]. Obviously, smaller and younger patients are risk factors for RV to PA conduit failure. Patient growth is accompanied by an attendant need for increased pulmonary blood flow resulting in functional stenosis. The freedom for reoperation in neonates implanted with a pulmonary homograft is only 22% at 5 years [19]. Oversizing of the homograft is, however, not a panacea and can result in kinking or compression of the conduit by the sternum. It remains questionable whether allograft longevity is affected by the immune response of the patient to the antigenicity of the allograft.

While there is limited data available for the implantation of mechanical heart valves in the pulmonary position, xenografts have been used extensively. One large series demonstrated a greater freedom from reoperation for porcine valved conduits than either irradiated or cryopreserved homografts. In this series, the Hancock valve in the RV to PA position had a freedom from reoperation of 87% at 5 years, 60.7% at 10 years, and 45.1% at 15 years compared with allograft survival of 65% at 5 years, 37% at 10 years, and 18% at 15 years [20]. In another study, xenograft survival in the pulmonary position has been reported to be comparable with that of homografts with a 10-year survival of 85% [21]. With regard to the Contegra xenograft, short- and midterm results demonstrate a freedom from reoperation that matches or exceeds that for pulmonary homografts [22].

More recently, several studies have been published relative to the use of mechanical valves in the pulmonary position. Historically, there has been little interest in this utilization because of what was thought to be an unacceptably high incidence of valve thrombosis in this location. This notion was based upon several small series, in mostly adult patients, albeit studies related to congenital heart disease have not found this to be the case [23, 24]. Another group proposed the hypothesis that the Monostrut tilting disk valve was less susceptible to pannus ingrowth and obstruction than the bileaflet mechanical valve [25]. Others have not found bileaflet valves to have any greater risk of thrombosis, the greater risk in the earlier studies being due to inadequate anticoagulation. These studies, although relatively small in number and for shorter periods of follow-up, have shown excellent valve function. Based on other published data, one group estimated the risk of reoperation at 15–20% at 10 years

for allografts or xenografts versus a risk of reoperation of 4% at 14 years in their study and a postulated lifetime risk of reoperation at 8% [24]. If these devices were to be used, that would seem to be most applicable to younger patients, though not so young they could "outgrow" their prosthesis. Also appropriate would be those patients who are taking coumadin for other indications, particularly atrial fibrillation or other cardiac prostheses, and those with no contraindication to anticoagulation, which would exclude young women in child-bearing age. The largest group of patients in which the greater implementation of these devices may be helpful are adult patients with tetralogy of Fallot. It is felt that the need for anticoagulation of mechanical valves in the aortic position is greater because the velocity of flow across the valve is less; however, the result of emboli to the lung is perhaps less morbid than systemic embolization. Clearly in counseling patients with regard to valve choice, the incidence of anticoagulation-related hemorrhage and the lifestyle changes have to be considered.

28.2.4 Aortic Valve Replacement (AVR)

In most small and growing children, the Ross procedure has become the standard operation for conditions requiring AVR. This operation which involves the transfer of the pulmonary valve to the aortic position (autograft) and replacement of the pulmonary valve (discussed at length elsewhere in this text) has supplanted much of the debate regarding types of AVR in children. For mechanical valve replacement, a mortality of 6–13% has been reported [26]. Turrentine compared pediatric AVR with pulmonary autografts, mechanical valves, xenografts, and aortic homografts. The survival rate at 10 years in these patients was 95.2% for pulmonary autografts and 87.8% for mechanical valves [27]. Much controversy, however, remains, when discussing AVR in children who are not candidates for the pulmonary autograft (connective tissue disorder, diseased pulmonary valve) or in those teens who have reached their full growth potential.

28.2.5 Mechanical AVR

In a review of 55 pediatric patients undergoing mechanical AVR, the event-free survival at 1, 5, and 20 years was 96, 92, and 88%, respectively. Freedom from reintervention at the same time periods was 98, 96, and 92%, respectively [28]. Another group reported the linearized rate of reoperation for mechanical AVR in children to be 4.2% per patient-year [13]. Lupinetti examined 100 consecutive AVRs at a single institution comparing mechanical to "human" (allograft or autograft) valve replacement with mean ages of 12.1 and 10.4 years, respectively. The 4-year actuarial survival was 83% in the mechanical group and 98% in the human group. When examining freedom from all valve-related complications, the same authors found it to be 61% for mechanical valves and 88% for human valves [29]. Alexiou reported on 56 children with a mean age of 11.2 (range 1–16 years) undergoing mechanical AVR. Mean follow-up was 7.3 years. He reported a 5.3% operative mortality and actuarial freedom from reoperation at 10 and 20 years of 86.4% which is a linearized rate of 1.3% per patient year. The authors do report using aggressive root enlargement techniques to optimize the size valve which they placed. The actuarial survival for the hospital survivors was 96.1% and 89.6% at 10 and 20 years, respectively [30].

28.2.6 Bioprosthetic AVR

28.2.6.1 Xenograft

Currently, there is little enthusiasm for xenograft bioprostheses in the pediatric patient population. They have been associated with high rates of early degeneration, calcification, and structural failure with reoperation rates as high as 50% at 4 years [31, 32]. Ruzmetov examined 174 AVRs over 31 years. This population included xenografts, allografts, mechanical valves, and autografts. The authors found that 60% of all xenografts placed in children had to be replaced at 5 years [33]. Few would argue that this type of valve is a viable option for the pediatric population except in the most limited of circumstances.

28.2.6.2 Homograft

Gerosa, McKay, and Ross compared 143 children undergoing pulmonary autograft or allograft (n = 106) AVR. This group found a 15.6% early mortality, a 16.7% late mortality, and a 54% 15 year actuarial freedom from reoperation in the homograft group [34]. In 336 adult patients undergoing aortic root replacement with 346 allografts, one group found the incidence of reoperation for structural deterioration to be 1.5% per patient year. The rate of deterioration decreased with increasing age at implant. Those implanted with a homograft at age 35 had a 70% freedom from structural valve deterioration at 10 years compared with an 80% freedom when implanted at 45 years, 88% at 55 years, and better than 90% freedom from reoperation if implanted at 65 years [35]. This type of longevity is not seen in children due to somatic growth and a much greater rate of calcium turnover and mineralization in the growing child. Ruzmetov, however, found that only 14% of homografts required replacement at

11 years in a small sample of patients with a mean age of 11 years [33].

While at this point in time allograft replacement of the aortic valve is the preferred operation in most pediatric centers, homograft and mechanical AVR are still commonly utilized with excellent outcomes. Much of the decision-making will be related to the tolerance of both the surgeon and the family to the risks of reoperation but also to the risks of anticoagulation and alterations in lifestyle required by the various choices.

28.3 Complications of Valve Replacement

In deciding which prosthesis should be placed into a given child, as has been discussed, the factors most commonly considered are the expected longevity of the valve, the complication rate, and the impact upon lifestyle. As has been demonstrated above, the longevity of the valve in children is primarily affected by two factors: somatic growth and valve degeneration. The effect of somatic growth is essentially the same for mechanical and bioprosthetic valves when compared to valves which have the potential for growth (autografts). Valve degeneration is particularly affected by the age of the patient, with an increasing rate of calcification in younger patients who have greater rates of calcium metabolism and turnover. The incidence of complications particularly thrombosis, thromboembolism, and bleeding complications or anticoagulant-related hemorrhage (ARH) does vary by valve type as well as valve location and can be considerable. For instance, in Beierlein's paper on the long-term follow-up of mechanical MVR in children, it was found that the freedom from all adverse events, including death, redo MVR, bleeding, thromboembolism, and endocarditis, was 45% and 17% at 5 and 10 years, respectively [11]. This means that, based on the rates observed in this study, nearly all children will have some complication, or require replacement, of their MVR in the 10 years following valve replacement. These risks have been best calculated in adult patients in large studies, while much smaller series of children provide the currently available information for this age group. Extrapolation from adult data is reasonable, but certainly is not an exact surrogate for the rates of pediatric complications. This is related to age, comorbidities, and other risks faced by the adult population as well as differing flow characteristics in different-sized patients.

The following examines the most common risks of prosthetic valve placement, their incidence in the adult population, and the available data for the pediatric population.

28.3.1 Thrombosis

In adults, thrombosis of the valve is an unlikely complication of mechanical or bioprosthetic valve replacement. In a large series of patients with the SJM bileaflet valve, the incidence of valve thrombosis was reported as 0.2% for AVR and 0.5% for MVR. In this series, the calculated incidence was 0.06% per patient-year for AVR and 0.18% per patient-year for MVR [36]. If one considers within the population of patients with thrombosis the nonstructural dysfunction of the valve, the incidence of valve failure in pediatric patients is probably much higher. This is related to pannus ingrowth particularly with regard to the mitral valve. Location plays a role in the incidence of mechanical valve thrombosis. Thrombosis of mechanical tricuspid valves has been reported to be 20 times more frequent than left-sided valves, and mechanical mitral valves develop thrombosis at a rate 2–3 times greater than aortic valves. In one series, the failure rate for MVR in children because of this ingrowth was as high as 31% [13]. Valve thrombosis is generally manifested by pulmonary congestion, evidence of decreased cardiac output, or systemic embolization. Patients generally have an acute deterioration, but at times there can be a slower onset of deterioration. Once the diagnosis is made, intravenous heparin therapy should be initiated. Depending upon the size of the thrombus, further therapy with fibrinolysis or surgery should be considered. Thrombolytic therapy, in adults, has been reported to have a success rate of 70% and a mortality of 9–10% but also carries a high risk of embolization and is reserved for critically ill patients with a highest risk of operative mortality [37]. Generally, pediatric patients should undergo valve replacement when presenting with this condition.

28.3.2 Thromboembolism

The incidence of thromboembolism of the SJM valve in adult patients has been reported as 1.9% per patient-year for AVR and 2.8% per patient-year for MVR. Shanmugam in a series of 55 pediatric patients with AVR and a mean follow-up of 12 years found no incidence of thromboembolism [28]. In examining 32 pediatric patients with both AVR and MVR, Sachweh found the incidence of thromboembolism to be 1.2% per year for both AVR and MVR [13]. Cannegieter in examining a large adult series including multiple types of mechanical valves found the incidence in adults of major embolization to be approximately 4% per patient-year with no anticoagulant therapy, 2% per year with only antiplatelet

therapy, and 1% per year with coumadin therapy [38]. Others have reported the rates of thromboembolism from 0.7 to 6% per patient year. Alexiou in examining the rate of thromboembolism in children with mechanical AVR found a linearized rate of 0.3% per patient-year [30]. The same author observed an incidence of 0.9% per patient-year in children following MVR [9]. Mazzitelli reported a 20-year freedom from thromboembolism of 91.2%, and Iyer reported the same variable to be 98.8% at 8 years [39, 40]. Champsaur and Milano reported linearized rates of thromboembolism to be 0.3% and 0.7% per patient year, respectively, in children [26, 41]. Based on this information, it would appear that the rates of thromboembolism in children undergoing mechanical AVR are less than in adults. This could be attributable to the lack of comorbidities which affect the rates of thromboembolism, such as atrial fibrillation which is less common in children. Additionally, children do not generally have other risk factors for stroke, not related to mechanical valve replacement, such as atherosclerotic disease, diabetes, and smoking. Poor ventricular function also increases the incidence of thromboembolism and may be present in children or adults.

28.3.3 Bleeding

Bleeding complications for prosthetic valves are related to long-term anticoagulation, generally with coumadin. Obviously, this risk is obviated by the lack of an anticoagulation requirement in those patients with bioprosthetic valves. Many authors will therefore refer to this complication as ARH. In Emery's review of over 4000 patients receiving the SJM valve, in adults this incidence was reported to be 2.7% per patient-year for AVR and the same for MVR [36]. When examining 41 pediatric patients implanted with mechanical valves in either the aortic or mitral position, Larsen observed no episodes of thrombosis or thromboembolism but an 11% incidence of ARH which is translated to an occurrence of 1.4% per patient-year [42]. In another series of 55 pediatric patients with AVR, the linearized rate of bleeding was found to be only 0.15% per patient-year [28]. This low incidence of ARH in children has been described by others and linearized to 0.65% per year for MVR and 0% per year for AVR [13]. Generally, the incidence of ARH is felt to be higher for MVR than AVR because of the necessity for higher INRs in these patients. Alexiou found the incidence of all bleeding complications in children to be 0.3% per patient-year following AVR, with no life-threatening bleeding episode [30] which has been confirmed by several others. In examining long-term follow-up for children following MVR, Beierlein found the freedom from important bleeding events to be 76% and 71% at 10 and 15 years, respectively [11]. For MVR in children, as in adults, the incidence of ARH is higher due to higher INRs (0.9% per patient year) [9]. While popular medical consensus would be that, anticoagulation of children is more difficult than adults, with regard to bleeding complications the data above suggest that children have equal to slightly lower incidences of ARH when being anticoagulated for mechanical valves.

28.3.4 Mechanical Failure

As discussed above, structural deterioration of bioprosthetic valves is an inevitable consequence of their utilization in the human. This incidence is nonlinear with deterioration and subsequent "failure" increasing a much greater rate after a certain period of time. In children this time frame is often very short. Mechanical valves on the other hand should have no incidence of intrinsic valve failure. While there have been notable exceptions in the past of valve failure, all of the currently marketed valves have been used for extended periods of time and demonstrated excellent durability [43].

28.4 Management

28.4.1 Anticoagulation

The same anticoagulation guidelines that have been developed for adults in regard to INR have been recommended for children. The Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines confirmed this finding based on published reports. They further recommended the addition of aspirin in those children with a lack of response to vitamin K antagonists or with a contraindication to the administration of the full dose of vitamin K antagonists [44]. The same conference, in an evidence-based review of the literature, recommended a target INR of 2.5 (range 2.0–3.0) for mechanical aortic valves and a target INR of 3.0 range (2.5–3.5) for mechanical mitral valves in the absence of additional risk factors [45, 46]. Because of the smaller numbers of patients, there are no currently guidelines with regard to anticoagulation of mechanical pulmonary valves, but most would treat for a higher INR as in the case of the mechanical mitral valve. Systematic follow-up of INR as part of an anticoagulation program is beneficial to both the patient and clinician.

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Chapter 29
Hypoplastic Left Heart Syndrome

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Abstract Hypoplastic left heart syndrome (HLHS) is the most common severe congenital heart defect comprising 1–2% of all congenital heart defects and 7–9% of all anomalies diagnosed within the first year of life. It is also the most common congenital cardiac malformation involving a single ventricle. It is encountered more frequently in males than in females, with a 67% male predominance. It is a uniformly fatal condition without surgical intervention, and 95% of these infants will have died within the first month of life. In most children with HLHS, the cause of this severe malformation is not known, and multifactorial mode of inheritance is likely for most cases (Freedom RM, Black MD, Benson LN, *Moss and Adams Heart Disease in Infants, Children, and Adolescents*. Lippincott Williams & Wilkins 1011–1025, 2001). It typically occurs sporadically in otherwise normal infants. In some children, HLHS is known to be genetically determined. These cases may be due to mutations in the GJA1 gene on chromosome 6q22 with autosomal recessive inheritance (HLHS1) or the NKX2-5 gene on chromosome 5q35.1 with autosomal dominant inheritance (HLHS2). Somatic mutations in the HAND1 gene have been identified in tissue samples from patients with HLHS [2, 3]. HLHS has also been reported in association with certain genetic disorders including Turner syndrome, Jacobsen syndrome, trisomy 13, and trisomy 18 (Martinez Crespo et al. Ultrasound Obstet Gynecol 21:490–493, 2003; Ye et al. Hum Mol Genet 19:648–656, 2010; Reis et al. Obstet Gynecol 93(4):532–535, 1999).

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29.1 Anatomy

HLHS (Fig. 29.1) defines a spectrum of cardiac abnormalities with a hallmark of hypoplasia of the left ventricle and ascending aorta. The aortic and mitral valves are also usually abnormal and could be affected to a variable extent from stenosis to hypoplasia and complete atresia. A large patent ductus arteriosus is usually present. The ventricular septum is usually intact. The exact cause of hypoplastic left heart syndrome is unknown. Most likely, the primary abnormality occurs during aortic and mitral valve development secondary to an inflammatory or ischemic event in utero the valves fail to develop normally. Minimal or absent blood flow because of aortic and mitral valve atresia does not allow growth of the left ventricle to occur. Studies that were performed earlier in lambs utilized mechanical alteration of blood flow in an early developmental stage as a means to induce development of HLHS like ventricular

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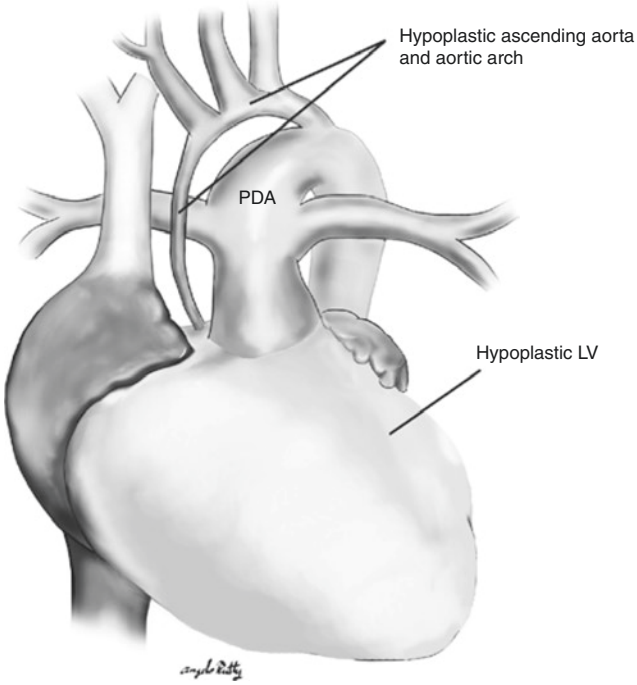

Fig. 29.1 Hypoplastic left heart syndrome

structures. In one of such studies, ventricular blood flow in fetal lambs during mid-gestation was altered through partial obstruction of left ventricular inflow or outflow [7]. Lambs with LV inflow obstruction showed decreased weight ratio of LV/RV as well as a decrease of about 50% in ventricular mean volume, mimicking the left ventricular HLHS phenotype in humans. Obstruction of the LV outflow tract showed a similar trend with a decrease in left ventricular volume and an increase in wall thickness. An artificial increase in LV afterload in this model caused hyperplasia of the left ventricular myocytes and thereby a large gain of LV mass. These findings suggest a more complex concept than "no flow-no grow" and highlight the ability of ventricular myocytes to induce localized proliferation due to external signals like shear stress and tension [8]. Another theory suggests that HLHS is caused by a premature closure or absence of the foramen ovale. This would eliminate fetal blood flow from the inferior vena cava to the left atrium, thus resulting in underdeveloped and small structures downstream. Growth and development of ascending aorta is affected in a similar way. The ascending aorta is frequently so diminutive that it mostly functions as a common coronary artery receiving its blood supply in retrograde manner from PDA.

Associated congenital heart defects:

- Coarctation of the aorta.
- Interrupted aortic arch (rare).
- Total or partial anomalous pulmonary venous return.
- Coronary artery abnormalities, coronary-cameral communications, and tortuosity were found to be associated with the mitral hypoplasia and aortic atresia [11]. Reports of coronary arteries originating from pulmonary artery are also found in literature [12, 13]. Ventricular septal defect is not considered a prominent part of HLHS complex, although it may be present in the HLHS variant of mitral atresia with normal aortic root, DORV with mitral atresia, and AVC defects.

29.2 Pathophysiology

The newborn infant with HLHS has a complex cardiovascular physiology. All patients with HLHS have ductal dependent systemic and coronary flow (unless proximal coronary arteries are arising from pulmonary artery trunk). Systemic venous return to the right atrium is mixing with the well-saturated pulmonary venous blood returning through PFO/ASD from the left atrium. While the left-sided structures are hypoplastic, pulmonary venous return must obligatorily shunt across the atrial septum. A severely restrictive or intact interatrial communication therefore results in marked hypoxemia and pulmonary venous congestion [9]. Pathologic findings of the lung vasculature include "arterialization" of pulmonary veins and lymphatic dilation. The severity of the changes is associated with the degree of interatrial restriction [10]. In the situation where PFO/ASD is absent, there might be concomitant total anomalous pulmonary venous connection. The normal pathway for the pulmonary venous return is absent or severely obstructed due to atresia, hypoplasia, or stenosis of the mitral valve. Therefore, systemic desaturation refractory to oxygen administration is almost always present because of complete mixing of pulmonary and systemic venous blood in the right atrium. In HLHS the right ventricle is a pumping chamber for both the pulmonary and the systemic circulations that are connected in parallel, by the ductus arteriosus. The proportion of flow to the pulmonary (Q_p) and systemic circulation (Q_s) depends on the pulmonary and systemic vascular resistances, and in order for a neonate to survive in the preoperative period, the two circulations have to be delicately balanced to achieve the most perfect ratio of $Q_p/Q_s = 1$.

Closure of the ductus arteriosus leads to the systemic and coronary underperfusion with profound metabolic acidosis and death.

Within 24–48 h, if ductal flow is maintained by PGE administration, the pulmonary vascular resistance starts to decrease, which increases Q_p to Q_s ratio. Although increased pulmonary blood flow results in higher oxygen saturation, systemic blood flow is decreased. Perfusion becomes poor,

and metabolic acidosis and oliguria may develop. Coronary artery and cerebral perfusion also are dependent on systemic blood flow through the ductus arteriosus. Therefore, increased pulmonary blood flow and increased saturation come at the expense of flow to the coronary arteries and brain as well, with a risk of myocardial and cerebral ischemia. The Q_p/Q_s ratio close to 1 is maintained when the systemic saturation is between 70 and 85% and P_aO_2 is between 30 and 40 mmHg [14].

29.3 Clinical Presentation

It has been suggested that prenatal recognition and delivery at or in close proximity to the center skilled in the care of critical congenital heart disease increases infant's chances for survival [15]. Infants with HLHS typically presents within the first 24–48 h of life. Most neonates are full term and initially appear normal. Infants present as ductus arteriosus begins to close with symptoms of decreasing systemic blood flow quickly progressing to shock (hypothermia, poor feeding, lethargy, tachycardia, tachypnea, grayish skin color, hepatomegaly, and weak pulses). Without prompt recognition and intervention, death ensues rapidly. Once the ductal patency is established and with resolution of shock, HLHS mostly manifests as tachycardia, tachypnea, and variable degree of cyanosis. Infants with pulmonary venous obstruction (absent or restrictive patent foramen ovale, obstructed total pulmonary anomalous venous return) may present sooner with symptoms of respiratory failure and severe cyanosis. Occasionally an infant with persistence of high pulmonary vascular resistance and the patent ductus arteriosus may present later because of balanced pulmonary and systemic blood flow. Auscultatory findings are usually nonspecific: single second heart sound, soft systolic ejection murmur of increased flow auscultated over pulmonary artery, occasional apical mid-diastolic murmur of increased flow across the tricuspid valve, and third heart sound gallop.

Chest radiograph is not specific for HLHS: right atrial enlargement, cardiomegaly, and pulmonary vascular markings ranging from lacy reticular pattern to frank pulmonary edema in infants with obstructed pulmonary venous return could be seen.

29.3.1 ECG

The electrocardiogram typically shows sinus tachycardia, right-axis deviation, right atrial enlargement, and right ventricular hypertrophy with a qR configuration in the right precordial leads. A paucity of left ventricular forces is noted in the left precordial leads [1].

29.3.2 Echocardiography

Echocardiographic diagnosis is relatively simple and all views are usually utilized. Once HLHS is suspected, the study should focus on the following aspects:

1. Morphologic variant of HLHS (aortic valve hypoplasia, stenosis, or atresia; mitral valve hypoplasia, stenosis, or atresia)
2. Right ventricular dimensions, thickness, and systolic function
3. Presence and severity of tricuspid regurgitation and pulmonary regurgitation
4. Ductal patency
5. Presence of coarctation, diameter of the ascending aorta and transverse aortic arch, and direction of flow in the ascending and transverse aorta
6. Direction and magnitude of shunts (left to right at the PFO/ASD, right to left at the PDA, presence of restriction of the atrial septum)
7. Direction of the systemic and pulmonary venous return [16]
8. Presence of ventriculocoronary communications and other coronary anomalies

29.4 Preoperative Management

Due to complexity of physiology and extent of monitoring, the preoperative management should always take place in the neonatal, pediatric, or, preferably, cardiac intensive care unit. The ultimate goal of preoperative management is to provide adequate systemic blood flow while limiting effect of unbalanced circulation (pulmonary overcirculation) [14]. Appropriate venous access includes central venous line, preferably umbilical venous line or a peripherally inserted central catheter (PICC) for continuous PGE infusion and total parenteral nutrition administration. It is safe and effective to administer PGE through a good peripheral line while obtaining central venous access. Arterial access may constitute peripheral or central umbilical arterial line that could be discontinued after initial stabilization of the patient. Frequent serial blood gas monitoring is mandatory. EKG, saturation, invasive blood pressure, and CVP should be monitored continuously. We currently routinely use near-infrared spectroscopy sensors (NIRS) for continuous monitoring of regional cerebral and renal tissue oxygenation index (rSO2) as an additional window into adequacy of systemic perfusion.

- *Medical care:*
  1. PGE infusion.
  2. Correction of metabolic acidosis with sodium bicarbonate 1–2 meq/kg/dose.

3. Prevent systemic underperfusion by limiting pulmonary overcirculation.

   – Addition of nitrogen or carbon dioxide to the inspired gas delivered via regular nasal cannula, high flow nasal cannula, or hood [14].
   – Hypoventilation with resultant increased pulmonary vascular resistance can be accomplished by intubation, sedation, and mechanical hypoventilation, although it is preferable not to intubate these infants in preoperative period.
   – Diuretics in therapeutic doses are helpful in management of pulmonary overcirculation and fluid retention.
4. Inotropic support is needed infrequently. It might be indicated in severely ill neonates with concurrent sepsis or low cardiac output in early postnatal period and severe acidosis.

   Epinephrine in low to moderate doses 0.02–0.1 μcg/kg/min has been used as an inotropic agent for support of neonatal myocardium.

   Dopamine 3–5 μcg/kg/min has also been found to be sufficient.

   Calcium chloride 10% (5–20 mg/kg/h) and calcium gluconate (100 mg/ml) (10–50 mg/kg/h) infusions may also be utilized in the early postnatal period as inotropic agents due to finding of neonatal myocardium to be more dependent on extracellular calcium for myocardial contractility [17].
5. Systemic afterload reduction with milrinone infusion 0.125–1 μcg/kg/min is currently used to avoid systemic underperfusion while reducing myocardial workload and improving inotropy and lusitropy. Nitroprusside 0.5–4 μcg/kg/min is used as well if infant could tolerate it without hypotension.
6. Intravenous antibiotics are indicated if the infant is at risk for perinatally acquired infection and when clinical suspicion of concurrent sepsis is high.

- *Cardiac catheterization:*
  Cardiac catheterization is no longer indicated prior to stage I, unless infant for various reasons is not a candidate for Norwood stage I repair and temporary palliation with ductal stenting, while awaiting heart transplant is necessary as a part of hybrid procedure. Elective catheterisation in SV patients is frequently performed in US congenital cardiac centers. In the study by Goldstein et al., cases were found to be more commonly diagnostic in the pre-BCPA (*bidirectional cavopulmonary anastomosis)* cohort (57%), whereas they were more commonly interventional in the pre-Fontan (69%) and post-Fontan (77%) cohorts [18].

29.4.1 Pre-BCPA (Stage II) Procedure

Left and right heart catheterization with hemodynamic measurements and several angiograms are done routinely at 4–5 months of age. If a clinical progress is lacking or echocardiographic data are indicative of a problem developing in the area of neoaorta or pulmonary artery, catheterization should be done earlier. Anatomy and first-stage procedure will dictate approach to angiography. Usual access is through the femoral vessels.

1. Norwood + BTS
2. Norwood + RV-PA conduit (Sano modification)
3. Hybrid approach (PA bands, PDA stent, ASD creation)

1. Superior vena cava and common atrium – to identify possible left superior vena cava (could serve as a decompressing collateral of the Glenn circulation and lead to significant desaturation) and presence of gradient between left and right atrium, necessitating atrial septectomy.
2. Right ventricle – for evaluation of right ventricular function, filling pressure, and presence of tricuspid regurgitation.
3. Aortic arch – to rule out recurrent aortic coarctation in an area of native-to-neoaortic anastomosis, neoaortic regurgitation, and in search of aortopulmonary collateral vessels for potential coil occlusion.
4. Right or left Blalock-Taussig shunt should be imaged to show pulmonary artery size, presence of possible distortion, and distribution.
5. Hemodynamic measurements – cardiac output and pulmonary vascular resistance to ascertain patient's suitability for the stage II procedure.

29.4.2 Pre-Fontan (Stage III) Procedure

The goals of pre-Fontan cardiac catheterizations are similar. Routine catheterization and hemodynamic measurements are done before completion of the operation. Access is through the right internal jugular vein in addition to arterial and venous femoral vessels. Conflicting data exist on the additive value of cardiac catheterization prior to the Fontan procedure. Based on the emerging data, up to 50% of the patients presenting for Fontan completion may be able to avoid routine catheterization safely, but echocardiography-based imaging strategy alone utilized by most of US centers is insufficient to allow proper identification of those who could be evaluated noninvasively [19]. Cardiovascular magnetic resonance is a noninvasive imag-

ing modality which is emerging as important tool for the investigation and management of patients undergoing staged palliation of HLHS [20].

1. Right ventricle – for evaluation of systolic and diastolic right ventricular function and presence of tricuspid regurgitation
2. Transverse aortic arch – to rule out recurrent aortic coarctation and in search of aortopulmonary collateral vessels for possible coil occlusion
3. Pulmonary artery anatomy – by performing an angiogram at the superior cavopulmonary anastomosis
4. PV saturation (AVMs)
5. Hemodynamic measurements – cardiac output, pulmonary vascular resistance, and transpulmonary gradient to ensure patient's suitability for the stage III procedure

29.5 Surgical Management

Without skilled preoperative management and effective surgical correction, HLHS is a uniformly lethal cardiac abnormality within the first few weeks of life. The repair is a series of three operations: the Norwood procedure or hybrid procedure (stage I), the bidirectional cavopulmonary anastomosis procedure (stage II) (Glenn procedure), and the Fontan procedure (stage III) with a goal of surgical separation of pulmonary and systemic circulations where a right ventricle remains the systemic pumping chamber and flow into the pulmonary circulation is passive. For patients with diminished right ventricular function and tricuspid regurgitation that can't be surgically corrected, orthotopic heart transplantation provides an alternative therapy, with results similar to those of the staged surgical palliation.

29.5.1 Norwood Procedure (Stage I)

The Norwood procedure requires cardiopulmonary bypass and a period of deep hypothermic circulatory arrest and/or low flow perfusion. This repair has undergone several modifications over the years, but there are three main basic surgical principles:

1. The construction of a reliable source of pulmonary blood flow (either a modified Blalock–Taussig shunt or a Sano shunt) without causing distortion of the pulmonary arteries.
2. The reconstruction of the transverse aortic arch with the incorporation of the proximal aortopulmonary anastomosis without compromising the coronary bloodflow and/or leaving residual arch obstruction.
3. The creation of a large interatrial communication (atrial septectomy), allowing unobstructed pulmonary venous return into the RA.

There has been a significant effort in trying to determine the best source of pulmonary blood flow for patients undergoing a Norwood procedure. Patients with an RV-to-PA conduit (Sano shunt) have a higher diastolic blood pressure when compared to patients with a BT shunt, which has theoretical advantages (minimizing coronary ischemia) in the management of these patients. However, it is still unclear whether the Sano shunt results in a survival advantage. The operative mortality for the Norwood procedure is 10–20% [22].

29.5.2 Hybrid Procedure

The experiments with hybrid procedure began in the early 1990s [23]. The search for the new technique was prompted by high first-stage and interstage mortality, concern for multiple exposures to cardiopulmonary bypass during traditional staged approach, and need to develop palliative technique for the infants awaiting cardiac transplantation. The procedure is a combination of surgical and interventional approach. Percutaneous stenting of the arterial duct and balloon atrial septostomy are done within the first few days of life in the catheterization laboratory followed by banding of the proximal branch pulmonary arteries, performed through a median sternotomy. An open atrial septectomy may also be done if balloon septostomy was not technically feasible. In the clinical trials of hybrid procedure, patients then had a palliative second-stage procedure that comprised reconstruction of the aortic arch and bidirectional cavopulmonary connection at the age of 3.5 to 6 months [24]. There are later reports of transcatheter Fontan completion with only one exposure to cardiopulmonary bypass, aortic cross-clamping, and circulatory arrest, using hybrid approach. However, authors report 27% mortality after hybrid procedure (hospital mortality and inter-stage) and 41% overall mortality and in a series of 29 patients [25].

Surgical options for stage II and III procedures as well as variations in operative technique and caveats of postoperative management are reviewed in the single ventricle chapter.

29.6 Postoperative Management

Infants are critically ill and unstable immediately after stage I Norwood procedure. Extreme attention to the details, technical sophistication, and sufficient patient volume are all prerequisites for successful patient's recovery.

29.6.1 Monitoring

Infants usually arrive from the operating room with chest open due to significant edema of the mediastinal structures. Invasive monitoring of arterial pressure, CVP, pulse oximetry, and regional cerebral and renal perfusion is done continuously. Arterial blood gases and electrolytes have to be monitored hourly; lactate level and mixed venous saturation (SvO2) should be checked every 2 h at least during first 12–24 postoperative hours or until it is completely normalized.

29.6.2 Respiratory Management

Mechanical ventilation with deep sedation and muscle relaxants is usually utilized. It is our regular practice to discontinue muscle relaxants once the chest is closed. If patient arrives from the operating room with the chest closed, muscle relaxants are usually discontinued within the first 24 postoperative hours. The extubation is usually planned within 24 h after chest closure in the absence of significant residual anatomic or hemodynamic lesions. Causes of pulmonary venous desaturation such as pneumothorax, atelectasis, or effusion should be treated aggressively.

29.6.3 Cardiovascular Management

Low cardiac output state (LCOS) is a significant problem complicating patients' course post-Norwood operation. It usually manifests as poor distal perfusion, oliguria, hypotension, metabolic acidosis, hyperlactatemia, and hypoxemia. Inotropic support with low-dose epinephrine (up to 0.12 mcg/kg/min), and occasionally dopamine (3–5 mcg/kg/min), is required. Afterload reduction with milrinone, if tolerated without worsening hypotension, is the mainstay of therapy.

Steroids have also being used to augment treatment of moderate to severe LCOS. There is currently no consensus between treating physicians regarding administration regimen or testing of the adrenal axis pre- and post-administration of steroids [26]. It has been demonstrated, though, that postoperative hydrocortisone reduces low cardiac output syndrome, improves fluid balance and urine output, and attenuates inflammation after neonatal cardiopulmonary bypass surgery [27]. In our center, the current strategy is to use bolus of the hydrocortisone 50 mg/m^2 and subsequent infusion of 50 mg/m^2/day for the patients who are demonstrating moderate to severe LCOS. The infusion is continued until resolution of LCOS and complete wean of epinephrine gtt. Hydrocortisone is then tapered over 3–5 days.

Technical surgical reasons for the LCOS should be sought and addressed promptly if found. Early and preferably semi-elective mechanical support of circulation with venoarterial ECMO is indicated in the cases of LCOS refractory to medical management. Cardiac arrest prevention should be the focus of the entire critical care team. Mortality in the group of patients who suffer cardiac arrest following stage I operation is four times higher than in the group of patients without cardiac arrest [22].

Balancing pulmonary and systemic flow remains the primary goal of postoperative management. Changing pulmonary vascular resistance in the immediate post-bypass period could lead to significant desaturation or systemic steal with resultant volume overload of the right ventricle and systemic hypoperfusion. Manipulation of sedation, mechanical ventilation, and systemic vascular resistance are usually necessary. Saturation of 70–80% with PaO2 30–40 mmHg is appropriate and reflects proper balance of pulmonary and systemic flow.

Bleeding is common after Norwood repair due to multiple suture lines, and transfusion of various blood products is frequently required. Mortality is twice higher in patients requiring reoperation for bleeding [22]. It is beneficial to achieve hemostasis as early as possible, and vigilance is required to replace all coagulation factors, platelets, and red blood cells if there is an ongoing hemorrhage. Fresh frozen plasma (FFP) drip could be utilized during the first 24 h to replace drainage. Thromboelastogram (TEG) provides useful information facilitating the choice of products to be utilized in patients with persistent bleeding.

Feeding is usually started once infant is stable from hemodynamic standpoint. Oral feeding is preferred, but gavage feeding of high-calorie formula 24–27 kcal/oz. is also used with the aim to provide increased caloric density, at least 120–140 kcal/kg/day. At hospital discharge 3–4 weeks after the surgery, most infants remain on afterload reduction with captopril or enalapril, on diuretics for right ventricular volume overload, and on aspirin to prevent thrombosis of the shunt.

29.7 Long-Term Outlook

Since the development of staged approach for the repair of HLHS in the early 1980s, the improvement in long-term outlook for these patients is tightly linked to advances in surgi-

cal technique and care. Better understanding of complex physiology of HLHS and well-structured follow-up care lead to improvement in interstage mortality. The largest report to date on outcome analysis and risk factors for death associated with Norwood procedure was done in 2003 by the Congenital Heart Surgeons Society [28]. Nine hundred eighty-five neonates were enrolled by 29 participating centers between 1994 and 2000. Seven hundred ten patients undergone Norwood procedure, with overall survivals after the Norwood operation of 72%, 60%, and 54% at 1 month, 1 year, and 5 years, respectively. The mortality between stages was reported at 37%. Almost 60% of patients reached cavopulmonary anastomosis stage by the 18 months of age. Risk factors for death occurring before subsequent transition (cavopulmonary shunt, cardiac transplantation or Fontan operation) were identified in three categories:

- Patient-specific variables: lower birth weight, smaller ascending aorta, older age at Norwood operation
- Institutional variables: institutions enrolling less than 10 neonates and 2 institutions enrolling more than 40 neonates
- Procedural variables: shunt originating from aorta, longer circulatory arrest time, and technique of surgical management of the ascending aorta

Of neonates undergoing cavopulmonary shunt, 91% had reached a subsequent transition state by 6 years after cavopulmonary shunt, consisting of Fontan operation (79%), death (9%), or cardiac transplantation (3%). Risk factors for death occurring before subsequent transition included younger age at cavopulmonary shunt and need for right atrioventricular valve repair. From the late 1990s, most large centers have been reporting significant improvement in early mortality after Norwood operation with few centers reporting stage I survival rates higher than 90% [29]. Accumulation of surgical experience with Norwood stage I repair and introduction of Sano modification have changed profile of factors affecting patient's survival. Introduction of Sano modification of Norwood stage I repair (NW-RVPA) as reported by Norwood et al. and Sano et al. as well as other authors has reduced early mortality and interstage mortality related to a more stable and efficient hemodynamics with higher diastolic blood pressure and a lower Qp/Qs ratio [30–32]. Although centers with large surgical volume and significant experience with Norwood Blalock-Taussig shunt modification (NW-BTS) and low stage I palliation mortality for HLHS did not appreciate similar differences in early morbidity and mortality between the NW-RVPA and NW-BTS procedures [33].

In 2005 to 2009, the National Institutes of Health funded a landmark randomized surgical trial, the Single Ventricle Reconstruction Trial, which was conducted via the Pediatric Heart Network and enrolled 549 infants with hypoplastic left heart syndrome across 15 North American centers. The primary aim of the trial was to compare 1-year transplant-free survival of newborns randomized to receive either a modified Blalock-Taussig shunt (MBTS) or a right ventricle to pulmonary artery shunt (RVPAS) as part of the Norwood procedure. The primary study outcome was the rate of death or cardiac transplantation at 12 months compared between the two shunt groups. The results of this trial showed that the RVPA shunt offered greater survival at 12 months (74% for RVPA versus 64% for MBTS). Authors also concluded that after 12 months, available data showed no significant difference in transplantation-free survival between the two groups; in addition, RVPA shunt group had more unintended interventions and complications [22].

A follow- up analysis of the same cohort was published by Newburger et al. in 2014. It demonstrated equivalent survival between the RVPA and MBT groups at 3 years. In addition, RVPAS subjects had slightly worse right ventricular ejection fraction and underwent more catheter interventions with increasing hazard ratio over time.

These results were consistent with the original hypothesis of the adverse effect of a ventriculotomy on performance of a single ventricle over time [34].

Additional longitudinal studies of this cohort will help elucidate complex time dependence of survival between the two surgical approaches.

An emerging new strategy for a subset of patients with HLHS is fetal aortic valvuloplasty. This procedure is appropriate for a specific group of fetuses that fulfill particular anatomical and physiological criteria predictive of a successful recruitment of the left side of the heart. The study by Freud et al. reported outcomes of the first 100 patients to undergo fetal aortic valvuloplasty. Of those, 88 survived to birth and 38 achieved a biventricular circulation. There was 11% fetal demise in this study in addition to the fact that all but one of the biventricular patients required postnatal intervention as well as high frequency of aortic and mitral valve replacement in this cohort [35].

Infants with hypoplastic left heart syndrome and an intact or highly restrictive atrial septum (HLHS-IAS) represent probably the highest risk subset in the entire group of HLHS patients. The mortality for these patients is known to be as high as 50%. Fetal cardiac interventions (FCI) for fetuses with HLHS-IAS have been reported in a few of single-institution series as a therapy that may reduce morbidity and mortality. One of the latest multi-institutional study utilized the International Fetal Cardiac Intervention Registry (IFCIR) to examine fetal and maternal characteristics and neonatal outcome data for FCI in this population. Seventy-two maternal-fetal dyads were included in the analysis; 47 undergone FCI. Fetal demise rate was 13%; no maternal deaths were reported. Overall survival to discharge was poor, 35%

with comparable survival in an FCI and non-FCI group. The 1-year survival in the group that maintained unrestrictive PFO at delivery was 59% versus 19% in non-FCI fetuses. Authors concluded that their analysis confirmed poor survival in this population despite successful intervention [36].

Continuing research is important to evaluate performance of these new techniques as emerging results will be influenced by abnormal myocardium, EFE resection, impaired valvar function, disease of pulmonary veins, and onset of secondary pulmonary hypertension.

Some cardiac centers perform transplantation for management of HLHS. Survival following transplantation has improved as advances in the pre- and postoperative management continue, along with new options for immunosuppression. The overall 5-year survival rate after cardiac transplantation is approximately 70%, or close to the results for surgical approach with staged reconstruction.

Most studies report some degree of neurodevelopmental disabilities in patients with HLHS compared to general population or patients with other single ventricle physiology.

The substrate for it is complex and is likely a reflection of abnormal underlying morphology of the brain such as impaired maturation as well as ongoing cumulative injury [37]. Preoperative magnetic resonance imaging frequently demonstrates ischemic lesions in infants with HLHS. Postoperative magnetic resonance imaging performed in one study demonstrated new or worsened ischemic lesions in 73% of patients, with periventricular leukomalacia and focal ischemic lesions occurring most commonly [38].

In one of the earlier multicenter study by Mahle et al. of neurodevelopmental outcomes of 48 school-age patients who had undergone primary heart transplantation or the Norwood procedure for palliation of HLHS, the mean neurocognitive test results were significantly below population normative values regardless of the surgical approach [39]. The American Heart Association recommendations for surveillance, screening, evaluation, and management strategies to optimize neurodevelopmental outcome in the pediatric congenital heart disease (CHD) population were published in 2012. This consensus statement emphasized the risk of developmental disorders, disabilities, and developmental delays in patients with CHD. It was recommended to conduct periodic developmental surveillance, screening, evaluation, and reevaluation throughout childhood to facilitate identification of significant deficits. Timely identification may allow appropriate therapies and educational modifications to improve academic, behavioral, psychosocial, and adaptive functioning [40].

As the mortality associated with HLHS is decreasing and survival is approaching of that for the other complex congenital heart defects, the neurodevelopmental outcome and long-term quality of life for patients and families with palliated HLHS is becoming a new focus of attention.

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Chapter 30
Single Ventricle: General Aspects

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Abstract This chapter provides an overview of the very basic aspects of the diagnosis and management of patients with single ventricle anatomy or physiology. Specific chapters elsewhere in this book will further discuss the Fontan physiology and the hypoplastic left and right heart syndromes.

30.1 Introduction, Anatomy, and Physiology

Single ventricle anatomy characterizes a large spectrum of complex congenital cardiac defects, with an incidence of 5/100.000 alive newborns, and an equal gender distribution. *Single ventricle physiology* can also be found in some biventricular hearts affected by congenital malformations.

Single ventricles, of left, right, or undefined morphology, are often associated with cardiac malpositions and heterotaxia with levo- or dextro-isomerism. These congenital malformations, complex by definition, may have atrioventricular concordance or discordance, different types of atrioventricular connections, and concordant or discordant ventriculoarterial connections and may be associated with multiple other defects with or without aortic (less frequent) or pulmonary (more frequent) valvular or subvalvular obstruction or both (exceptional).

In the context of heterotaxia, anomalous systemic venous returns (i.e., interrupted inferior vena cava with azygos continuation) or pulmonary venous connections (partial or total anomalous pulmonary venous return with or without obstruction) may also be present and significantly complicate the surgical and medical management of these patients, as well as their outcome.

The atrioventricular connection may be a single inlet (i.e., mitral or tricuspid atresia), a double inlet (two functional atrioventricular valves), or a common inlet (similar to the complete atrioventricular septal defect). Atrioventricular valves may be overriding or straddling across large interventricular communications. Often, the normal and functional ventricle communicates with a rudimentary or undeveloped ventricle through the bulbo-ventricular foramen which plays an important role in the pathophysiology of the single ventricle, when restrictive. Such restriction may be the source of a sub-vascular aortic or pulmonary obstruction depending on the ventriculoarterial relationships. The same principle applies to anatomic forms where complex sub-vascular obstructions, often due to septal muscular conus or fibrous structures, are present.

Ventriculoarterial connections may be concordant or discordant and aortic or pulmonary stenosis or atresia may be found.

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From the functional standpoint, *a single ventricle physiology characterizes any cardiac defect that does not allow a biventricular repair,* including the following:

1. Complex congenital cardiac malformations with a single functional ventricle, with right, left, or undetermined morphology:
   (a) Hypoplastic left heart syndrome (HLHS)
   (b) Right-sided heart malformations:
      (i) Pulmonary atresia with intact interventricular septum and severe right ventricular hypoplasia (non-tripartite ventricle)
      (ii) Tricuspid atresia
      (iii) Severe forms of Ebstein malformation of the tricuspid valve
   (c) Heterotaxia syndromes with left or right isomerism (i.e., Ivemark syndrome)
   (d) "Criss-cross" type anomalies
2. Cardiac defects with significant ventricular unbalance and/or with straddling of the atrioventricular valve:
   (a) Atrioventricular septal defect
   (b) Double outlet right ventricle
3. Cardiac defects with multiple interventricular septal defects ("swiss-cheese" type ventricular septal defects)

Depending on the combination of anatomic features, multiple physiological scenarios may be found, alone of combined:

1. Decreased systemic flow in the presence of left subvalvular and/or valvular and/or vascular obstruction
2. Decreased pulmonary flow in the presence of right subvalvular and/or valvular and/or vascular obstruction
3. High pulmonary flow with pulmonary hypertension if there is no pulmonary protection; this may coexist with left-sided obstructions
4. Restrictive intracardiac mixing at the atrial and/or the ventricular level may be associated with any of the above

30.2 Diagnosis

30.2.1 Clinical

Clinical manifestations of single ventricle depend on the anatomic and physiological characteristics. Most patients are diagnosed in the neonatal period if not on fetal evaluation, particularly those who have a ductal-dependent circulation because of right- or left-sided heart obstruction. These patients present with profound cyanosis or progress toward cardiogenic shock, once the ductus arteriosus becomes restrictive or closes.

Depending on the associated malformations, patients may have a cardiac murmur, usually ejective in nature if there is a vascular obstruction, regurgitant in case of incompetent atrioventricular valves, or continuous if there is a largely patent ductus arteriosus or in the presence of collateral circulation. The first heart sound is usually normal but may be split in severe Ebstein malformation of the tricuspid valve, and the second sound is unique and loud whenever pulmonary hypertension is associated. When there is an obstructive systemic physiology, pulses will be weak, absent, or asymmetrical and the patient will display signs of low cardiac output or shock with progressive letargia, diaphoresis, difficulty to feed, tachypnea and tachycardia, and ultimately poor peripheral perfusion, vasoconstriction, or pallor and profound hypotension and lactic acidosis. When an obstructed total anomalous pulmonary venous return is concurrent, patients rapidly progress to cardiogenic shock in the context of a "white lung" syndrome. An immediate workup is vital to establish a differential diagnosis, namely, with severe pneumonia, streptococci B infection, lung lymphangiectasias, or persistent pulmonary hypertension of the newborn. As a matter of fact, many neonates are admitted with primary suspicion of noncardiac disease – frequently sepsis – and the diagnosis of cardiac disease is evoked in the setting of refractoriness to medical therapy. A similar pathophysiology may be found in patients with hypoplastic left heart syndrome in whom the atrial septal defect is restrictive or even absent, requiring an emergent intervention at birth to enlarge the communication.

30.2.2 Chest X-Ray

Radiological findings are very heterogeneous and depend of the anatomic characteristics and the pathophysiology. Heterotaxic or isomeric forms often show radiological features of situs inversus or ambiguous with left of right isomerism, levo- or dextrocardia. Forms with pulmonary obstruction will present with oligemic lungs. When the pulmonary bed is unprotected, the chest X-ray will display excessive blood flow with increased vascular markings and eventually lung edema as the pulmonary vascular resistances decrease over the first few days of life. The presence of diffuse interstitial infiltrates or a "white lung" aspect strongly suggests an obstructed pulmonary venous return. There may be various degrees of cardiomegaly.

30.2.3 Electrocardiogram

The ECG, although unspecific, may provide information regarding axis deviation and predominance that may be useful in steering the diagnosis. It is also useful to rule out any associated arrhythmias or conduction disorders and is particularly important in patients with heterotaxia or with Ebstein malformation of the tricuspid valve.

30.2.4 Echocardiography

Transthoracic echocardiography remains the cornerstone of diagnosis in single ventricle patients, allowing the fine identification of the anatomical and physiological characteristics of the disease [1]. Echocardiographic evaluation has to be exhaustive, thorough, and meticulous. Figures 30.1, 30.2, 30.3, 30.4, 30.5, 30.6, 30.7, and 30.8 demonstrate some

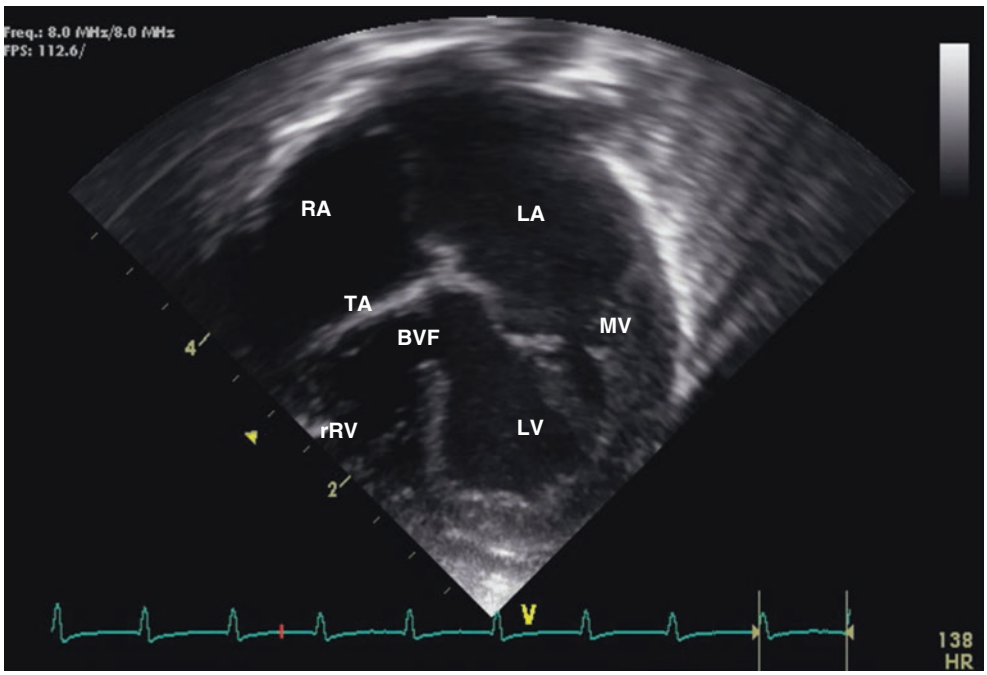

Fig. 30.1 Echocardiography documenting a tricuspid atresia; the ventriculoarterial concordance is not seen in this view. RA right atrium, LA left atrium, MV mitral valve, TA tricuspid atresia, LV left ventricle, rRV rudimentary right ventricle, BVF bulbo-ventricular foramen

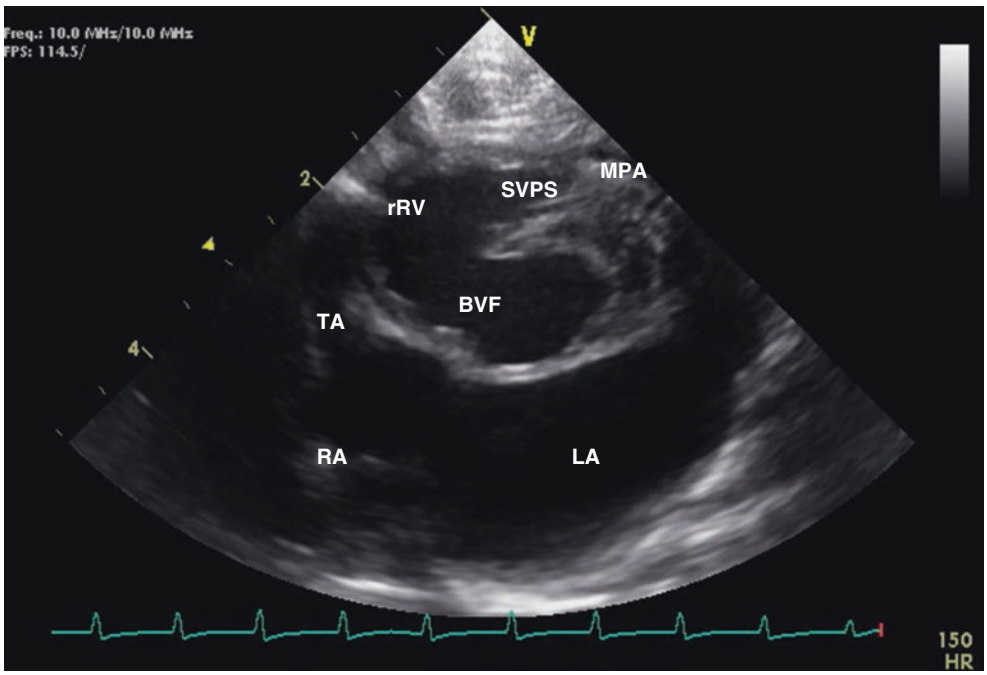

Fig. 30.2 Tricuspid atresia type 1b. LA left atrium, RA right atrium, TA tricuspid atresia, rRV rudimentary right ventricle, BVF bulbo-ventricular foramen, PMA main pulmonary artery, SVPS severe subvalvular pulmonary stenosis

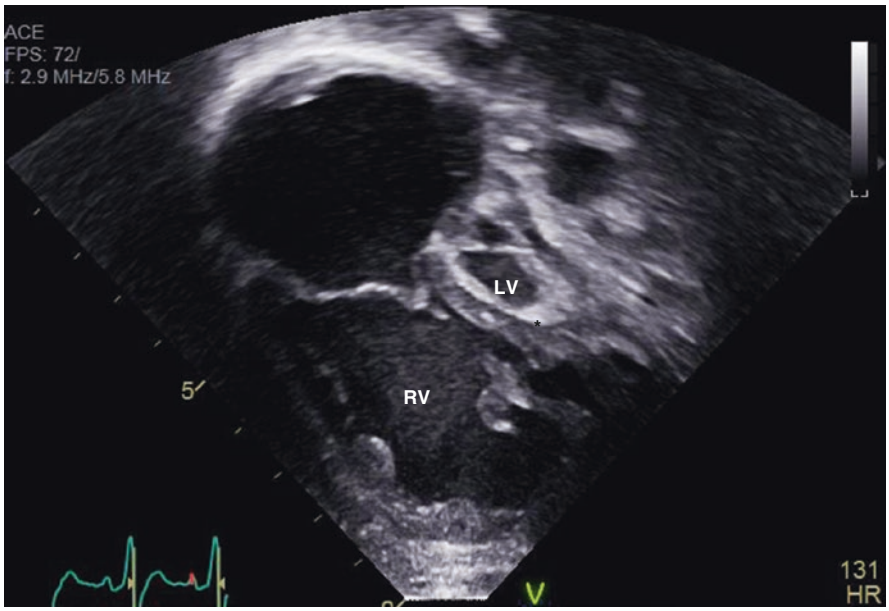

Fig. 30.3 Apical horizontal long-axis view in a patient with hypoplastic left heart syndrome. The systemic right ventricle (RV) can be seen to be appropriately dilated and hypertrophied. The left ventricle (LV) is hypoplastic with an echo-bright myocardium consistent with endomyocardial fibroelastosis

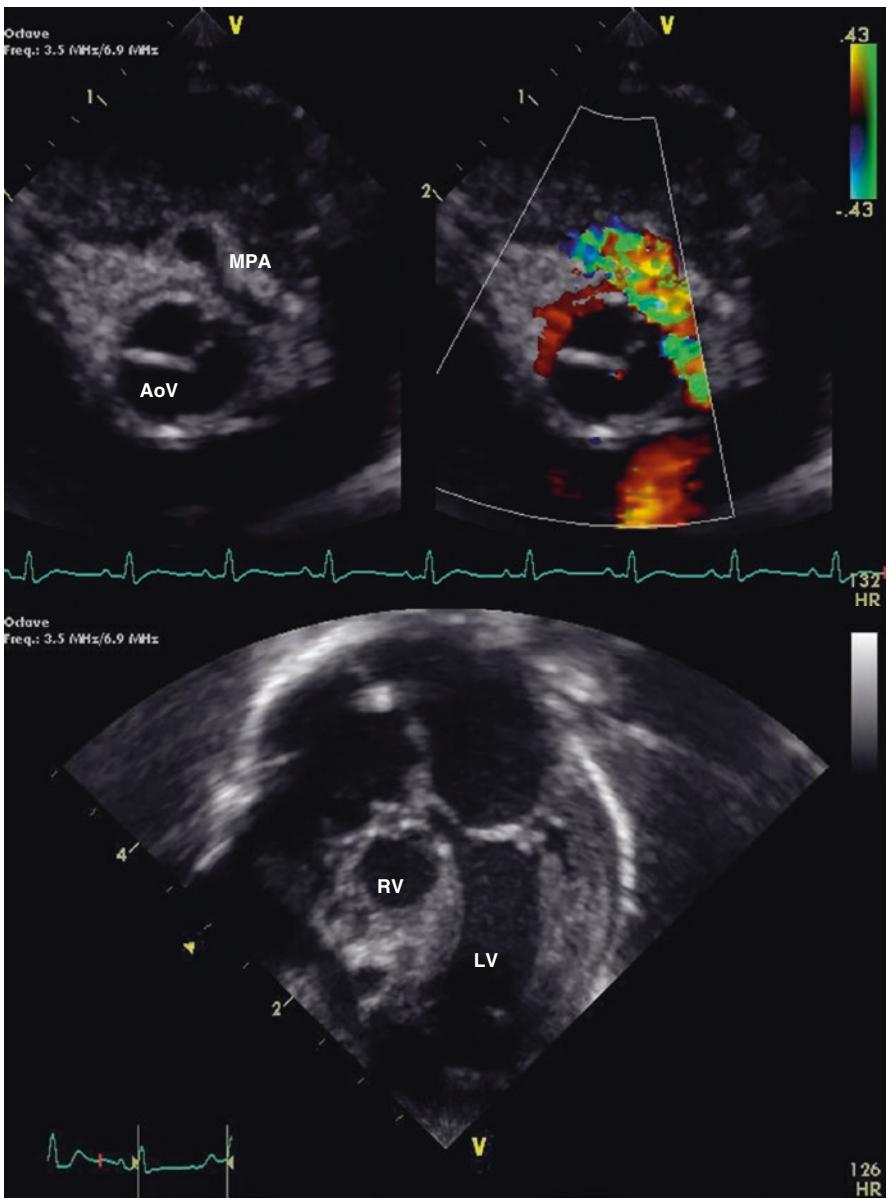

Fig. 30.4 (Panel **a**) Parasternal short-axis view with color Doppler comparison showing an atretic main pulmonary artery (MPA) anterior to the aortic valve (AoV) with retrograde filling from the patent ductus arteriosus (turbulent retrograde flow). (Panel **b)** Apical horizontal long-axis view of the same patient shows a diminutive right ventricle (RV) with no ventricular septal defect

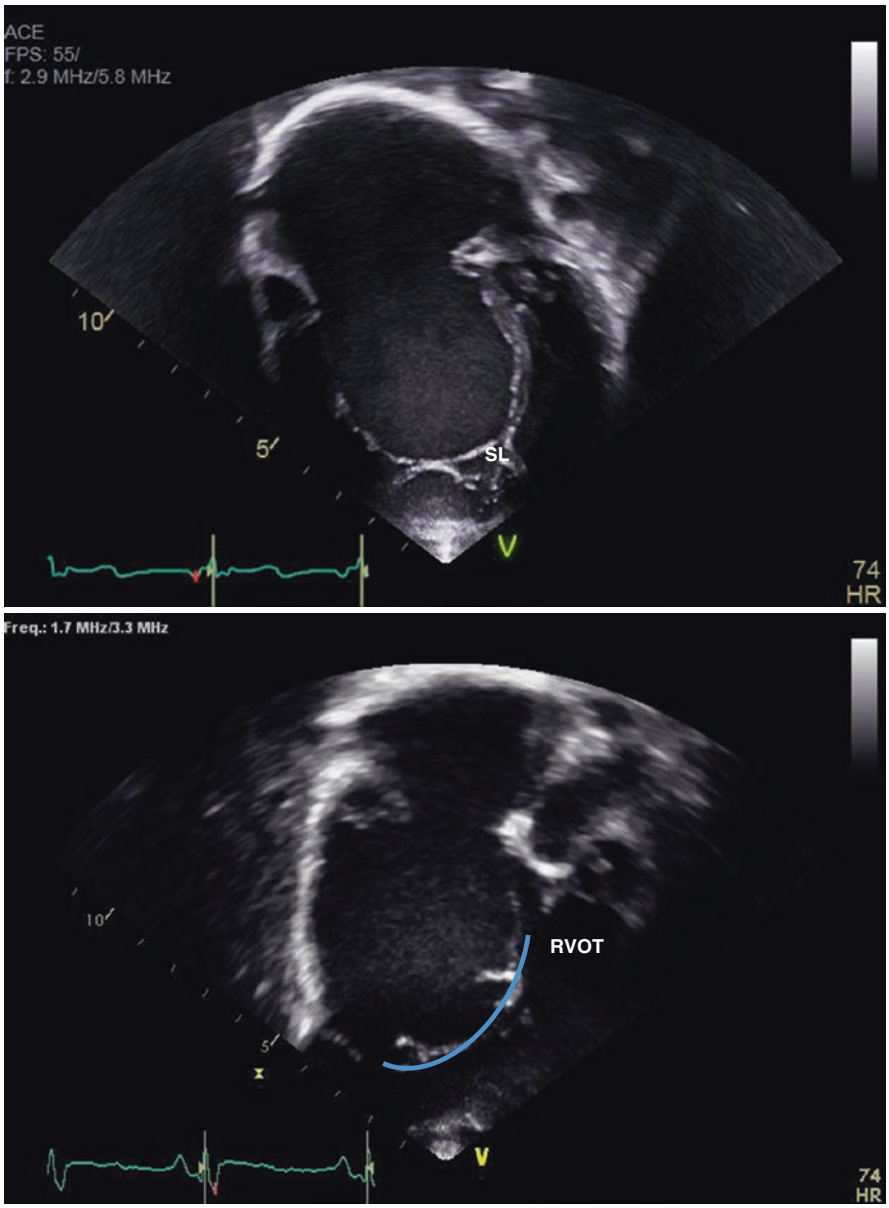

Fig. 30.5 (Panel **a**) Apical horizontal long-axis view showing severe apical displacement of the septal leaflet (SL) of the tricuspid valve. If the displacement is severe, the coaptation plane (line) will not be apparent in apical horizontal long-axis view and will only be apparent in long-axis views of the right ventricle in the right ventricular outflow tract (RVOT) (Panel **b**)

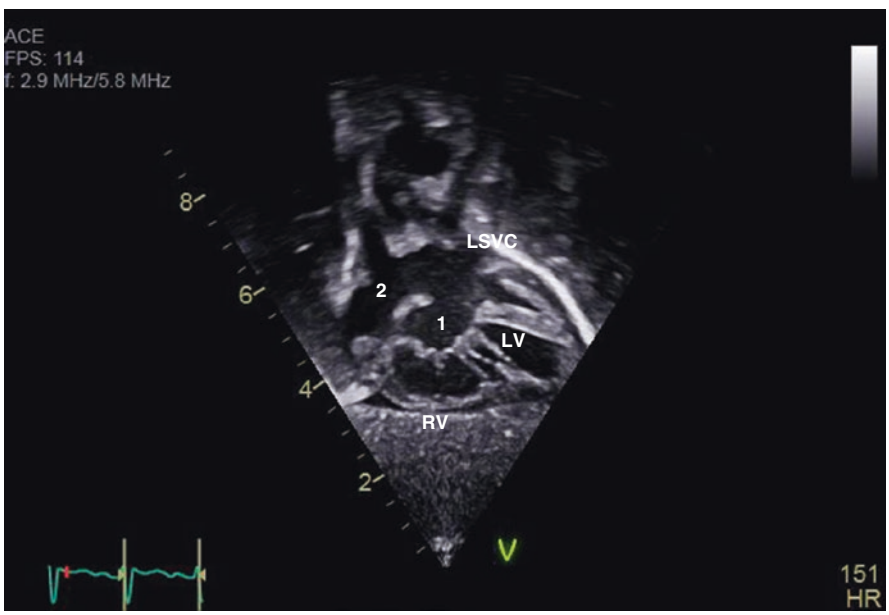

Fig. 30.6 Subcostal coronal view of a patient with right atrial isomerism. This view demonstrates a complete, unbalanced atrioventricular canal with right ventricular (RV) dominance. There is an ostium primum (1) and an ostium secundum (2) atrial septal defect. Also, typical of this lesion, there is a left superior vena cava (LSVC) which connects directly to the roof of the left atrium

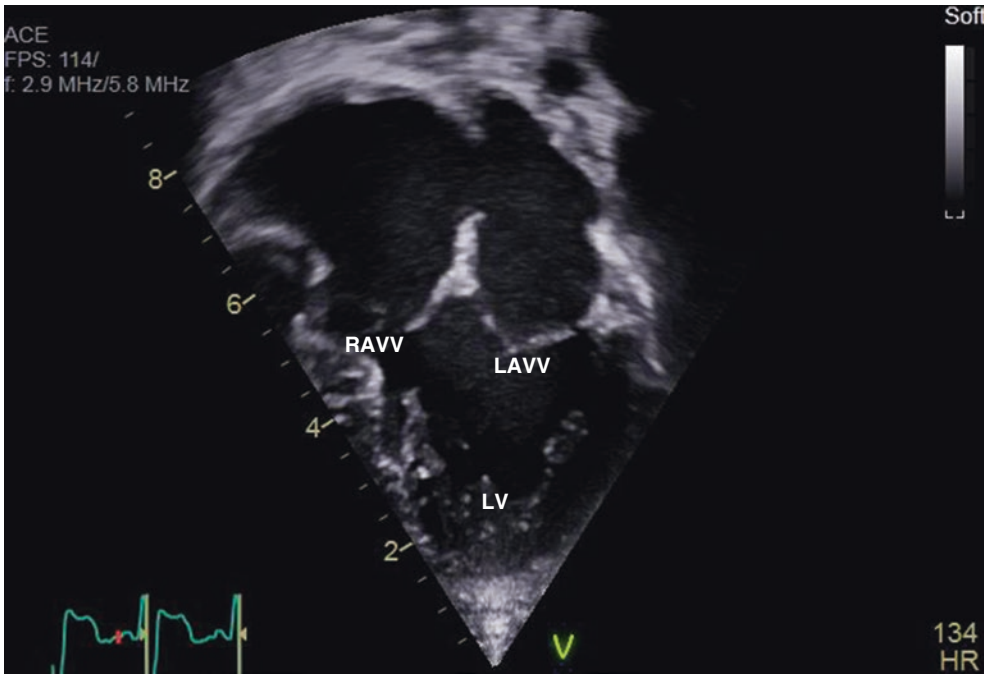

Fig. 30.7 Apical four-chamber view of a patient with double inlet left ventricle. Typical for this lesion, both the right (RAVV) and the left (LAVV) atrioventricular valves connect to a single left ventricle (LV)

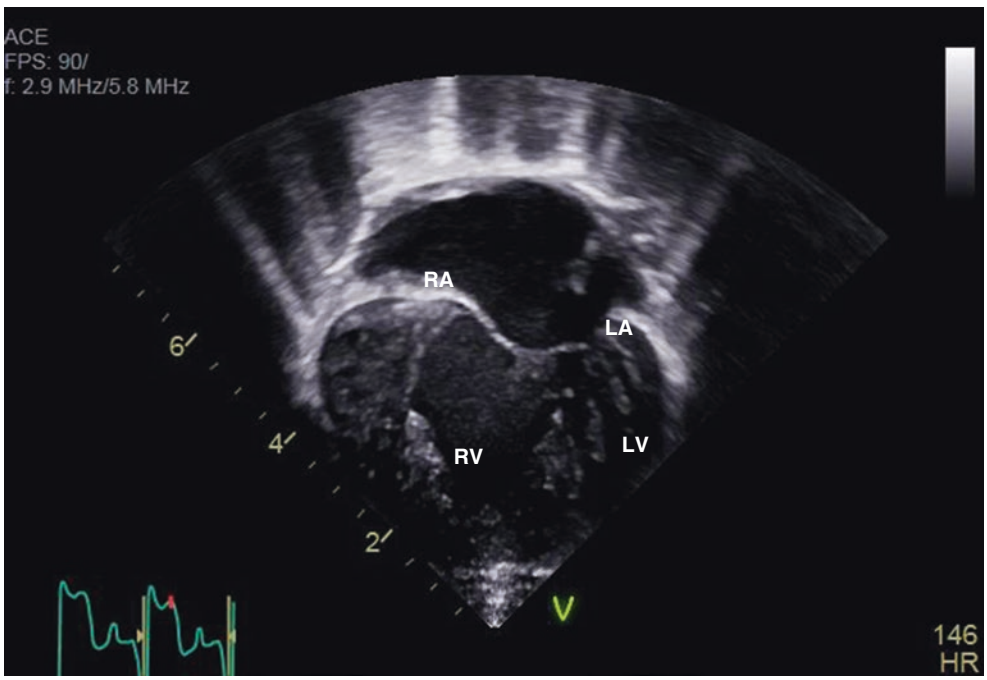

Fig. 30.8 Apical horizontal long-axis view showing a complete, unbalanced atrioventricular septal defect with right ventricular (RV) dominance. There is a common atrioventricular valve committed to the right ventricle and a large ostium primum defect. Note the atrial septum which is shifted to the left resulting in a hypoplastic left atrium (LA). The hypoplastic left ventricle (LV) is difficult to appreciate in this view due to the large inlet ventricular septal defect

examples of single ventricle anatomy. Transesophageal echocardiography is often used in the operating room to further elucidate intracardiac anatomic details and postoperative results.

30.2.5 Cardiac Catheterization

In the neonatal patient, diagnostic cardiac catheterization of patients with single ventricle is seldom indicated unless there is a complex venous return requiring further anatomic clarification or when there are doubts about the pulmonary vascular resistances. Many of these indications for cardiac catheterization are being progressively replaced by advanced noninvasive cardiac imaging like CT scan, CTA, or CMR. Nevertheless, cardiac catheterization remains an important diagnostic assessment of patients awaiting a partial or a total cavopulmonary connection.

Interventional procedures play a very important role in the collaborative management of these anomalies with the

surgical team, or else for electrophysiological studies or interventions. Not infrequently, patients with single ventricle benefit from embolization of collateral vessels and/or balloon dilatation and stent implantation particularly in the pulmonary arteries. Patients with pulmonary vein pathology may also need recurrent interventional procedures. Moreover, hybrid procedures may be indicated in some circumstances, particularly but not exclusively in patients with hypoplastic left heart syndrome.

30.2.6 Advanced Cardiac Imaging

Both cardiac MR (CMR) and cardiac CT have taken a more important role in noninvasive imaging of patients with single ventricle in recent years.

In general, cardiac MRI (Figs. 30.9 and 30.10) produces similar information to echocardiography and CT without the use of ionizing radiation. Using gadolinium contrast, an MR angiogram (MRA) produces a three-dimensional dataset with excellent visualization of both arterial and venous anatomy, without the limitations of acoustic windows. The three-dimensionality of the dataset also allows reformatting in multiple planes which is invaluable in understanding complex anatomy. Cardiac MRI can also produce cine images which are used to visualize cardiac anatomy, valve function, and ventricular function. Unlike volumetric measurements with echocardiography, MRI uses a highly reproducible contiguous slice measurement of ventricular volumes which is not dependent on geometric assumptions. CMR sequences can specifically image for intracardiac or vascular thrombus and myocardial infarction and quantify intracardiac shunts and aortopulmonary collateral flow and lymphatic abnormalities.

Although CMRs produce a wealth of data, they can be lengthy and require multiple breath holds. In patients under 8 years of age, CMR may require sedation and/or mechanical ventilation. It is important to note that a majority of adverse events at two high-volume congenital CMR centers involved single ventricle patients with either BT shunts or right ventricle to pulmonary artery conduits [2–4]. CMR in this patient population requires specialized expertise and should be done in centers with knowledgeable CMR practitioners and experienced anesthesia providers. Pacemakers are common in single ventricle patients and historically have been an absolute contraindication to CMR. Nonetheless, with modern pacemakers and leads, CMR is becoming more a routine in these patients [5].

Similar to a MRA, CTA (Figs. 30.11 and 30.12) produces a three-dimensional dataset which shows venous and arterial anatomy with excellent resolution (e.g., pulmonary arteries, BT shunt, cavopulmonary anastomoses, and coronary arteries). Unlike MRI, CT is generally performed with a single phase (arterial versus venous). Therefore, CT must be carefully planned to highlight the anatomy of interest. Multiple phases can be acquired but this increases the dose of ionizing radiation. With a gated technique, enough phases can be acquired to collect a single cardiac cycle that can be used to calculate ventricular volumes and systolic function. The temporal resolution of this technique is low, so it should be used with caution in smaller patients with higher heart rates. CTA is also particularly useful for visualizing small vessels such as coronary arteries in patients with pulmonary atresia with intact ventricular septum or with major aortopulmonary

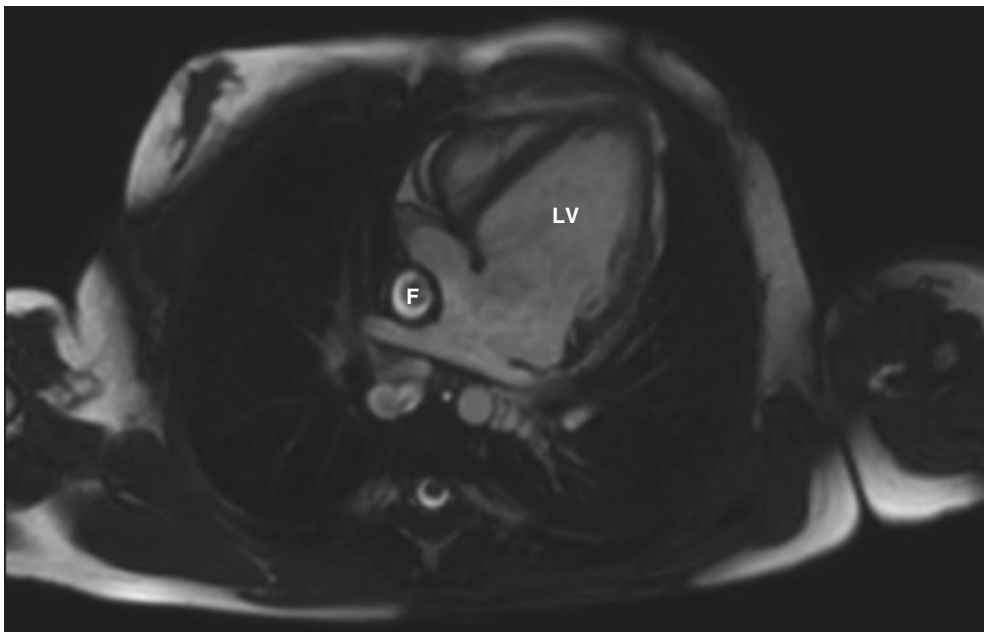

Fig. 30.9 Cardiac MRI showing the apical four-chamber view of a patient with tricuspid atresia. The extracardiac Fontan (F) can be seen in cross section. This kind of imaging can be used to quantify cardiac function and visualize anatomy, valve function, and vascular stenosis

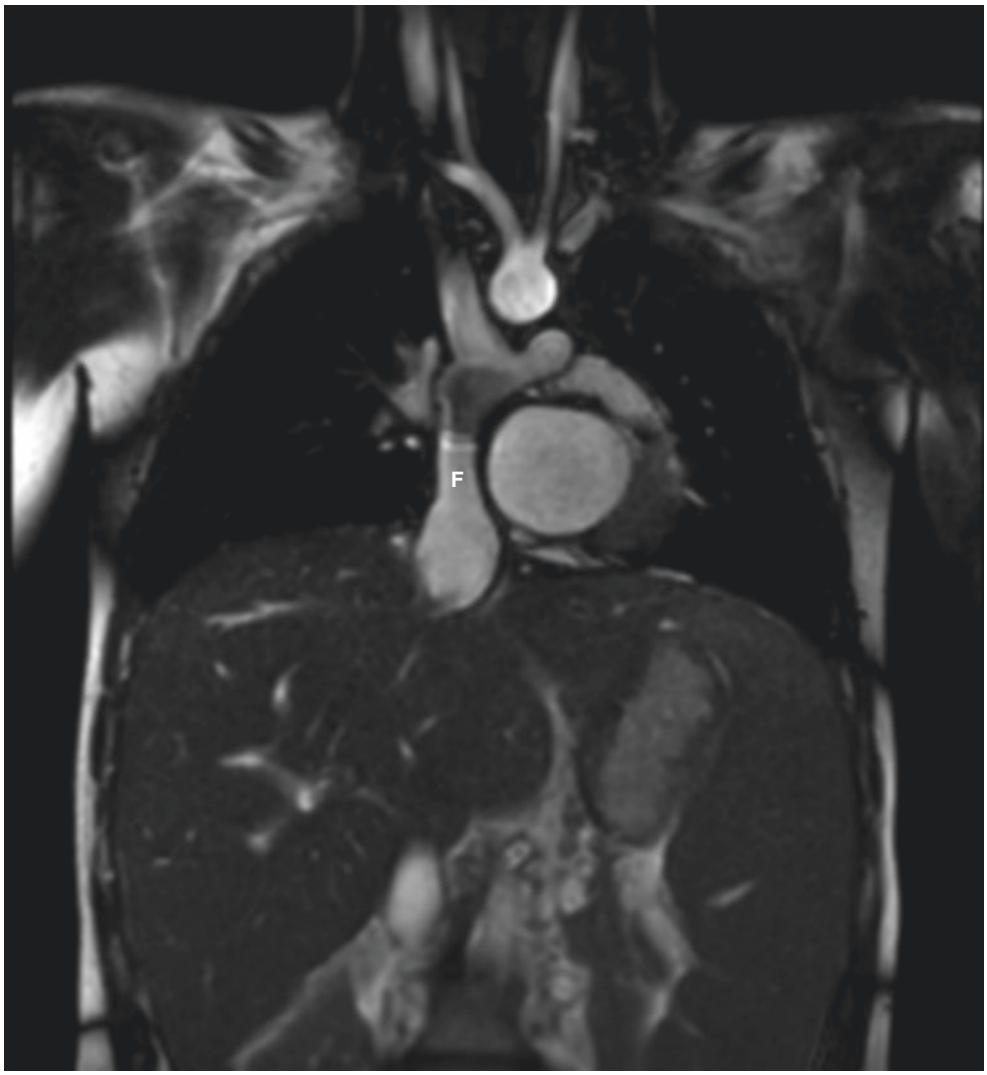

Fig. 30.10 Coronal MRI image showing the entire Fontan pathway. This is an excellent modality for screening for stenosis and thrombus

collaterals in the setting of pulmonary atresia with ventricular septal defect. A major benefit of CT angiography in this patient population who can be clinically unstable is that the scan can be performed very rapidly in a single breath hold. Smaller patients may need to have sedation and/or an artificial airway depending on institutional practices. CTA also produces excellent images of the airway which can be important in this population with a high incidence of airway anomalies. Additionally, CTs can be reformatted to show the three-dimensional relationship between the airway and the vasculature which is important for surgical or catheterization planning.

A drawback to CTA is the use of ionizing radiation in a patient population that will be exposed to numerous radiologic studies (e.g., cardiac catheterization and chest films), so it should be used judiciously.

30.3 Basic Principles of Single Ventricle Management

The concept of univentricular type "repair" implies that patients will need a sequence of palliative interventions steering the therapy toward a common pathway with the ultimate goal of a total cavopulmonary connection (Fontan-Kreutzer procedure) that separates circulations [6–9].

There are essentially three palliative phases or stages, but more interventions are often required through the interphases:

1. Neonatal palliation
2. Partial cavopulmonary connection: modified Glenn connection, bidirectional Glenn connection, hemi-Fontan, or

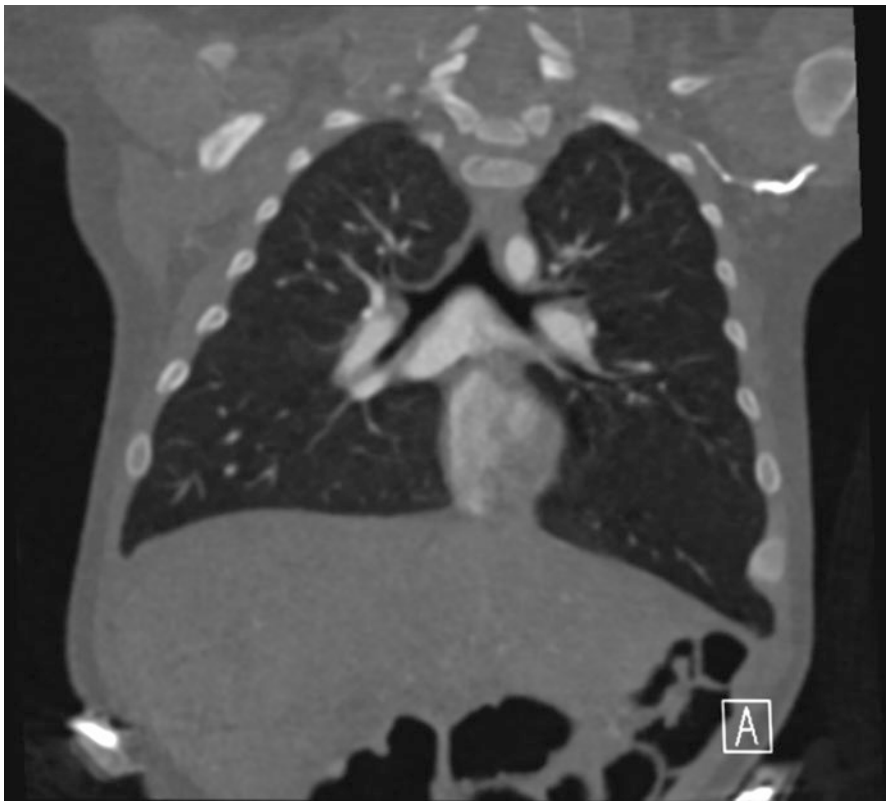

Fig. 30.11 Coronal reformat of a CT scan in a patient with right atrial isomerism which shows bilateral morphologic right airway anatomy with a steep angulation of the mainstem bronchus and an early takeoff of the upper lobe bronchus

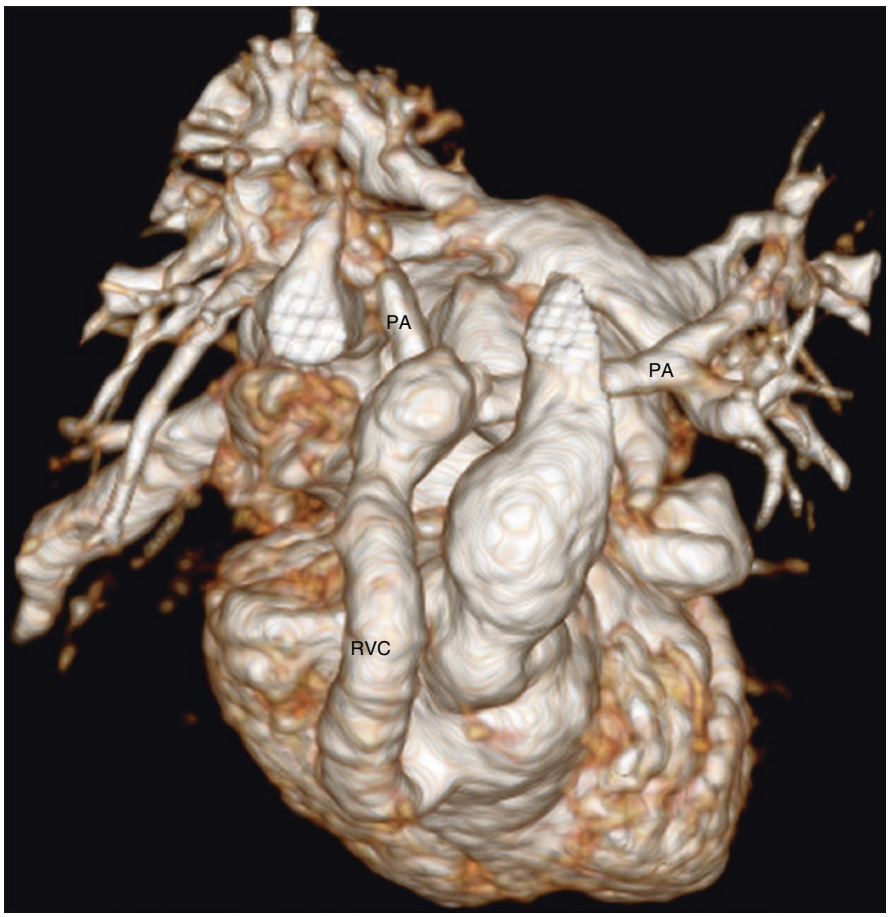

Fig. 30.12 Three-dimensional volume rendering of a CT scan of a patient with hypoplastic left heart syndrome after stage 1 palliation with a Norwood and right ventricle to pulmonary artery conduit (RVC). The right ventricle to pulmonary artery conduit can be seen originating from the anterior right ventricle and inserting into the pulmonary arteries (PA)

partial cavo-bi-pulmonary connection (or bi-cavo-bi-pulmonary, in case of right and left superior vena cava)
3. Modified intra- or extracardiac Fontan connection or total cavopulmonary connection

The most commonly followed therapeutic algorithm that varies with the specific diagnosis is as follows:

- *Stage 1: Neonatal palliation*
  - Modified Blalock-Taussig or a central shunt in case of a right obstruction. Alternatively, some patients may be candidates for stenting of the ductus arteriosus or the sub-pulmonary outflow tract.
  - Surgical repair of any left obstruction, i.e., aortic coarctectomy
  - Norwood, Sano, or Damus-Kaye-Stansel operations, hybrid approach, or orthotopic heart transplant
  - Pulmonary artery banding in case of high pulmonary flow with pulmonary arterial hypertension (unprotected pulmonary flow)
- *Stage 2: 3–6 months of age*
  - Partial cavopulmonary connection (modified Glenn procedure or hemi-Fontan procedure)
- *Stage 3: 2–6 years of age*
  - Total cavopulmonary connection (modified Fontan procedure; intra- or extracardiac; with or without fenestration)

30.4 Preoperative Management of the Neonatal Patient

Preoperative stability is key for good postoperative outcomes, notably in the neonatal patient. The main objective prior to intervention is to maintain the patient in a balanced physiological and homeostatic state with an efficient Qp/Qs ratio, allowing for adequate tissue perfusion. Very seldom do these patients need mechanical ventilation, except when diagnosed late and in cardiogenic shock. Maintaining the patients on spontaneous ventilation allows a more physiological stability, ad libitum feeding, and an opportunity to invest on mother-infant interactions. Safe venous lines are mandatory for the administration of drugs (i.e., PGE_1), blood sampling (to be minimized), and reliable access in case of decompensation. Close monitoring and follow-up of tissue perfusion markers is essential to evaluate trends anticipating a breach of the Qp/Qs balance with compromise of the systemic perfusion. Patients with physiology allowing pulmonary overcirculation to the detriment of the systemic perfusion may need systemic vasodilators and eventually the use of subatmospheric gas if refractory to medical therapy. In patients with such trend, the indication for intervention would be the only way to effectively address this physiology without exposing the patients to avoidable side effects and the risk of shock.

30.5 Surgical Neonatal Palliations

30.5.1 Variants with Aortic or with Pulmonary Obstruction

30.5.1.1 Patients with Subvalvular or Valvular Pulmonary Obstruction

These patients have a significant ductal-dependent and therefore PGE_1-dependent physiology requiring a neonatal palliation. The classic intervention is a modified Blalock-Taussig or a central shunt. In some cases, the alternative of interventional percutaneous balloon dilatation of the sub-pulmonary outflow tract or ductal stenting may be considered.

30.5.1.2 Patients with Obstruction of the Aortic Arch

This anatomy is almost always associated with unrestricted pulmonary flow and pulmonary hypertension. Therefore, patients require a surgical palliation associating aortic arch repair (i.e., aortic coarctectomy) with a pulmonary artery banding. Surgical techniques are decided upon the surgeon's preference and the degree of aortic hypoplasia and may be performed through a thoracotomy or else through a sternotomy with cardiopulmonary bypass and hypothermic circulatory arrest or using specific cannulation techniques to ensure an adequate cerebral perfusion (selective brain perfusion).

30.5.1.3 Patients with Hypoplastic Left Heart Syndrome (HLHS) or with Complex Left Ventricular Outflow Tract Obstructions

Details concerning therapy of HLHS will be further discussed in a specific chapter in this book. HLHS is a complex disease for which different alternatives might be considered:

1. Therapeutic abstention: may be an option in certain environments or by family choice, or else in patients with unfavorable anatomy and reserved prognosis.
2. Stage 1 Norwood type intervention (with a modified Blalock-Taussig shunt) or Sano modification (with a systemic ventricle-to-pulmonary conduit).
3. The hybrid approach: following this approach, a stent is inserted in the ductus arteriosus to ensure its patency, and pulmonary circulation is protected by selective surgical pulmonary branch bandings. Patients may subsequently progress toward a combination of stage 1 and 2 procedures (associating the removal of the ductal stent, plasty of pulmonary arteries, the creation of a neo-aorta with repair of the isthmic aortic obstruction, and a partial cavo-pulmonary connection) or toward an orthotopic heart transplant, in which case the need for neonatal pulmonary protection is controversial. Indications for this approach vary depending on the institutions but may include team's preference, prematurity, low birth-weight, significant ventricular dysfunction, significant tricuspid regurgitation, lung disease or other associated malformations, contraindications to cardiopulmonary bypass, or religious principles (i.e., avoidance of the use of blood products).
4. Orthotopic heart transplant.
5. Other situations: in some anatomic forms like the type IIc tricuspid atresia with d-transposition of the great arteries, unprotected pulmonary flow, and partially restrictive bulbo-ventricular foramen at the origin of significant sub-aortic obstruction, the alternative of an arterial switch may be discussed, transforming the aortic obstruction into a protective sub-pulmonary obstruction.
6. Some borderline anatomic forms allow a biventricular repair often associated with endomyocardial fibroelastosis resection, mitral plasty, and resection of complex subaortic obstructions. Other patients with small left outflow tracts and ventricular septal defect may be candidates to the Yasui operation.

30.5.1.4 Patients with Hypoplastic Right Heart Syndrome

This group of cardiac malformations is initially approached as any severe right-sided obstruction, by creating a modified Blalock-Taussig or a central shunt associated with an atrioseptectomy. Depending on the degree of right ventricular hypoplasia, if the cavity is small but tripartite and the tricuspid valve considered viable, these interventions may be combined with the opening of the right ventricular outflow tract by surgery or by interventional catheterization in the hope that the patient becomes a candidate for a biventricular or a ventricle-and-a-half repair.

30.5.2 Variants Without Pulmonary Protection (May Be Associated with Left Obstructions)

Such patients need an intervention aiming to protect their pulmonary vascular bed from high flow and pulmonary hypertension. Hence, a pulmonary artery banding is the indication.

30.5.3 Complex Variants with Heterotaxia

In the context of heterotaxia, single ventricles are usually associated with cardiac malpositions and with anomalous systemic or pulmonary venous returns that require complex interventions at the time of the above-described palliations. Other associative defects have been described and are intimately linked to the type of isomerism, dextro or levo. These include anomalies of the atrioventricular concordance, the ventriculoarterial concordance, and often aortic or pulmonary subvalvular or valvular obstructions. Rhythm disturbances are not uncommon and have a significant impact on decision-making and on outcomes.

30.6 Postoperative Management of Neonatal Palliations

30.6.1 General Aspects

Management of HLHS, aortic coarctation, and anomalous pulmonary venous returns is discussed in specific chapters elsewhere.

Pulmonary artery banding and modified Blalock-Taussig or central shunts usually have an uneventful postoperative course, but in some patients, particularly in low weight or premature newborns, postoperative management may be fraught with hemodynamic challenges. Therefore, caregivers need to be meticulous and prudent. The Qp/Qs balance is often difficult to achieve and maintain. Most patients require some degree of inotropic or lusitropic support with low-dose epinephrine or dopamine combined with milrinone. The Qp/Qs balance is a complex equation that needs to be customized to patient's physiology. Interventions target the management of resistances in both the systemic and the pulmonary circulations with ventilatory maneuvers, control of pH, use of cardiovascular drugs, sedation, and core temperature control, to mention some. The ultimate objective is to maintain adequate systemic tissue perfusion while avoiding the

intracellular anaerobic threshold, achieve an oxygen saturation of around 75–80%, and protect the patient against multiorgan dysfunction.

Patients with *high pulmonary resistances* are characterized by pulmonary under-circulation (desaturation, oligemic lungs) and require specific management as described in the chapter dedicated to pulmonary hypertension, namely, with ventilation targeting a slightly alkalotic pH, and the use of inhaled pulmonary vasodilators. Other causes for under-circulation to be systematically ruled out and promptly addressed relate to significant systemic vasoplegia, to small pulmonary arteries, or to partial shunt or right ventricle-to-pulmonary artery conduit obstruction. Some patients may require cardiac catheterization to elucidate anatomic or physiological patterns behind the lack of Qp/Qs balance.

Patients with *high pulmonary flow* (overcirculation expressed by saturations above 80%, low diastolic pressures with a high pulse differential, radiological signs of pulmonary volume overload, progressive metabolic or lactic acidosis by lack of adequate tissue perfusion) may benefit from a "pharmacological banding" associating the maintenance of high blood viscosity (hematocrit above 40–45%), diuretics (usually loop diuretics eventually associated with hydrochlorothiazide or with spironolactone), and systemic IV vasodilators to optimize afterload reduction (milrinone, sodium nitroprusside, nitroglycerine, phentolamine, phenoxybenzamine). In patient refractory to medical therapy, a comprehensive anatomic assessment by echocardiography and eventually cardiac catheterization should be undertaken to assess function and the presence of residual lesions (i.e., residual aortic coarctation).

If the mixed venous and the pulmonary venous saturations are normal, a saturation of 80% reflects a Qp/Qs of approximately 1:1. Nevertheless, caution ought to be exerted in patients with desaturated pulmonary veins, in which case the same 80% of systemic saturation would reflect a much higher Qp/Qs predisposing the patient to a compromise of the systemic tissue perfusion.

The aim of this "pharmacological banding" is to decrease the Qp/Qs following the principles described in Poiseuille's law: flow is directly proportional to the ratio of resistances and the diameter of the shunt and inversely proportional to the length of the shunt and blood viscosity.

Pulmonary artery banding may sometimes be too loose or too tight at the origin of over or under-circulation, respectively. It may also migrate peripherally, producing distortion of the pulmonary arteries or even total occlusion. When the banding is too close to the pulmonary valve, it may also induce pulmonary regurgitation that must be addressed, particularly in those patients in whom the pulmonary valve will become a neo-aortic valve in the future.

Particular caution is necessary in patients with shunts, regarding the prevention of a hypercoagulability and risks of thrombosis. This includes avoiding dehydration or disproportionate negative hydric balance, using in the absence of bleeding, and introducing antiplatelet therapy once the patients resumes enteral feeding.

30.6.2 Monitoring

These patients require a peripheral arterial line ideally inserted in the right radial artery if an aortic coarctation was repaired and a central venous line, as indwelling catheters. Other parameters to be monitored are cardiac and respiratory rate, peripheral oxygen saturation, ECG, and cerebral and somatic near-infrared spectroscopy (NIRS).

30.6.3 Inotropic and Vasodilator Drugs

After a pulmonary artery banding or a shunt, patients may require inotropic support. *A cornerstone principle of management in these patients is to target the ultimate goal of circulation: tissue perfusion, rather blood pressures.*

Whenever necessary, an elective drug combination may include dopamine and milrinone. Nevertheless, it is essential to understand the patient's physiology to implement a goal-oriented therapy rather than universal "drug recipes". For that, a thorough physical examination, evaluation of invasive and noninvasive data, as well as biomarkers and indices of tissue perfusion usually provide the necessary information. The latter may need to be complemented by echocardiography and sometimes by cardiac catheterization in patients who do not respond as expected to medical therapy. Patients with overcirculation may require more selective systemic vasodilators such as sodium nitroprusside.

When an aortic coarctation is repaired, patients might have tachycardia and hypertension, needing therapy with systemic vasodilators and beta-blockers, usually sodium nitroprusside or IV nicardipine and esmolol (further details can be found on the chapter related to aortic coarctation).

Vasoplegia related to inflammation and/or side effects of some drugs, namely, milrinone, may need to be antagonized in some patients with vasopressors. Another indication for the use of these drugs may be the need to provide enough kidney or target-organ perfusion and a physiological trans-organ gradient, in patients with elevated central venous pressures. Vasopressin is gaining popularity in the world of cardiac intensive care for this purpose, all the more that it can be a selective vasodilator in some critical vascular beds, including the coronaries.

30.6.4 Respiratory Management

Neonatal patients after any surgery for single ventricle physiology need ventilation for at least the first postoperative hours while achieving an adequate hemodynamic balance. This is notably important in patients with low weight or prematurity, syndromic, or else with high pulmonary resistances or with overcirculation, who may require prolonged ventilation. Cardiopulmonary interactions are vital in these patients and will be discussed at length elsewhere in this book. The need for positive pressures does not necessarily justify mechanical ventilation and may be overcome with noninvasive positive pressure ventilation. In case of delayed chest closure, extubation can be accomplished within 12–24 hours after closure.

30.6.5 Sedation and Analgesia

Most patients achieve effective analgesic levels with nonopioid therapy associated with morphine or fentanyl and benzodiazepines (i.e., midazolam, clonazepam) at minimal efficient doses, for at least the first 48 hours, particularly in patients having required an intervention by thoracotomy. Dexmedetomidine is an attractive alternative in these patients. Children requiring prolonged use of opioids and benzodiazepines should be monitored for potential withdrawal syndrome. Also, caution is needed in patients requiring longer intensive care admissions with regard to delirium.

30.6.6 Anticoagulation

In case of systemic-pulmonary shunt, it is important to anticoagulate patients once postoperative bleeding is under control. Antiplatelet therapy (aspirin, dipyridamole, or eventually clopidogrel) ought to be prescribed as soon as patients resume enteral feeding, allowing to suspend the heparin.

30.6.7 Specific Problems

Specific problems are mostly those associated with the balance of the ratio between the systemic and the pulmonary resistances as previously discussed. Other occurrences and complications may be diaphragmatic palsy or paresis, chylothorax, or Horner's syndrome by phrenic or recurrent laryngeal nerve lesions.

30.7 Partial Cavopulmonary Connections

Single ventricle physiology is shared by various and heterogeneous entities. Their common characteristic is that there is a complete mixing of oxygenated and desaturated blood that will be distributed in both the systemic and the pulmonary circuits. The main objective of the univentricular type repair or palliation is to individualize the systemic and the pulmonary circulations to achieve almost normal systemic saturations with a more effective ventricular workload. The partial cavopulmonary connection performed with the modified Glenn intervention is the first step toward this goal. William E. Glenn firstly described his technique in 1958. The classic Glenn procedure consisted in completely dividing the left from the right pulmonary branches, connecting the latter to the right superior vena cava while preserving the anterograde flow from the heart toward the left branch. Some of these patients have survived to adulthood, but many have developed left pulmonary hypertension, having therefore become cyanosed, as an equivalent to the Eisenmenger's complex. In case of surgical intervention, these patients would require a double-lumen endotracheal tube allowing differential ventilation of the right and the left lung. The current modified Glenn connection (since the 1980s) allows passive flow from the superior vena cava to both pulmonary branches, and the continuity with the ventricular mass is ceased by sectioning the pulmonary trunk or restricted by further tightening the banding, in which case a degree of anterograde pulsatile flow will persist into the pulmonary arteries.

30.7.1 Preoperative Evaluation

Patients with single ventricle physiology will become candidates for partial cavopulmonary connections throughout the first months of life. To summarize, the required conditions to indicate a cavopulmonary connection are the confirmation of normal rhythm and conduction and the absence of any anatomical or functional obstructions throughout the future cavopulmonary circuit:

- Anatomic criteria
  - No significant stenosis or deformation of the pulmonary arteries
  - No pulmonary venous stenosis
  - Nonrestrictive communication between the atrial cavities (in case of stenosis or atresia of an atrioventricular valve)
  - No subvalvular or valvular aortic obstruction

  - No residual aortic coarctation
  - No thrombus within the vascular bed
- Functional criteria
  - Low pulmonary pressures and resistances
  - No significant atrioventricular valvular regurgitation
  - Normal ventricular function, both systolic and diastolic
  - Normal sinus rhythm and no conduction disorders

    The main general objectives of the cavopulmonary connection are:
    - To facilitate the diastolic unload of the systemic ventricle
    - To prevent deformation of the pulmonary arteries
    - To avoid the negative impact of the continuous diastolic "steal" on the myocyte which, associated with the diastolic volume overload, may induce irreversible myocardial changes

These objectives are accomplished by diverting venous blood from the superior vena cava toward the pulmonary artery with a modified Glenn connection, or else with a hemi-Fontan procedure. Usually, this intervention is proposed when the pulmonary arteries have an adequate diameter, and the pulmonary vascular resistances are low, around 4 months of age and ideally before 6 months of age.

30.7.2 Preoperative Cardiac Catheterization

Cardiac catheterization is a common procedure in preparation for the cavopulmonary connection [10–12]. The objectives of such procedure are as follows:

1. To measure saturations and pressures in the pulmonary branches and to estimate the Qp:Qs ratio and the pulmonary vascular resistances. In patients with borderline values, cardiac catheterization allows the performance of pharmacological tests aiming to reduce the pulmonary resistances.
2. To perform angiographies in the ventricular cavities, the innominate vein, the pulmonary arteries, and the aortic arch.
3. To perform interventional procedures like balloon dilatation and stent insertion in localized pulmonary stenosis or on residual obstructions of the distal suture of the neoaorta and also to dilate or stent any residual aortic coarctation. It may also be instrumental for the percutaneous embolization of veno-venous pulmonary collateral vessels, arteriovenous malformations, or aortopulmonary collateral vessels. Last, but not least, cardiac catheterization is useful to occlude fenestrations after completion of the total cavopulmonary connection.

30.7.3 Surgical Techniques

30.7.3.1 The Glenn Procedure

The modified Glenn anastomosis (Fig. 30.13) may be performed on cardiopulmonary bypass with beating heart or without cardiopulmonary bypass in patients with anterograde flow who do not require any intracardiac intervention. The superior vena cava is sectioned from the atrial mass after ligation of the azygos return, and its caudal portion is directly anastomosed onto the right pulmonary artery. Any previous aortopulmonary shunt is ligated and/or sectioned. When a previous pulmonary banding has been performed, some groups maintain a persistent anterograde flow from the ventricular mass, although tightening the banding, while others favor the section of the pulmonary trunk and even the resection of the pulmonary valve to remove any pouches that would become a potential source of thromboembolism. The theoretical advantage of the first approach is to provide the lungs with a hepatic angiogenesis inhibitor factor that would decrease the risk for pulmonary arteriovenous fistula formation, but there is no evidence confirming this theory. Potential disadvantages of preserving the pulmonary anterograde flow are pulmonary diastolic overload and potential for distortion of the pulmonary artery anatomy by the

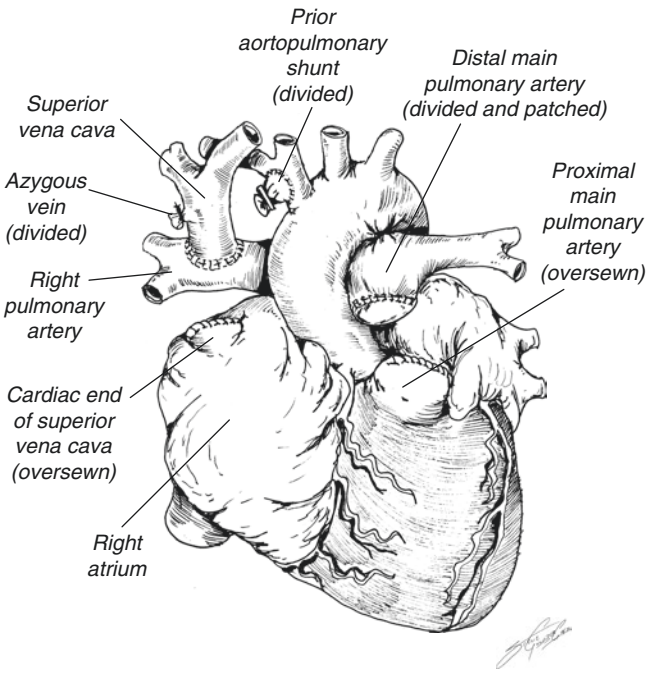

Fig. 30.13 The partial cavopulmonary connection (Glenn procedure)

banding, particularly if it migrates toward the pulmonary branches bifurcation. During the same operating time, other interventions might be indicated: atrioventricular valvular plasty, atrial septectomy, pulmonary artery plasty or patch enlargement or repair of any residual aortic arch obstruction. Arteriovenous fistulas have a significant hemodynamic impact on the Fontan circulation as a source of persistent hypoxemia and are more common in patients with heterotaxia and with interrupted inferior vena cava and azygos continuation in whom a Kawashima procedure is performed. If identified, such collaterals require ligation if not occluded in the catheterization laboratory.

The Glenn anastomosis is more laborious and may carry an increased morbidity when performed in patients with HLHS and previous hybrid approach, in whom it is required to remove the ductal stent and perform an atrial septectomy, a plasty of the pulmonary arteries, and an extensive reconstruction of the aortic arch.

30.7.3.2 The Hemi-Fontan Procedure

This is an alternative to the modified Glenn connection [13]. It might facilitate the second step toward the total cavopulmonary connection if the choice is an intracardiac tunnel. It consists in creating an anastomosis between the right atrium and the pulmonary artery by septalizing the atrial cavity with a Goretex® patch to divert the flow drained from the superior vena cava onto the pulmonary bed while ensuring the drainage of the flow arriving from the inferior vena cava toward the ventricular mass, across the atrioventricular valve.

30.7.4 Postoperative Management of the Partial Cavopulmonary Connection

30.7.4.1 Monitoring

These patients require the conventional postoperative monitoring (cardiac rate and ECG, respiratory rate, oxygen saturation, arterial pressure both invasive and noninvasive) eventually complemented by a transthoracic right atrial catheter to appraise filling pressures and an internal jugular indwelling catheter to assess the pulmonary artery pressure. The presence of these catheters allows the estimation of the transcapillary gradient that often proves useful in the postoperative management. Near-infrared spectroscopy (NIRS) is commonly utilized to assess trends on regional perfusion, and some centers also use technologies based on thermodilution and on pulse wave analysis.

30.7.4.2 General Measures

After a partial cavopulmonary connection, general measures to be undertaken do not change significantly from the measures adopted for any postoperative case, with a few important details to be highlighted:

(a) Patients should be positioned in a 45-degree semi-fowler decubitus, to promote passive venous drainage by gravity.
(b) Enteral feeding should be resumed as soon as possible.
(c) Early extubation and mobilization are essential.
(d) Any indwelling lines, particularly those in the superior venous segments, should be removed as early as possible.
(e) Caution should be taken with regard to the pleural drains; the trend is to be conservative and leave them in situ for at least 48 hours, considering the accrued risk for pleural effusion and chylothorax.

30.7.4.3 Inotropic and Vasodilator Therapy

Usually, these patients require low doses of inovasodilators (i.e., milrinone). Target saturations are between 75 and 80%, central venous pressures are around 5–8 mm Hg, and mean pulmonary pressures should be below 15 mm Hg with a low trans-pulmonary gradient. It is common to observe a transient systemic hypertension, quite likely of central origin.

30.7.4.4 Respiratory Management

Cardiopulmonary interactions are fundamental in the context of the cavopulmonary connections. Ventilatory parameters should be rigorously monitored to preserve both the pulmonary and the cerebral blood flow. Hyperventilation should be avoided, since although facilitating pulmonary flow (by raising pH), it may decrease cerebral flow (by decreasing CO_2) which provides the main preload of the cavopulmonary system. As a matter of fact, mild permissive hypercapnia should not preclude extubation as it increases the cerebral blood flow and therefore the Glenn flow. Also, positive intrathoracic pressures induce a reduction of both the pulmonary flow and the systemic ventricle preload with an increase of pulmonary vascular resistances. Therefore, most patients are extubated in the operating room or during the first 6 postoperative hours, once there is evidence of hemodynamic, neurologic, respiratory, and homeostatic stability and controlled bleeding. Ventilation is better tolerated after the partial connection rather than the total connection because in the first

case, flow from the inferior vena cava to the heart fills the systemic ventricle independently. Any respiratory complications like atelectasis, pneumothorax, or pleural effusions should be promptly rectified.

30.7.4.5 Sedation and Analgesia

Postoperative sedation and analgesia should target proper levels of comfort while ensuring spontaneous breathing autonomy allowing early extubation. A balance must be established to avoid pain, allow proper cough and airway protection (to reduce risks of atelectasis), and reduce the typical irritability that characterizes these patients, secondarily to transient cerebral venous congestion and changes in cerebral flow patterns.

30.7.4.6 Anticoagulation

Prophylactic anticoagulation with heparin should be started in the absence of bleeding. Once feeding is resumed, antiplatelet therapy with aspirin (3–5 mg/kg/day) may be started.

30.7.5 Postoperative Complications

The four main complications observed after the partial cavopulmonary connection are increased pressures in the cavopulmonary circuit, hypertension and bradycardia, low cardiac output syndrome (LCOS), and hypoxemia.

30.7.5.1 Increased Pressures in the Cavopulmonary Circuit

Immediately after surgery, there may be a transient increase of pressures in the cavopulmonary circuit, secondarily to the inflammatory changes induced by the cardiopulmonary bypass, volume overload, and the mechanical ventilation with positive pressure. The clinical expression of this complication is the development of a superior vena cava syndrome, associated with increased pulmonary pressures, progressive cyanosis, and decrease in the systemic stroke volume. It is therefore important to establish a spontaneous breathing pattern as early as possible, to aggressively manage any respiratory occurrence (atelectasis, pneumothorax, or pleural effusions), and to use pulmonary vasodilators as required, mostly nitric oxide and sildenafil [14, 15], and loop diuretics to induce diuresis and a negative fluid balance. When pressures remain high in spite of these measures, further investigations (echocardiography, cardiac catheterization) may be indicated to rule out stenosis at the anastomotic site or else, distally in the pulmonary arteries, thrombosis, or high pulmonary vascular resistances.

30.7.5.2 Hypertension and Bradycardia

The mechanism behind hypertension might be inadequate analgesia and sedation, stress response with release of endogenous catecholamines, or a down-regulator effect to maintain cerebral perfusion in the context of high venous pressure and congestion. This phenomenon is usually transient and well controlled with angiotensin inhibitors, but during the acute phase, these patients might need the use of sodium nitroprusside or intravenous calcium inhibitors.

Bradycardia is usually a reflex response to the sudden unload induced by the Glenn connection, although in a small percentage of cases, it may be due to a lesion of the sinus node, in which case it is unresponsive to drugs like atropine or isoproterenol.

30.7.5.3 Low Cardiac Output Syndrome (LCOS)

Significant low cardiac output syndrome is seldom observed after a partial cavopulmonary connection, except in patients with previous ventricular dysfunction or with atrioventricular valve regurgitation, in whom a sudden unload may have an impact in cardiac output.

30.7.5.4 Hypoxemia

Hypoxemia is the most common short- and long-term complication after a partial cavopulmonary connection. Initial saturations are expected to be between 75 and 85%. Persistent saturations below 70% justify further investigations. Etiology of persistent hypoxemia is variable and heterogeneous and may include decreased cerebral flow (hypocapnia, hypotension), ventilation/perfusion mismatch (pleural effusion, atelectasis, pneumothorax, pneumonia, arteriovenous malformations), increased oxygen consumption (sepsis, low cardiac output, ventricular dysfunction, anemia), or decreased pulmonary blood flow (increased pulmonary vascular resistances, stenosis of the cavopulmonary anastomosis, veno-venous collateral vessels, restrictive intra-atrial communication). Veno-venous collateral vessels between the superior and inferior venous territories induce a persistent desaturation by decreasing the effective pulmonary flow, and some may be occluded by percutaneous interventional catheterization. Arteriovenous malformations (AVM) are a common cause of late hypoxemia and are more frequently documented in heterotaxic syndromes with interrupted infe-

rior vena cava and azygos continuation. They are thought to develop because of the absence of a hepatic angiogenesis inhibitor factor. Diagnosis is suggested by echocardiography with contrast test and confirmed by angiography. AVMs tend to progress after the completion of the Fontan circuit. Patients are more prone to develop AVMs and chronic hypoxemia after a Kawashima intervention.

Currently, partial cavopulmonary connections carry a very low morbidity and mortality is close to 0%.

30.8 Total Cavopulmonary Connections

30.8.1 The Fontan-Kreutzer and Modified Fontan Procedures

Francis Fontan originally described a procedure [16–18] by which the right atrial cavity would be directly anastomosed onto the pulmonary artery. Guillermo Kreutzer described a similar technique contemporarily. This original Fontan-Kreutzer operation lately showed to have a number of disadvantages, due to persistent blood stasis in the right atrium. Concomitantly, it was recognized in the early 1980s that to proceed with a total cavopulmonary connection in one surgical step would have a significant mortality due to a significant acute remodeling of the systemic ventricle. Since inception of the original technique, three essential modifications were described and developed for patients who had already undergone the Glenn or the hemi-Fontan connection as a first step intervention [19, 20], in order to avoid or limit the remodeling phenomenon. Firstly, the anastomosis between the inferior vena cava, the hepatic veins, and the pulmonary artery was performed as an intracardiac shunt created with the wall of the right atrium and with Goretex® and diverting the blood draining from the inferior segment of the body toward the pulmonary artery [21]. Secondly, a more recent modification was proposed by diverting the blood with an extracardiac conduit [22–26] (Fig. 30.14), a less traumatic surgery and theoretically reducing the risks for arrhythmia, the latter not having been demonstrated so far. The third modification consists in the creation of a fenestration [27, 28] between the intra- or the extracardiac conduit and the atrial mass. This fenestration acts like a "pop-off" structure that is functionally useful in patients in whom the pulmonary pressures and resistances are above the desired levels. Although inducing cyanosis, this fenestration allows a more stable and adequate hemodynamic profile and decreases the risk of persistent "right failure" with superior vena cava syndrome, peripheral edema, pleural effusions, ascites, and protein-losing enteropathy. More recent modifications such as the one proposed by Viktor Hraska (diversion of the innominate vein to the atrial mass to reduce strain on the thoracic duct drainage) [29] have been proposed but have yet to show consistency or reproducibility.

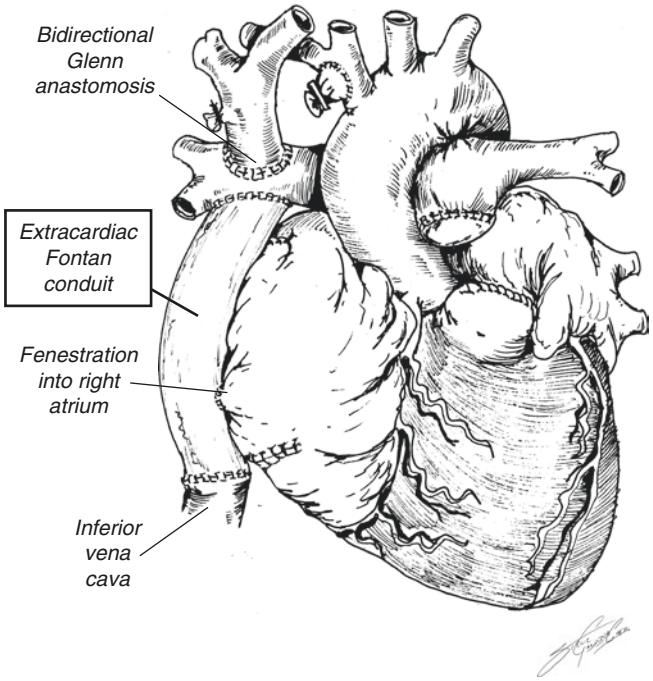

Fig. 30.14 Extracardiac fenestrated modified Fontan or total cavopulmonary connection

30.8.2 Postoperative Management

30.8.2.1 Monitoring

After a total cavopulmonary connection, patients are comprehensively monitored with heart rate and ECG, respiratory rate, oxygen saturation, and arterial pressure both invasive and noninvasive and also have a transthoracic atrial catheter and an internal jugular indwelling catheter to assess the pulmonary artery pressure. Indwelling catheters should be removed as soon as possible to minimize risks for thrombosis in the cavopulmonary circuit. Near-infrared spectroscopy (NIRS) and modern technology by thermodilution may also be instrumental in taking therapeutic decisions with these patients.

30.8.2.2 General Measures

As for the partial cavopulmonary connections, general measures are the same as for any postoperative case [30–32], but once again, there are a number of specific details to cautiously follow:

(a) Patients should be positioned in a 45-degree semi-fowler decubitus with partly folded legs, to promote passive venous drainage from both the superior and the inferior segments of the body.
(b) Enteral feeding should be resumed as soon as possible.
(c) Early mobilization is crucial.
(d) Any indwelling lines should be removed as early as possible.
(e) Caution should be taken with regard to the pleural and mediastinal drains since these patients are prone to develop pericardial and pleural effusions and chylothorax, mostly when the pulmonary pressures are high or in the upper normal range.

30.8.2.3 Inotropic and Vasodilator Therapy

After a total cavopulmonary connection, patients often need low to moderate doses of inovasodilators or lusitropic drugs (milrinone). Target saturations are expected to be above 90%, and central venous pressures that correspond to mean pulmonary pressures should be below 15 mm Hg with a low trans-pulmonary gradient. As for the Glenn procedure, it is common to observe a transient systemic hypertension or transient peripheral and central edema.

30.8.2.4 Respiratory Management

Cardiopulmonary interactions are fundamental after the total cavopulmonary connection. Ventilatory parameters should be rigorously monitored in order to preserve both the pulmonary and the cerebral blood flow. Hyperventilation should be avoided. Caregivers need to keep in mind that positive intrathoracic pressures induce a reduction of both the pulmonary flow and the systemic ventricle preload with an increase of pulmonary vascular resistances. Ventilation is better tolerated after the partial connection rather than the total connection because in the first case, flow from the inferior vena cava to the heart fills the systemic ventricle independently. Consequently, most Fontan patients are extubated in the early phase of their postoperative course, once there is evidence of hemodynamic, neurologic, respiratory, and homeostatic stability and controlled bleeding. Any respiratory complications like atelectasis, pneumothorax, or pleural effusions should be promptly rectified.

Patients with persistent low saturations ("right-to-left" shunt through the fenestration) and high pulmonary pressures may benefit from inhaled nitric oxide, although its administration has to be cautious when the function of the systemic ventricle is borderline.

30.8.2.5 Sedation and Analgesia

Postoperative sedation and analgesia should target proper levels of comfort while ensuring spontaneous breathing autonomy allowing early extubation. A balance must be established to avoid pain, allow proper cough and airway protection (to reduce risks of atelectasis), and reduce the typical irritability that characterizes these patients, secondarily to transient cerebral venous congestion and changes in cerebral flow patterns.

30.8.2.6 Anticoagulation

There is no current consensus regarding the potential benefit of long-term anticoagulation versus antiplatelet aggregation therapy after a total cavopulmonary connection. Nevertheless, acute prophylactic anticoagulation is universally ensured with heparin as previously described. Once feeding is resumed, heparin is replaced by antiplatelet therapy with aspirin (3-5 mg/kg/day), alternatively with dipyridamole or clopidogrel or by anticoagulation with antivitamin K agents as opposed to antiplatelet drugs.

Patients with dysfunctional Fontan physiology or with documented pro-coagulant status should be considered for active anticoagulation with oral antivitamin K agents and/or with subcutaneous heparin, taking into account their risk for thrombosis.

30.8.3 Complications

A*nticipated potential complications* after the total cavopulmonary connection are similar to the occurrences after the partial connection (increased pressures in the cavopulmonary circuit, low cardiac output syndrome, hypoxemia), but there is a higher prevalence and risk of pleural effusions, chylothorax, pericardial effusion, arrhythmias, and thromboembolic events [33, 34]. Other chronic complications are the development of venous collaterals, pulmonary arteriovenous malformations or systemic-pulmonary arterial collaterals, failure to thrive, protein-losing enteropathy (PLE) [35], low functional capacity, plastic bronchitis, and liver disease, cirrhosis, and neoplasia [36].

Management of acute complications follows the recommendations described herein in the section dedicated to the postoperative course of the partial cavopulmonary connection. There are a few peculiarities related to the Fontan operation though.

Significant low cardiac output syndrome may be observed after a total cavopulmonary connection, mostly in patients

with previous ventricular dysfunction, with severe atrioventricular valve regurgitation or with a tenuous hemodynamic stability. Treatment is based on the use of inotropic, vasodilator, or lusitropic drugs, induced hypothermia, diuretics, and eventually re-synchronization strategies. Patients with refractory LCOS may require mechanical assistance and may be considered for cardiac transplant.

Hypoxemia is rather common in patients with fenestrations and moderately or severely increased postoperative pulmonary resistances. Persistent saturations below 90% justify further investigations as described above for patients with increased pulmonary pressures, situation that usually coexists with the hypoxemia. A cardiac catheterization may also be necessary to rule out anatomic or functional obstructions, thrombosis, or high pulmonary vascular resistances. It may also identify veno-venous or arterial-venous fistula requiring embolization [37–39]. In some circumstances, it is useful to transiently occlude the fenestration and reassess hemodynamics. When the pulmonary pressures remain below 18 mm Hg, systemic saturations increase significantly, and there is no impact in the cardiac function, a definite occlusion of the fenestration with an intra-vascular device may be considered.

Acute and chronic effusions confined to the thorax (pleural or pericardial effusions, chylothorax) or extra-thoracic (ascites, peripheral edema) are common after total cavopulmonary connections [40]. Conceivably, the presence of a fenestration is a favorable preventive factor. These patients may require intra-thoracic drains for long periods of time. In case of persistent chylothorax, an adequate diet with middle-chain triglycerides and the use of parenteral feeding is indicated. In refractory cases, somatostatin or octreotide followed by pleurodesis may be considered. Selective thoracic duct embolization is a promising interventional technique that fosters encouraging prognosis in patients with refractory effusions, PLE, and plastic bronchitis [41, 42]. The partial hepatic vein exclusion reported by Yves Lecompte [43, 44] is not currently performed since most patients develop intrahepatic venous collaterals with significant right-to-left shunts. Nevertheless, recent case reports describe modifications of the technique with varying degrees of success, namely, in patients with associated PLE [45, 46].

Patients with total cavopulmonary connections tolerate very poorly any arrhythmia [47, 48] or conductive disorder and must be aggressively managed. Atrioventricular synchrony is vital in these patients. Nodal or junctional rhythm is a common immediate "benign" postoperative finding, usually well tolerated but sometimes requiring AAI pacing. Atrial flutter is the most common potentially life-threatening arrhythmia in this context and is often associated with sinus node dysfunction, which complicates its management. It often gives a sign of alert for serious hemodynamic complications. As previous mentioned, the use of extracardiac conduits has not reduced the incidence of arrhythmias or sinus node dysfunction. Atrial flutter may be preceded by sinus bradycardia in which case the use of a prophylactic epicardial pacemaker may be a benefit, although this has yet to be demonstrated. Technical complications for the use of mono- or dual-chamber pacemakers are related to the fact that these can only be epicardial, in patients who often have chronic adhesions secondary to multiple surgeries.

30.9 Conclusions

Single ventricle anatomy and physiology displays a very wide anatomic spectrum. Although medical and surgical management of these patients has been relatively standardized, there remain multiple outliers and challenges in the perioperative management of these complex patients. Constant innovation, data collection, patient- and family-centered interdisciplinary team collaboration focused on quality and safety, and multicentric research are key factors for further understanding and consistently and efficiently managing single ventricle patients.

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Chapter 31
Anomalous Pulmonary Veins

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Abstract This chapter discusses different types of anomalous pulmonary venous returns, including the main subtypes of total anomalous pulmonary venous return and partial anomalous pulmonary venous return.

31.1 Introduction

In total anomalous venous return (TAPVR), all the pulmonary veins drain into one or several systemic veins, while in partial anomalous pulmonary venous return (PAPVR), only one or more, but not all, of the pulmonary veins drain into the systemic veins.

In some forms of TAPVR, obstruction to pulmonary venous return can develop, and its degree is the most important determinant of patient stability. Obstructed TAPVR is unique among neonatal cardiac emergencies because there are no medical or interventional means of definitively addressing its consequences. Unlike in many other cardiac lesions, prostaglandin E1 (PGE1) is contraindicated in this setting, and despite occasional reports of successful interventional procedures to address the obstruction, this approach has not been widely adopted. Depending on the degree of obstruction, these patients either require urgent surgical repair or a short stabilization using extracorporeal membrane oxygenation (ECMO) followed by elective repair.

31.2 Anatomy and Embryology

Anomalous pulmonary venous return can result from a number of deviations of the pulmonary venous development. Initially the lung buds are drained by the splanchnic plexus, which interconnects extensively with the cardinal and the vitelline systems (which by that point are forming the systemic veins and the right atrium (RA)), but that plexus does not reach the heart. Eventually, the common pulmonary vein buds off the posterior wall of the left atrium (LA) and connects the pulmonary venous plexus to the sinoatrial portion of the heart, after which the pulmonary-splanchnic connections disappear, leaving four major pulmonary veins that empty into the common pulmonary vein, which in turn drains into LA. This common pulmonary vein is ultimately incorporated into LA, while the four pulmonary veins connect to LA separately and directly. Maldevelopment of the common pulmonary vein may lead to persistent pulmonary-splanchnic connections and abnormal drainage of the pulmonary veins into the systemic venous or right heart circulation, resulting in TAPVR or PAPVR.

Based on the anatomy of the anomalous pulmonary venous drainage, there are four types of TAPVR: supracardiac (~45–50%), cardiac (~25%), infradiaphragmatic (~15–25%), and mixed (~5–10%) [1–3]. Anatomical features common to all of them include an interatrial communication (atrial septal defect (ASD) or patent foramen ovale (PFO)), which is necessary for survival, and smaller left-sided cardiac structures resulting from the failure to incorporate the common pulmonary vein into LA [4].

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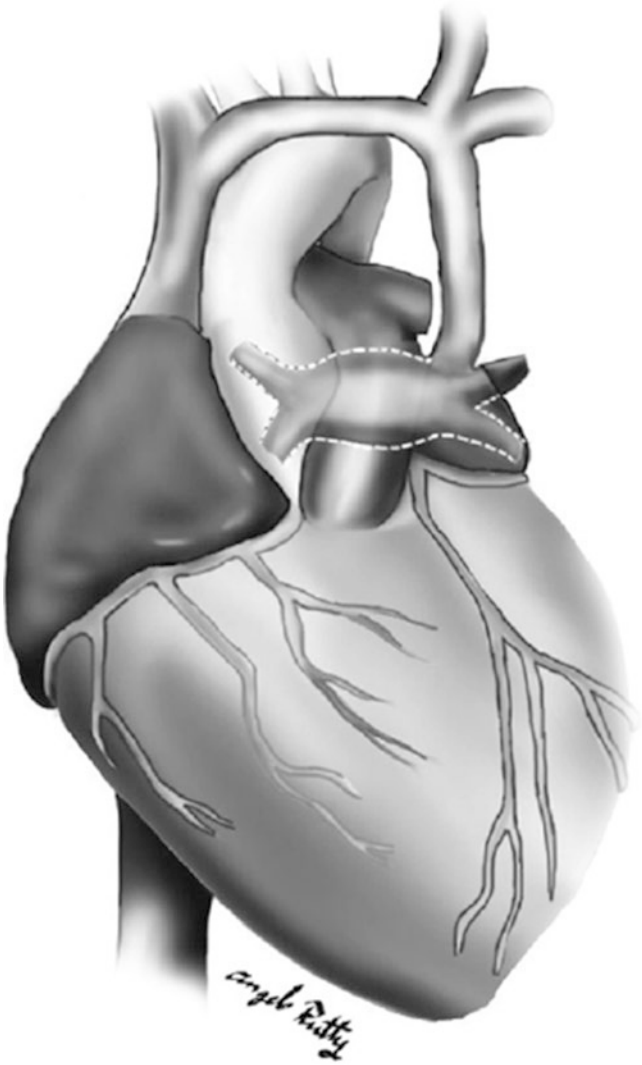

Fig. 31.1 Supracardiac type total anomalous pulmonary venous return (TAPVR). The vertical vein drains the pulmonary vein confluence into the innominate vein

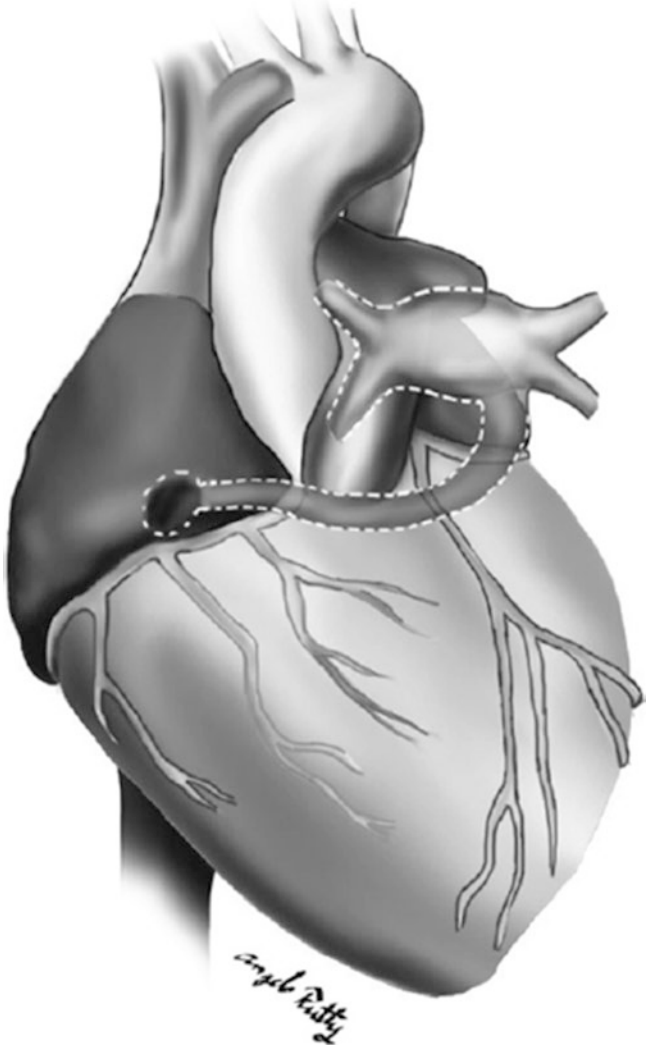

Fig. 31.2 Cardiac type TAPVR. The pulmonary vein confluence drains into the coronary sinus

Supracardiac In the most common subtype of this drainage pattern, the four pulmonary veins join at a venous confluence (remnant of the common pulmonary vein) behind LA and drain up the left side of the chest as the vertical vein (Fig. 31.1). Usually this vein passes in front of the pulmonary artery (PA) and the mainstem bronchus, but it may pass between them and become obstructed (thus obstructing the pulmonary venous return). This vertical vein connects to the left innominate vein, which, in turn, joins the SVC. Other possible supracardiac subtypes include a direct connection between the vertical vein and either the right SVC, the azygous system, or the left SVC.

Cardiac Here, all four pulmonary veins drain into the common pulmonary vein, which connects to either the coronary sinus around the atrioventricular groove or to the right atrium (Fig. 31.2). The coronary sinus follows its normal path to the right atrium, where it is either normally placed between the orifices of the venae cavae or displaced posterior to the IVC opening. The direct connection of the common pulmonary vein to the RA is most frequently seen in cases of right isomerism.

Infracardiac Here, pulmonary venous blood is collected by a common pulmonary vein behind the heart, passes down a venous channel through the esophageal hiatus of the diaphragm, and drains into a subdiaphragmatic vein (portal vein (most commonly), ductus venosus, hepatic vein, or directly to IVC) (Fig. 31.3). The pulmonary venous blood then reenters the heart through the IVC.

Mixed Here, the anomalous connections of the pulmonary veins are present at two or more of the above levels.

Infants with TAPVR as part of a heterotaxia syndrome are more likely to have other major cardiac congenital anomalies

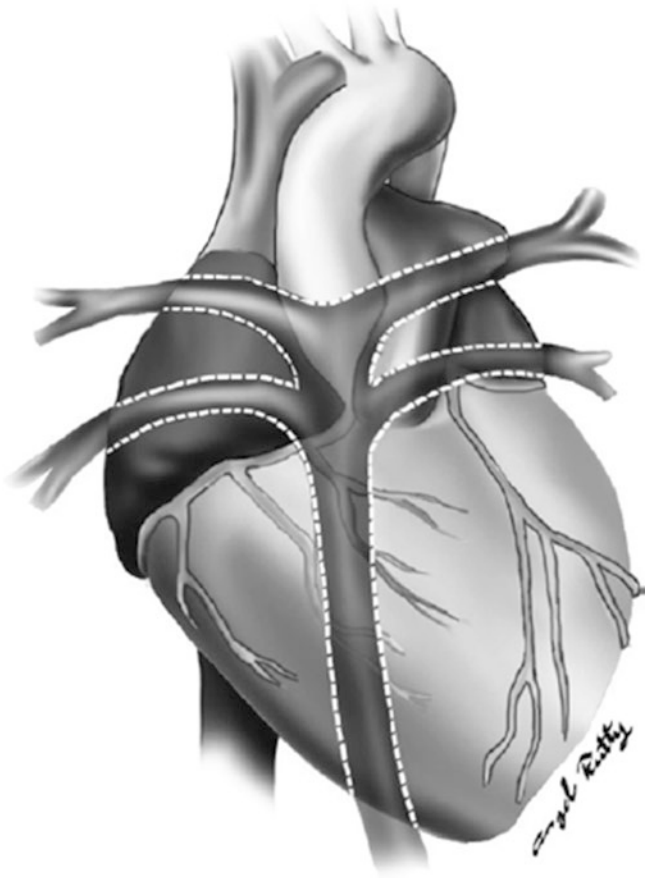

Fig. 31.3 Infracardiac type TAPV. The descending vertical vein drains into the portal vein

(tetralogy of Fallot, double outlet right ventricle, hypoplastic left heart, and hypoplastic aortic arch), abnormal venous drainage, polysplenia, asplenia, and cat's eye syndrome [5]. Any degree of pulmonary venous obstruction may be accompanied by pulmonary venous fibrosis, abnormal PA muscularization, and pulmonary lymphangiectasis.

PAPVR refers to a range of condition in which almost every imaginable combination of connections between one or more – but not all – pulmonary veins and the systemic venous drainage has been observed. The left pulmonary veins typically connect anomalously to the derivatives of the left cardinal system (coronary sinus, left innominate vein), while the right pulmonary veins typically connect anonymously to the derivatives of the right cardinal system (SVC or IVC). Two subtypes of PAPVR deserve special mention: sinus venosus PAPVR (the most common subtype, characterized by the presence of sinus venosus ASD and often associated with the drainage of right upper or right middle pulmonary vein to SVC) and scimitar syndrome (connection between a right pulmonary vein and IVC, ASD (in the majority of cases), bronchial abnormalities, dextrocardia, hypoplasia of the right lung and of the right PA, and right pulmonary sequestration) [3]. Connections between the left upper pulmonary vein, the left innominate vein, the coronary sinus, the LA, the right SVC, and [5] the hemiazygos vein (many of them associated with ASD) have also been reported. These patients exhibit RA, RV, and PA dilation. Due to RV dilation, the intraventricular septum is deviated toward LV, which appears "smallish." PAPVR is associated with other cardiac defects and syndromes, including heterotaxia and Turner syndrome [6].

31.3 Pathophysiology

In all forms of TAPVR, the pulmonary venous blood completely mixes with systemic venous blood through an obligatory left-to-right shunt and returns to RA via the systemic veins. To provide LV preload (and cardiac output), a right-to-left shunt must also exist. This shunt most frequently occurs via either PFO or ASD. Oxygen saturations in all cardiac chambers are identical and dependent on the amount of pulmonary blood flow, which is mostly governed by the degree of pulmonary venous obstruction. If the pulmonary venous return is unobstructed, the pulmonary blood flow is increased, oxygen saturations in all cardiac chambers are relatively high, and congestive heart failure with minimal cyanosis soon develops. Although these infants appear pink, their pulmonary vascular resistance is labile, and they can experience episodes of PA hypertension with associated cyanosis. In contrast, in TAPVR with severe pulmonary obstruction, pulmonary venous hypertension and pulmonary edema are always present; in addition, there is a degree of PA constriction (and thus PA hypertension). The overall result is severe RV and PA hypertension, poor pulmonary compliance, high bronchial resistance to airflow, and, ultimately, hypoxemia, RV failure, and cardiogenic shock. Most infants born with TAPVR present with some degree of pulmonary venous obstruction, and their individual physiologic state falls between the two extremes described above.

The pathophysiology of PAPVR is that of ASD with RV volume overload secondary to left-to-right shunt, resulting in progressive RV dilation. Patients with long-standing unrepaired PAPVR and left-to-right shunt may develop pulmonary hypertension.

31.4 Preoperative Assessment and Management

31.4.1 Clinical Presentation

Infants with obstructed TAPVR present soon after birth with cyanosis and respiratory distress in proportion to the degree of pulmonary venous obstruction. Feeding may worsen

cyanosis in those with infradiaphragmatic drainage due to compression of the vertical vein by the food-filled esophagus. On physical examination, signs of pulmonary edema and pulmonary hypertension (loud P2, the murmur of tricuspid regurgitation, or a gallop rhythm) are present, and hepatomegaly is not uncommon.

Conversely, infants with unobstructed TAPVR present later than their obstructed counterparts and not as dramatically. They are not severely ill but may have a history of failure to thrive and frequent pneumonias. On physical exam, mild cyanosis and mild hepatomegaly may be seen. Cardiac findings include a fixed-split S2 with a loud P2 and the soft systolic murmur of relative pulmonic stenosis (similar to large ASD).

Those with PAPVR may present at any age, from infancy to adulthood, generally with mild symptoms, similar to those with ASD, including respiratory infections, exertional dyspnea, and arrhythmias. Infants with scimitar syndrome may present with failure to thrive.

31.4.2 Chest Radiography

In infants with obstructed TAPVR, the chest X-ray shows gross pulmonary edema without cardiomegaly. A pleural effusion may also be present. These findings may be misinterpreted as surfactant deficiency, severe neonatal pneumonia, or lymphangiectasia.

In infants with unobstructed TAPVR, the chest X-ray typically shows cardiomegaly (the characteristic "snowman heart" appears only after a few months of age) and increased pulmonary blood flow but not severe pulmonary edema.

In children and adults with PAPVR, the chest X-ray may be normal or show increased pulmonary vascularity and mild cardiomegaly. In those with scimitar syndrome, the "scimitar vein" may be apparent along with right lung hypoplasia and sequelae of respiratory infections characteristic of this disease.

31.4.3 EKG

In obstructed and unobstructed TAPVR, EKG shows RVH (which may be dismissed as "physiologic") and occasionally p pulmonale and the RSr' configuration. The EKG of patients with PAPVR is similar to that of patients with ASD. Older patients with PAPVR may exhibit arrhythmias.

31.4.4 Echocardiography

Echocardiogram is the first-line imaging study of choice in patients with developmental pulmonary venous anomalies and associated defects. Those with TAPVR will show large right-sided and small left-sided structures, dilated PAs, features of pulmonary hypertension, and an intra-atrial communication with a pure right-to-left shunt. The dilated vertical vein and its connections to the anomalous pulmonary veins are best visualized behind LA from the suprasternal notch. Determining which type of TAPVR is present is very important. The features of the supracardiac type are best imaged in the short axis through the suprasternal notch using color mapping and Doppler interrogation to define the left SVC flow. The large coronary sinus (characteristic of the cardiac type of TAPVR) may be imaged in the apical four-camber and parasternal short-axis views. Subcostal views may demonstrate a dilated vein descending through the diaphragm in the infradiaphragmatic type. Echocardiographic findings of obstructed vs. unobstructed TAPVR are similar, except for the signs of obstruction (engorged vertical vein) and the relative frequency of the specific anatomic subtypes found (i.e., features of subdiaphragmatic drainage are less likely to be present in an infant with unobstructed TAPVR). The possibility of the mixed type of TAPVR or of PAPVR is only eliminated if all four pulmonary veins are visualized connecting to the confluence.

31.4.5 Magnetic Resonance Imaging

Magnetic resonance imaging of the heart and pulmonary veins supplements echocardiographic findings, especially if adequate echocardiographic images cannot be obtained, and visualizes small intrapulmonary veins, the presence of which is associated with poor surgical outcome in TAPVR. The scimitar vein and associated vascular anomalies (aortic collaterals into the pulmonary sequestration, etc.) are easily seen.

31.4.6 Cardiac Catheterization

Perioperative diagnostic angiography is only occasionally needed in the cases of TAPVR, most often to relieve a restrictive atrial communication. Despite reports of successfully relieving pulmonary venous obstruction interventionally [7–10], this approach has not been widely accepted. On the other hand, in children with scimitar Syndrome a preoperative cardiac catheterization may be useful deliniating the location of the scimitar vein and the presence of aortic collaterals to the sequestered lung. The anatomy of the pulmonary venous drainage can be demonstrated by pulmonary artery wedge injections, on levophase (Fig. 31.4a, b), or by systemic venous balloon-occlusion angiography within the vein to which the pulmonary veins drain.

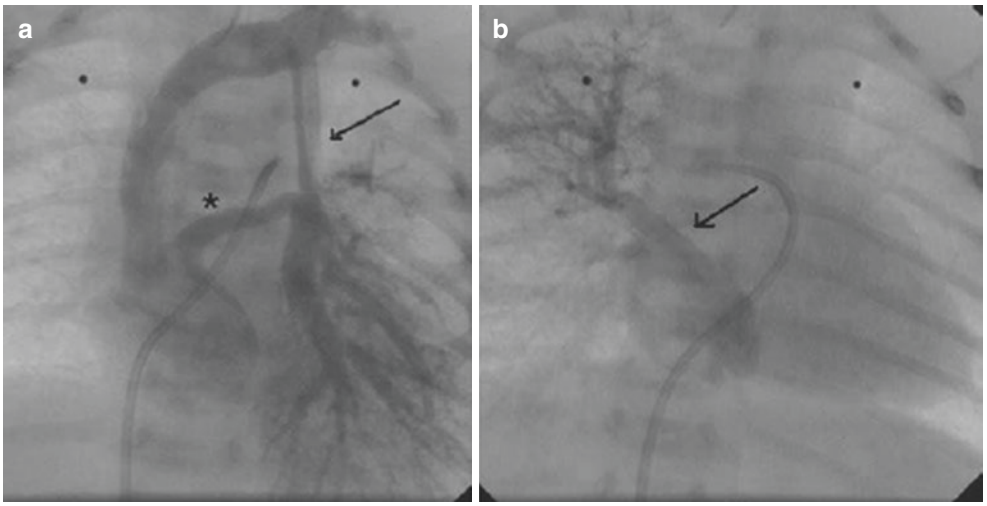

Fig. 31.4 (**a**) Following a left pulmonary artery wedge injection on levophase, the complex anomalous pulmonary venous connection is demonstrated. The left pulmonary veins drain dually into the innominate vein via a vertical vein (arrow), as well as to the pulmonary venous confluence which drains to the coronary sinus via a horizontal vein (∗). (**b**) Following wedge injection in the right pulmonary artery, the levophase demonstrates the right pulmonary veins (arrow) returning to the coronary sinus with a large unobstructed confluence

31.5 Preoperative Management

The goal of preoperative management of severely ill infants with obstructed TAPVR should be to maintain adequate oxygenation and cardiac output and prevent end-organ damage while preparing for an emergent repair. Occasionally, due to intractable hypoxemia and acidosis, this is unachievable without resorting to extracorporeal membrane oxygenation (ECMO). Such infants are stabilized on ECMO for 1–2 days and then taken to the operating room. Ultimately, expedient repair as soon as the infant is stable is crucial.

Severely ill infants with obstructed TAPVR should be emergently intubated with a cuffed endotracheal tube in anticipation of poor pulmonary compliance, high airway resistance, and high airway pressures. Positive end-expiratory pressure (PEEP) as high as 10–12 mmHg and peak inspiratory pressure (PIP) as high as 35–40 mmHg may be necessary to minimize pulmonary edema and maximize oxygenation and ventilation. Maneuvers that decrease PA pressure and increase pulmonary blood flow (such as induction of alkalemia and use of nitric oxide (NO)), albeit frequently necessary, should be implemented very carefully, since in the setting of pulmonary venous obstruction they will lead to pulmonary edema and worsen respiratory status. Nevertheless, high supplemental oxygen fraction (FiO_2) (usually 100%) is indicated to maximize systemic O_2 delivery, and some advocate judicious use of NO to acutely control the pulmonary arteriolar component of pulmonary vascular resistance, optimize ventilation/perfusion matching, and perhaps decrease the risk of postoperative pulmonary hypertension [3]. Inotropic support, blood transfusion, and volume loading also help to maintain cardiac output and systemic O_2 delivery. Lastly serum electrolytes (especially ionized Ca^{++}, Mg^{++}, K^{+}, and glucose) should be normalized, and sedation and muscle relaxation should be used to reduce oxygen consumption in these infants.

The preoperative management of infants with non-obstructed TAPVR is significantly more straightforward. Although some patients might benefit from mild inotropic support and decongestive therapy, many can be managed preoperatively outside the ICU setting.

PGE1 may worsen pulmonary edema and systemic hypotension and is contraindicated in the setting of TAPVR, whether obstructed or unobstructed.

Patients with PAPVR and scimitar syndrome do not typically require any inpatient care preoperatively.

31.6 Surgical Management

Repair of TAPVR requires the use of cardiopulmonary bypass. Circulatory arrest is frequently utilized when performing the repair in neonates and small infants, but in older patients it can be avoided with the use of bicaval cannulation.

The repairs of supracardiac (Fig. 31.5) and infracardiac TAPVR are similar, involving the creation of an anastomosis between the pulmonary venous confluence and LA and ASD closure through a left or right atriotomy. Some surgeons ligate the vertical vein to eliminate the source of left-to-right shunt; others do not, citing its utility as a pop-off valve during the early postoperative course, when pulmonary hypertensive events are likely [1, 11].

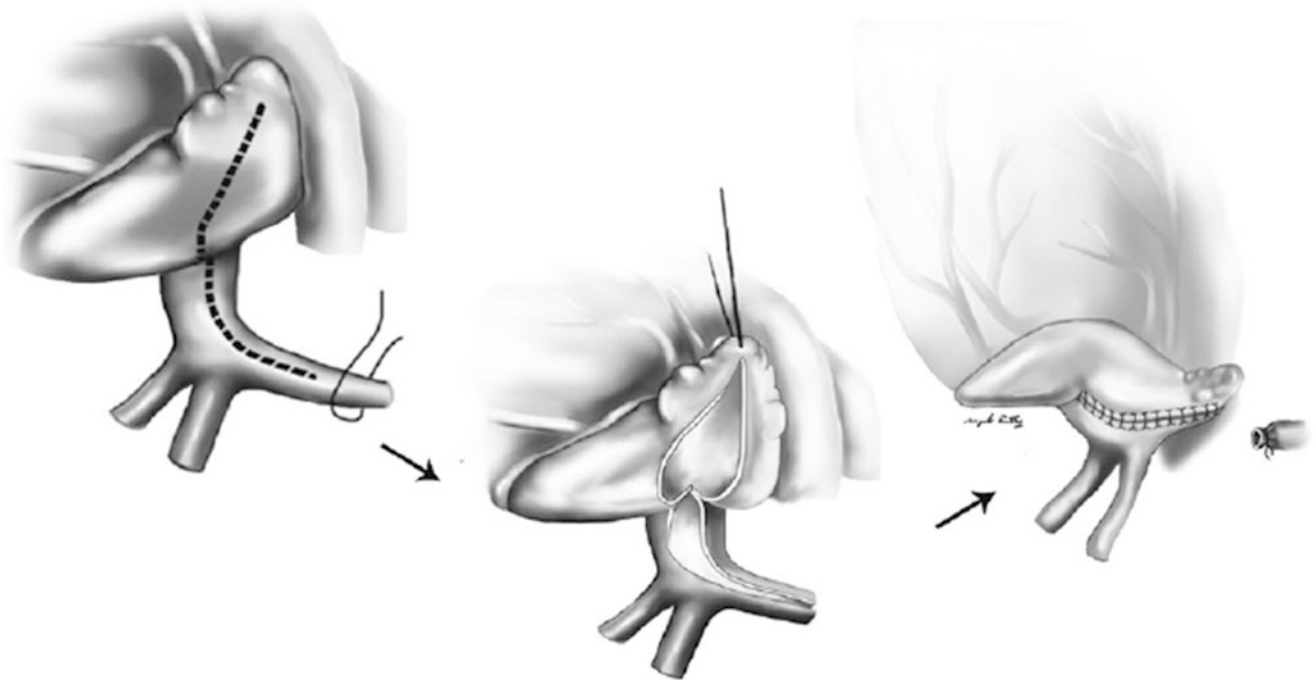

Fig. 31.5 Supracardiac TAPVR repair. With the apex of the heart elevated and retracted rightward, the left atrium (LA) and the pulmonary vein confluence are opened. The anastomosis is then performed with a running suture, and the vertical vein is ligated and divided

In the cardiac type, the pulmonary veins drain into RA either directly or via the coronary sinus. In the first case, the repair consists of funneling the pulmonary venous return into LA through ASD, which frequently needs to be enlarged. A piece of pericardium is used to create the pulmonary venous channel. In the second case, unroofing of the coronary sinus into LA and patch closure of ASD are required (Fig. 31.6).

The mixed type usually requires a combination of the previously mentioned techniques as dictated by the specific anatomy. Finally, a single anomalous pulmonary vein can occasionally be left uncorrected without a major hemodynamic consequence.

PAPVR is most commonly repaired using the Warden procedure, while the repair of the scimitar vein involves its redirection to LA using a baffle. Both surgical techniques are discussed in more detail elsewhere in this volume.

31.7 Postoperative Management

Postoperative pulmonary hypertension and low cardiac output are frequently seen in infants with TAPVR due to young age, exposure to cardiopulmonary bypass, medial muscularization of the pulmonary arterioles leading to labile PA pressures, and small left-sided structures. Infants not obstructed preoperatively are at a lesser risk for postoperative pulmonary hypertension, while those with residual postoperative pulmonary venous obstruction are at an increased risk for it. Therefore, all attempts should be made to obtain postoperative pulmonary venous gradients, and RV pressure by echocardiography is important. The use of transthoracic PA or LA lines in addition to the standard monitoring is helpful.

To mitigate their risk for pulmonary hypertension, the post-TAPVR repair patients may be sedated and muscle-relaxed during early recovery. Noxious stimuli (endotracheal suctioning, bathing, invasive procedures) should be minimized during this period and adequate sedation and hyperventilation used preemptively as appropriate [1].

The ventilatory strategy should avoid acidosis, hypercarbia, and alveolar under- and overdistension. Thus, PEEP is titrated to avoid atelectasis, pulmonary edema, and hyperexpansion, and other ventilatory settings are adjusted to produce a Vt of 10–12 cc/kg and normocarbia or mild respiratory alkalosis.

The chest may be left open for 24–48 h after repair (especially in neonates), and ECMO and NO (or, in some centers, isoproterenol infusion used as pulmonary vasodilator) [1] may be necessary early on. In more stable patients, routine deescalating postoperative hemodynamic support is used. Supraventricular arrhythmias, common after TAPVR repair (5–18%, with a higher incidence among patients with cardiac-type TAPVR) [12, 13], are treated in the standard fashion.

Fluid management should initially be conservative (total fluids at half maintenance on postoperative day one, slowly liberalized to full maintenance over 3–4 days) in order to avoid overloading the small left-sided structures and causing pulmonary edema.

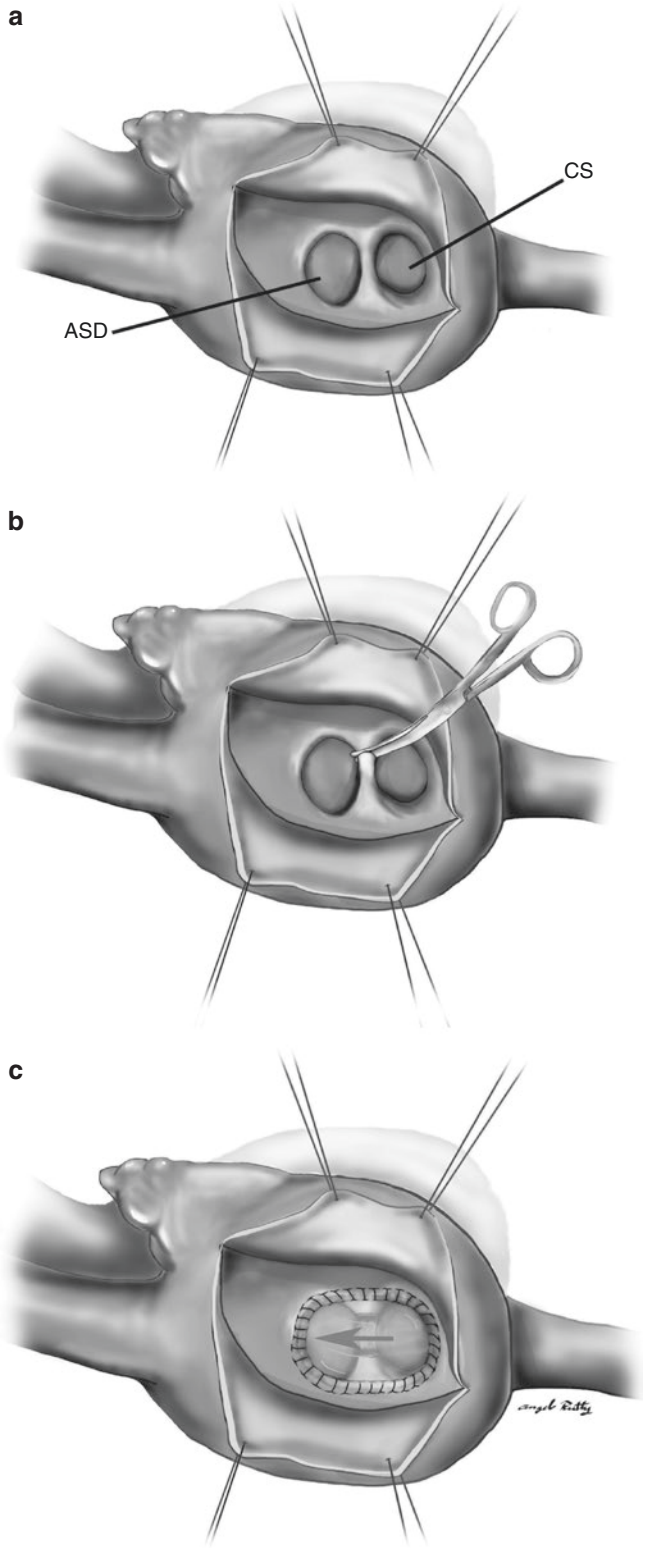

Fig. 31.6 Cardiac TAPVR repair. (**a**) Via a right atriotomy, the large coronary sinus (CS) and the interatrial communication (atrial septal defect (ASD)) are visualized. (**b**) The coronary sinus is unroofed into the LA. (**c**) The coronary sinus and the ASD are closed with a single patch, creating a new pulmonary venous channel

The postoperative care of the PAPVR is usually uncomplicated, although pulmonary hypertension may complicate their recovery as well. Patients with PAPVR draining into SVC may develop SVC obstruction and obstruction of the baffle which reroutes the right pulmonary veins into LA. Patients with scimitar syndrome may also develop baffle obstruction. Chest X-ray is useful in the postoperative care of both TAPVR and PAPVR repair – bilateral or unilateral opacification may be an early indicator of residual pulmonary venous obstruction [14].

31.8 Long-Term Outlook

The long-term outlook for patients with repaired TAPVR continues to be good, with an operative mortality of 5–10% (vs. 10–15% 10 years ago) [15] and intermediate- and long-term survival of around 95% and 85%, respectively, in patients with biventricular hearts [11, 16, 17]. Significant risk factors for early mortality include postoperative single ventricle physiology (both short- and long-term survival is significantly lower in this group), young age (below 1 year in most studies), low weight, and long bypass time [11, 17]. Postoperative stenosis of the individual pulmonary veins or the pulmonary venous confluence is common (around 15% after 1–2 years), especially in the infradiaphragmatic and mixed types, and some authors advocate for primary sutureless repair in this patient population as a means to prevent it [18]. This repair, however, has its own set of limitations and is not universally accepted in these patients. Nevertheless, with successful neonatal repair, the outlook is very good even in this group [15, 19].

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Chapter 32
Dextro-Transposition of the Great Arteries (D-TGA)

Rukmini Komarlu, Victor O. Morell, Jackie Kreutzer, and Ricardo A. Munoz

Abstract Transposition of the great arteries (TGA) is the second most common form of cyanotic congenital heart disease (5–7% of congenital heart disease) and consists of ventriculoarterial discordance with the aorta arising from the right ventricle and the pulmonary artery arising from the left ventricle. It can occur as an isolated anomaly or in association with other cardiac defects. Extracardiac anomalies are less common in TGA, and it is rarely associated with chromosomal abnormalities. With aggressive medical and surgical therapy, this disease which was initially thought to be fatal has now resulted in patients having excellent short- and mid-term outcomes with survival into adulthood and an excellent quality of life. Lifelong cardiology follow-up is recommended following surgical repair to monitor for long-term complications.

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32.1 Introduction

Transposition of the great arteries (TGA) is a conotruncal abnormality which results in ventriculoarterial discordance with resultant parallel circulation of the systemic and pulmonary circuits. It is the second most common cyanotic congenital heart defect presenting in neonates, accounting for 5–7% of congenital cardiac malformations [1, 2]. A recent meta-analysis of 41 studies revealed a mean incidence of 315 per million live births [3] and a recent update revealed prevalence of 3/10,000 live births [4]. There is a significant male preponderance of 2:1 [5]; this defect is less commonly associated with extracardiac malformations [6], but it can be associated with dextrocardia, DiGeorge syndrome, and heterotaxy syndromes (asplenia) [7, 8]. The precise embryologic basis of this heart defect has not been completely delineated; two theories exist. The theory by de La Cruz et al. suggests that the linear (than spiral) development of the aortopulmonary septum puts the aorta in contact with the anterior conus on the right ventricle [9, 10]. The other theory originally proposed by Goor and Edwards and corroborated by Anderson and Van Praagh involves differential conal development. Normal conus is subpulmonary, anterior, and left-sided resulting in tricuspid–pulmonary discontinuity. In TGA, abnormal growth and development of the subaortic infundibulum and underdevelopment of the subpulmonary infundibulum results in the aorta being placed above the anterior right ventricle [11–13]. With the advances in fetal echocardiography, this is now most often a prenatally diagnosed condition, although the detection rates continue to remain low [14, 15].

32.2 Anatomy

The characteristic finding of TGA is discordant ventriculoarterial alignments, with the aorta arising from the right ventricle and the pulmonary artery arising from the left ventricle (Fig. 32.1). The varying relationships of the atria, ventricles, and great arteries to each other result in several anatomic configurations in TGA [16].

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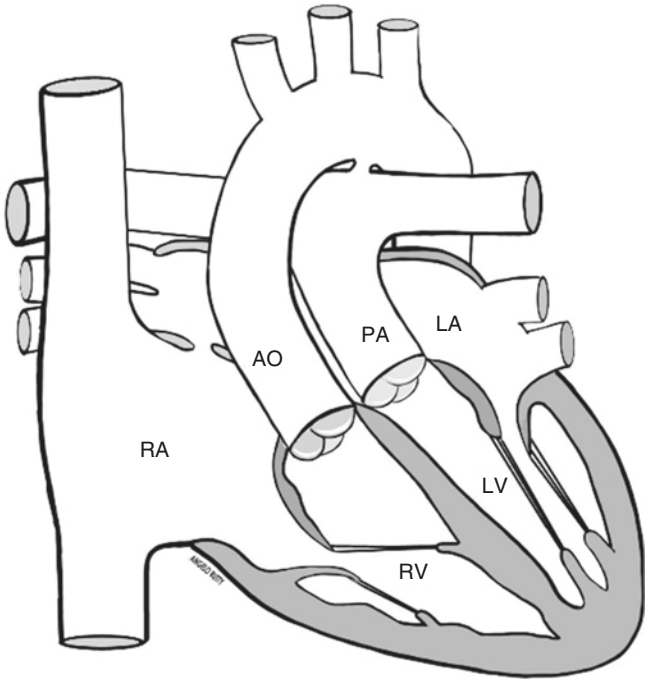

Fig. 32.1 Transposition of the Great Arteries

Position: Levocardia/Dextrocardia

1. {S, D, D}: S- atrial situs solitus, D- d-looped ventricles (right-sided RV and left-sided LV), and D- dextro transposed great arteries, with the aortic valve to the right of the pulmonic valve. There is atrioventricular concordance and ventriculoarterial discordance.
2. {S, D, A} or {S, D, L}: The aortic valve is directly anterior (A) or to the left (L) of the pulmonic valve. These variants are less common.
3. {S, L, L}: S- atrial situs solitus, L- l-looped ventricles (right-sided LV, left-sided RV), and L- levo transposed great arteries, with the aortic valve to the left of the pulmonic valve. There is atrioventricular discordance and ventriculoarterial discordance but atrial arterial concordance. This results in congenitally physiologically corrected TGA.
4. {I, L, L} or {I, L, D}: I- atrial situs inversus, L- l-looped ventricles (right-sided LV, left-sided RV), levo (L, aortic valve to left of pulmonic valve), or dextro (D, aortic valve to right of pulmonic valve) transposed great arteries. There is atrioventricular concordance with ventriculo arterial discordance and atrial arterial discordance. Visceroatrial situs inversus occurs.
5. {I, D, D}: I- atrial situs inversus, D- d-looped ventricles (right-sided RV, left-sided LV), and D- dextro transposed great arteries (aortic valve to the right of the pulmonic valve). Atrioventricular discordance and ventriculoarterial discordance occur with atrial arterial concordance. This results in physiologically corrected TGA.
6. {A, D, D} or {A, L, L}: A- atrial situs ambiguous, D- d-looped ventricles (right-sided RV and left-sided LV), and D- dextro transposed great arteries (aortic valve to right of pulmonic valve). There is ventriculoarterial discordance. A- atrial situs ambiguous, L- l-looped ventricles (right-sided LV, left-sided RV), and L- levo transposed great arteries. There is ventriculoarterial concordance. There is visceroatrial situs ambiguous in both.

32.3 Co-Existing Anomalies

Approximately 50% of patients with TGA have no other anomalies, besides a patent foramen ovale (PFO) or patent ductus arteriosus (PDA). About 40–45% of patients will have an associated ventricular septal defect (VSD) although the VSD may be small or insignificant in about a third of patients [16]. The knowledge of associated cardiac defects, presence, and size of the patent foramen ovale/atrial septal defect, ventricular septal defect, and the patent ductus arteriosus are extremely important in the postnatal management of these patients. Left ventricular outflow tract obstruction (LVOTO) can occur in 25% of patients, more commonly with VSD [16]. Assessment should evaluate for other co-existent lesions of the atrioventricular valves (especially straddling AV valves or mitral valve attachments in the LVOT), coronary arteries, aortic arch [hypoplasia, coarctation (seen in 5%) or interruption], right ventricular outflow tract obstruction (RVOTO), and hypoplasia of the right ventricle which can alter management strategies. A specific type of TGA with malalignment VSD and resultant RVOTO is called Taussig Bing anomaly. In uncorrected transposition physiology, the right ventricular pressure is higher than the left ventricular pressure with the septum bowing toward the LV which may result in overestimation of the LVOT gradient.

The orientation of the great vessels to each other should be defined as well (side by side, oblique, or anteroposterior). The great vessel orientation causes rotation of the facing sinuses. Since the coronary arteries follow the shortest course to the aortic sinuses in the aortic root, accurate delineation of their origins and course are of paramount importance for surgical management as well as for the intensivist to anticipate problems postnatally. Summary of aortic sinuses in the aortic root/the coronary artery location and great vessel orientation:

1. Side by Side: Aortic valve rightward position, anterior and posterior facing sinus
2. Oblique: Aortic valve anterior/rightward, left anterior facing sinus, and right posterior facing sinus
3. Anterior–Posterior: Aortic valve in anterior position, right facing sinus, and leftward facing sinus

Coronary artery patterns are variable in TGA with multiple classifications existent in the literature. In 1978, Yacoub and Radley Smith proposed a simple surgically oriented method of classifying the coronary arteries: Types A to E with type A (left anterior descending and left circumflex from anterior sinus) being most common and type D (circumflex from right coronary artery) being second most common type. In 1983, the

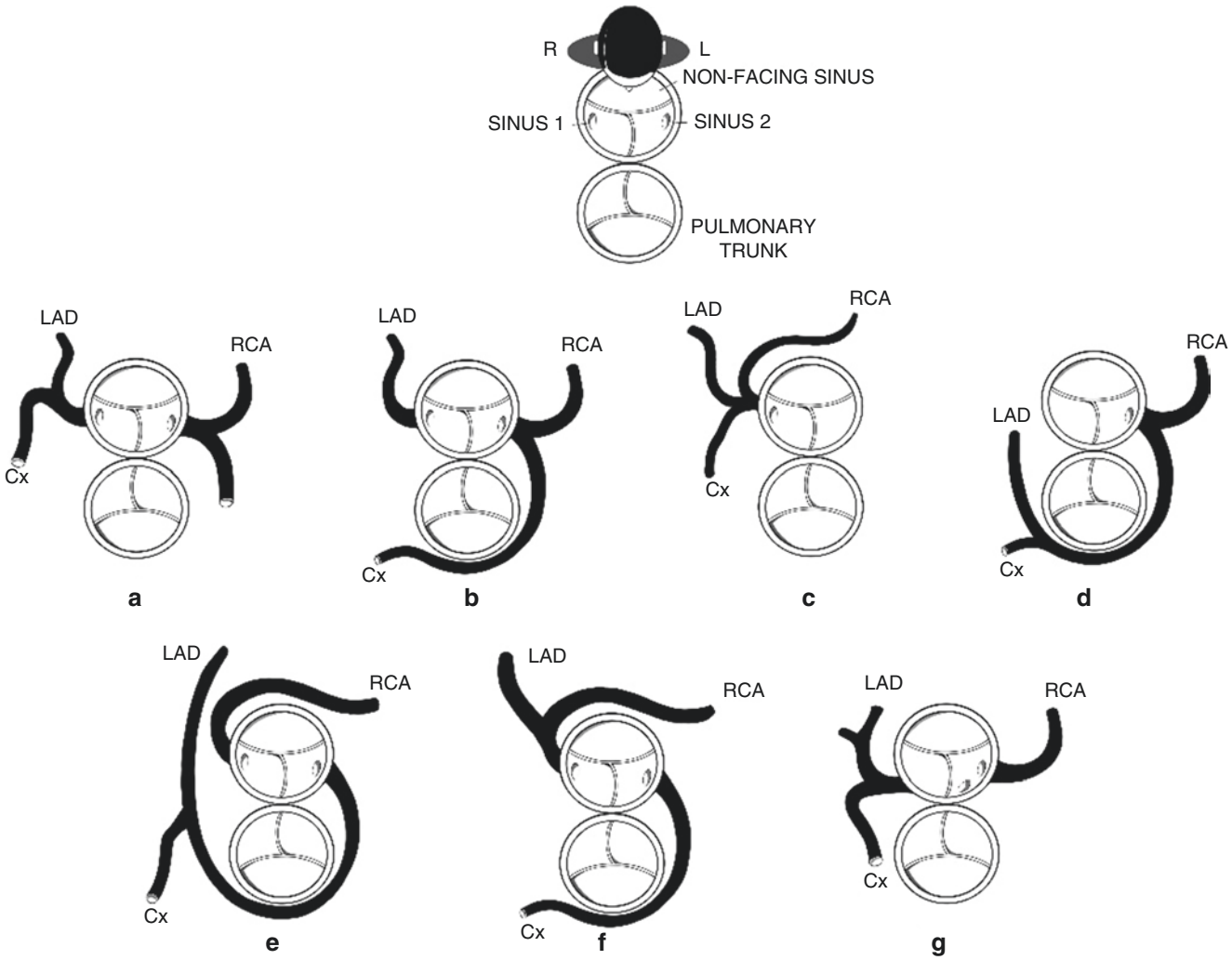

Fig. 32.2 *Frequent coronary patterns in TGA*. (**a**) Normal anatomy, (**b**) Circumflex artery from the RCA, (**c**) Single left coronary artery, (**d**) Single right coronary artery, (**e**) Inverted coronary pattern, (**f**) RCA from LAD and circumflex from sinus 2, (**g**) Intramural left main from sinus 2

Leiden classification was put forth, the coronary arteries are described with a person sitting in the non-facing sinus, looking toward the pulmonary artery: sinus 1 represents right-hand facing sinus and sinus 2 represents left-hand facing sinus (Fig. 32.2). Single coronary ostium and intramural course had higher associated postoperative mortality [17, 18] whereas newer surgical approaches have ameliorated this difference [19].

32.4 Physiology

32.4.1 Fetal Physiology

The fetus with TGA appears to tolerate this physiology well in utero, due to the presence of the foramen ovale and ductus arteriosus, with resultant normal gestational development and in some cases large babies. In simple TGA, the left ventricle connects with the pulmonary trunk which connects with the ductus arteriosus (DA). The left ventricular afterload is determined by the pulmonary vascular resistance and through the DA by the low-resistance placental circulation. The ventricular afterloads will affect their emptying and could influence the relative proportion of the IVC blood into the right and left ventricles. Normally, the SVC carrying the lower oxygenated blood is directed to the RV and pulmonary tree. In the fetus with TGA, the lower oxygenated blood will be directed toward the aorta, especially the ascending aorta (supplying the coronaries and the carotid arteries). This may result in lower head circumference and structural abnormalities of the brain in TGA fetuses [20]. Additionally, the IVC blood will be directed toward the LV with resultant lowered pulmonary vascular resistance. The shunting of oxygen- and glucose-rich blood through the ductus arteriosus to the descending aorta may result in increased somatic growth and hyperinsulinism [21]. Hypermobility of the atrial septum and reverse diastolic patent ductus arteriosus flow may predict need for urgent balloon atrial septostomy in the postnatal period [22], while another study showed that a foramen ovale to total atrial septal length of <0.5 and fixed appearance of the flap valve indicated the need for emergent postnatal balloon atrial septostomy [23].

As stated above, the circulations in TGA exist in parallel rather than in series. Assuming a normal gas exchange, the oxygenated blood from the left atrium will be ejected by the left ventricle back into the pulmonary circulation without reaching the body. The de-oxygenated blood returning from the superior and inferior vena cavae is pumped back to the body through the aorta, without reaching the left-sided structures for oxygenation. The physiologic consequence of this anatomic arrangement is a profound hypoxemia incompatible with life unless intracardiac (PFO/ASD or VSD) or extracardiac (patent ductus arteriosus–bronchial circulation) communications are appropriately patent. This would enable systemic venous blood to enter the pulmonary circulation to be oxygenated and the pulmonary venous blood to enter the systemic arterial system to provide oxygen to the tissues [21].

The key concepts relevant to pre- and postoperative management should be elucidated to understand the preoperative physiology of this condition. To avoid confusion, it is important to differentiate between anatomic and physiologic shunts:

- The anatomic left-to-right shunt represents the amount of blood crossing from left side of the heart to the right side of the heart.
- The physiologic left-to-right shunt is the amount of oxygenated blood that returns to the left side of the heart through the lungs.
- The anatomic right-to-left shunt is the amount of blood passing from the right side of the heart to the left-sided structures (left atrium, left ventricle, and pulmonary artery).
- The physiologic right-to-left shunt is the amount of de-oxygenated blood that reaches the systemic circulation without passing through the lungs.

From a functional standpoint, the amount of oxygen that can be taken up in the lungs is dependent on the volume of systemic venous blood reaching the lungs, termed effective pulmonary blood flow (Q_{EP}). In TGA, the maximal amount of systemic venous blood that can go to the lungs is the anatomic right-to-left shunt; but this would not be the effective pulmonary blood flow in the presence of bidirectional shunt. The effective systemic blood flow (Q_{ES}) would be the amount of oxygenated blood being sent back to the body to deliver oxygen, and this would be the anatomic left-to-right shunt. The anatomical right-to-left shunt must be equal to the anatomical left-to-right shunt in TGA. Inefficient effective systemic or pulmonary blood flow as a result of inadequate intracardiac or extracardiac communications is incompatible with survival.

Clinically, these infants may arrive in the intensive care unit with cyanosis, systemic hypoperfusion, cardiogenic shock, metabolic acidosis, oliguria, and multiorgan dysfunction. The degree of mixing can be assessed by identifying the combination of ventricular filling, size, and degree of shunting across the different communications, pulmonary vascular resistance, and other coexistent anomalies such as ventricular outflow tract obstruction. If there is effective mixing with pulmonary stenosis, the effective pulmonary blood flow will be low (poor oxygenation) with decreased oxygen saturation. Conversely, if there is a significant right ventricular outflow tract obstruction or coarctation of the aorta (closing PDA), the effective pulmonary blood flow would be sufficient with "appropriate" oxygenation, but the infant will experience systemic hypoperfusion.

Soon after birth, the pulmonary vascular resistance is high with resultant bidirectional flow across the PDA (PA to aorta in systole and aorta to PA in diastole). This leads to reverse differential cyanosis characteristic of TGA (lower half of the body will be pink, upper half will be cyanotic); however, this is only transiently present and resolves once the pulmonary vascular resistance quickly declines leading to flow almost entirely from the aorta to pulmonary artery.

32.5 Diagnosis

32.5.1 D-TGA, Intact Ventricular Septum, and Inadequate Intra and Extracardiac Shunts

32.5.1.1 Clinical Presentation

Initially the neonate is robust soon after birth as clinical stability is provided by the patent foramen ovale and patent ductus arteriosus. However, clinical symptoms appear with PDA closure or even sooner if there is a restrictive PFO. Profound cyanosis, tachypnea without retractions, and prominent cardiac impulse are commonly present. Murmurs are not usually heard and pulses are normal until cardiogenic shock develops. Arterial oxygen saturation will usually range between 50% and 70% and arterial blood gases show oxygen values in the low and mid-20s (unresponsive to oxygen administration) with metabolic acidosis and usually normal CO_2.

32.5.1.2 Chest X-Ray

Chest X-ray (antero-posterior view) shows no significant cardiomegaly and clear lung fields. The shape of the heart is described as "egg on a side." A narrow superior mediastinal shadow is seen with no evidence of the main pulmonary artery (Fig. 32.3).

32.5.1.3 ECG

Electrocardiogram is essentially normal with prominent right ventricular voltages.

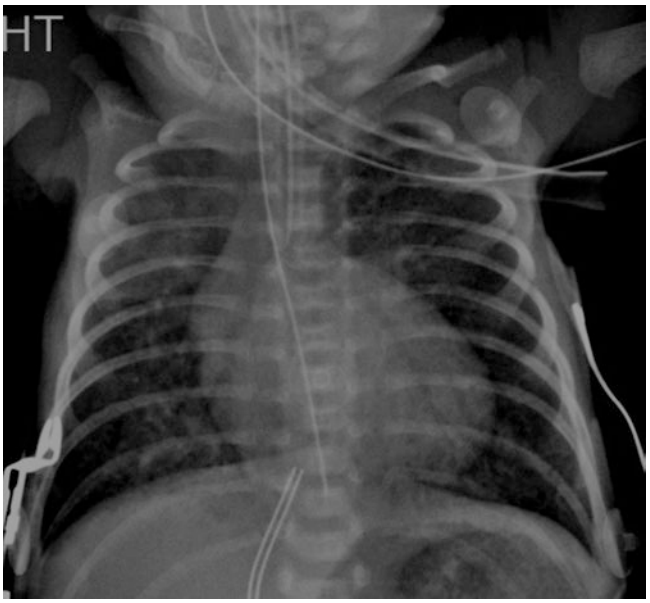

Fig. 32.3 Chest X-ray demonstrating narrow mediastinum ("egg on a side" appearance) and clear lung fields

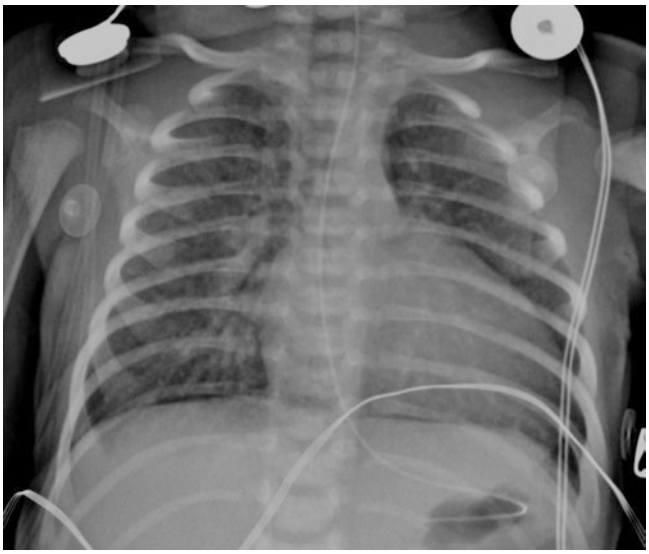

Fig. 32.4 Chest X-ray demonstrating cardiomegaly and increased pulmonary vascularity

32.5.2 D-TGA, and Ventricular Septal Defect

32.5.2.1 Clinical Presentation

Cyanosis may not be prominent in this group of patients, with higher saturations due to shunting across the VSD. However, in some patients, the VSD may be small and not ensure sufficient mixing with ultimate need for balloon atrial septostomy. The physical exam shows an apparently normal infant with comfortable tachypnea. Cardiac activity may be normal with a normal first sound and a loud narrowly split second heart sound. There is grade 2–3/6 holosystolic murmur best heard over the left lower sternal border. Arterial oxygen saturations range between 75% and 90%, and arterial oxygen level is approximately in the 40s with normal pH and pCO_2. Without surgical repair, these patients eventually develop heart failure due to increased pulmonary blood flow.

32.5.2.2 Chest X-Ray

Chest X-ray shows a narrow superior mediastinal area, cardiomegaly, and prominent vascularity (Fig. 32.4).

32.5.2.3 ECG

Electrocardiogram may be normal or may demonstrate RVH.

32.5.3 D-TGA and Pulmonary Stenosis

32.5.3.1 Clinical Presentation

Cyanosis is a prominent finding once the PDA constricts and a harsh 2–3/6 systolic ejection murmur best heard at the mid left sternal border is ascertained on physical exam. The first sound is normal and the second sound is loud. The right ventricular impulse is not hyperactive and there are no signs or symptoms of congestive heart failure.

32.5.3.2 Chest X-Ray

Chest X-ray shows no significant cardiomegaly with decreased pulmonary vascular markings (Fig. 32.5).

32.5.4 D-TGA, Coarctation of the Aorta, or Interrupted Aortic Arch

32.5.4.1 Clinical Presentation

The clinical presentation may not necessarily differ from isolated D-TGA, especially when the PDA is open. Nevertheless, the combination of D-TGA, VSD, and arch hypoplasia/interrupted aortic arch increases the risk of augmenting pulmonary blood flow, and these patients may experience tachypnea and respiratory failure. If the neonate develops pulmonary hypertension with high pulmonary vascular

resistance, reverse differential cyanosis might be present. Absent or diminished femoral pulses and systemic hypo-perfusion may be evident when the PDA becomes restrictive.

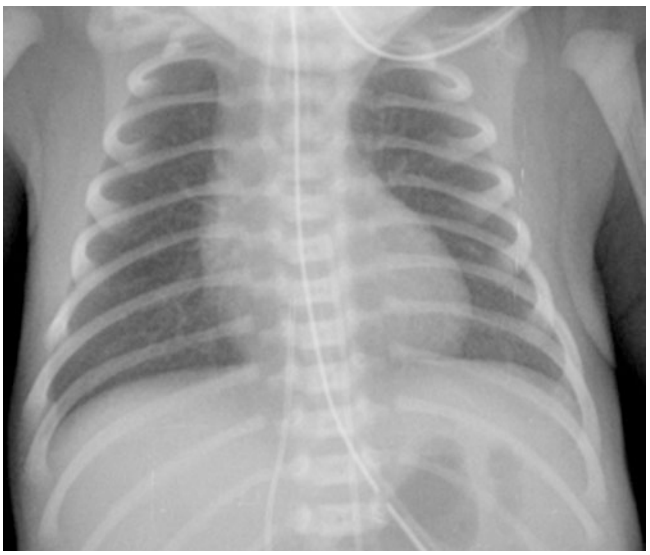

Fig. 32.5 Chest X-ray demonstrating normal cardiac size and oligemic lung fields

32.5.4.2 Chest X-Ray

Chest X-ray shows increased pulmonary vascular markings and cardiomegaly.

32.5.4.3 ECG

The electrocardiogram may be normal or may show biventricular hypertrophy. Left axis deviation can occur with TGA and inlet VSD. Isolated left ventricular hypertrophy suggests TGA/VSD and an associated hypoplastic right ventricle [24].

32.5.4.4 Echocardiography

Echocardiography is a readily available tool that allows comprehensive assessment of cardiac anatomy and associated anomalies. Subcostal views help to assess for restrictive atrial communication (Fig. 32.6), as well as the ventriculoarterial relationships, presence of ventricular septal defects, and outflow tract obstruction. Parasternal long axis views reveal the pulmonary artery arising posteriorly from the left ventricle (and bifurcating into the branch pulmonary arter-

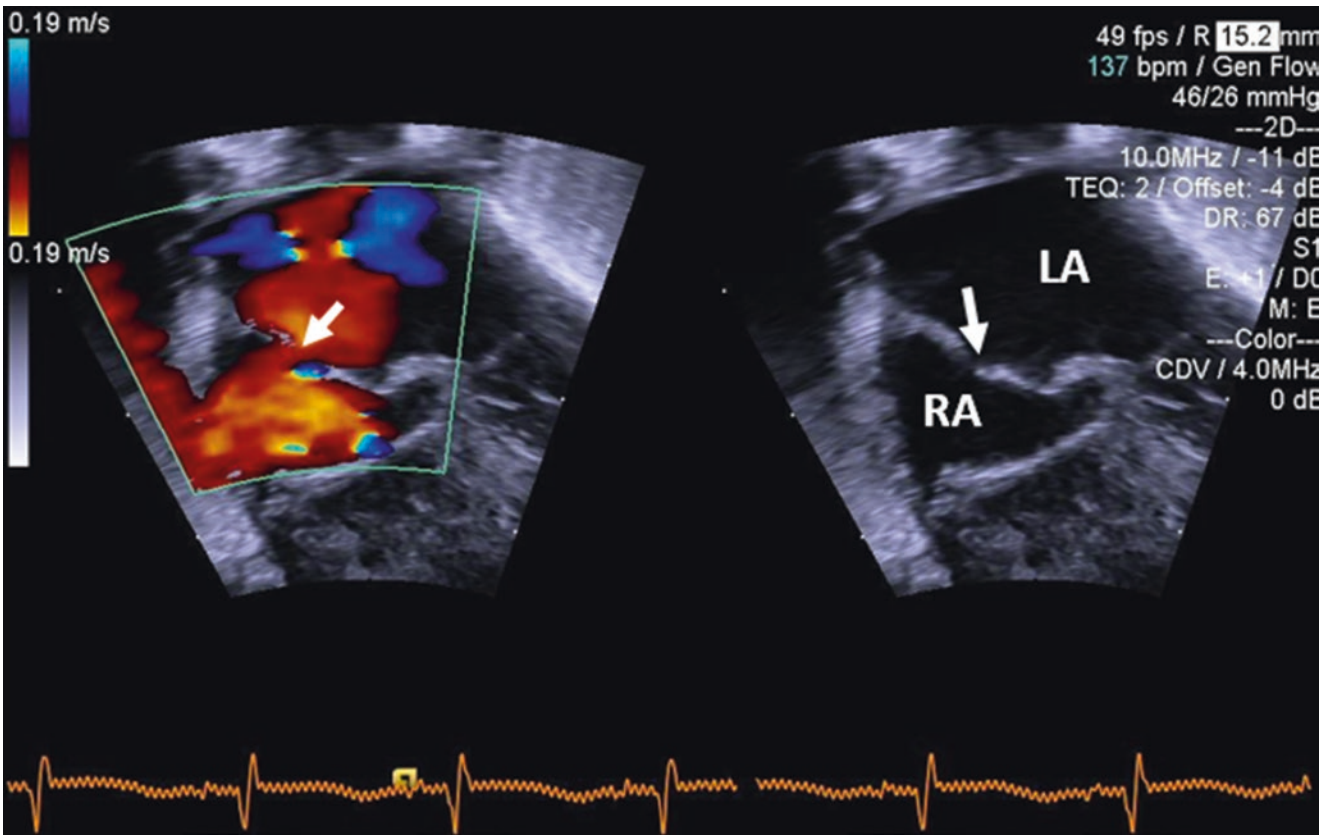

Fig. 32.6 Subcostal long axis view (Color compare and 2D) demonstrating restrictive patent foramen ovale (PFO). Arrows point to the PFO (RA right atrium, LA left atrium)

ies) and aorta arising anteriorly from the right ventricle in the same plane (Fig. 32.7). The exact relation of the aorta to the pulmonary artery, coronary arterial anatomy, and biventricular size and function can be evaluated from parasternal short axis views. The size and direction of PDA flow, arch hypoplasia, and coarctation of the aorta can be assessed from suprasternal views (Fig. 32.8).

32.6 Preoperative Management

Essentially, these patients can be transferred to the intensive care unit with two clinical presentations:

1. Unstable patient with cyanosis and cardiogenic shock.
2. Stable infant with prenatal diagnosis.

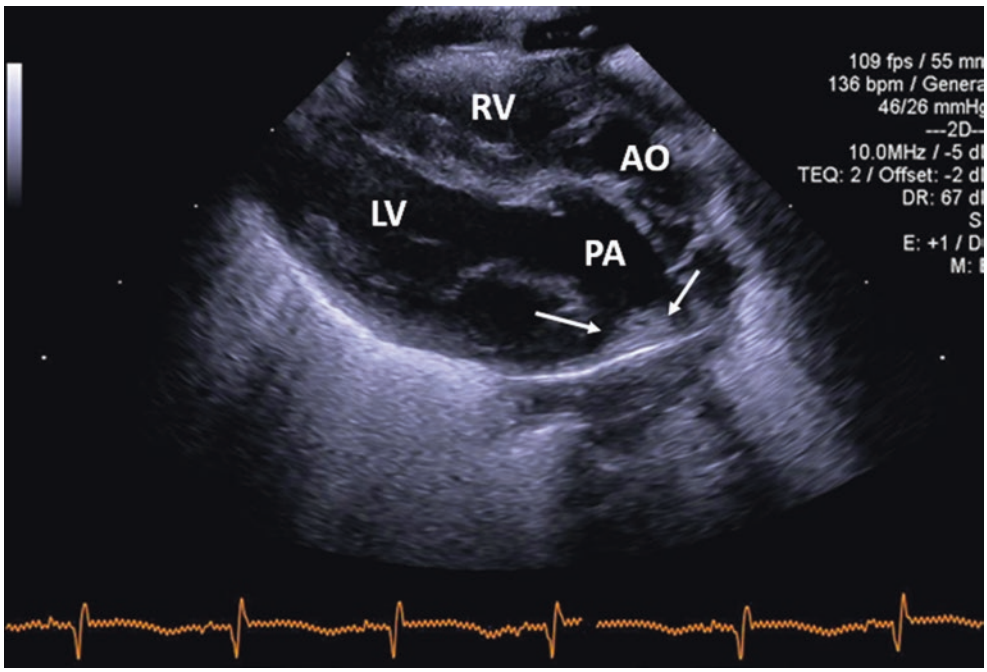

Fig. 32.7 Parasternal long axis view demonstrating pulmonary artery (PA) arising from left ventricle (LV) and aorta (AO) arising from right ventricle (RV). Arrows point to branch pulmonary arteries

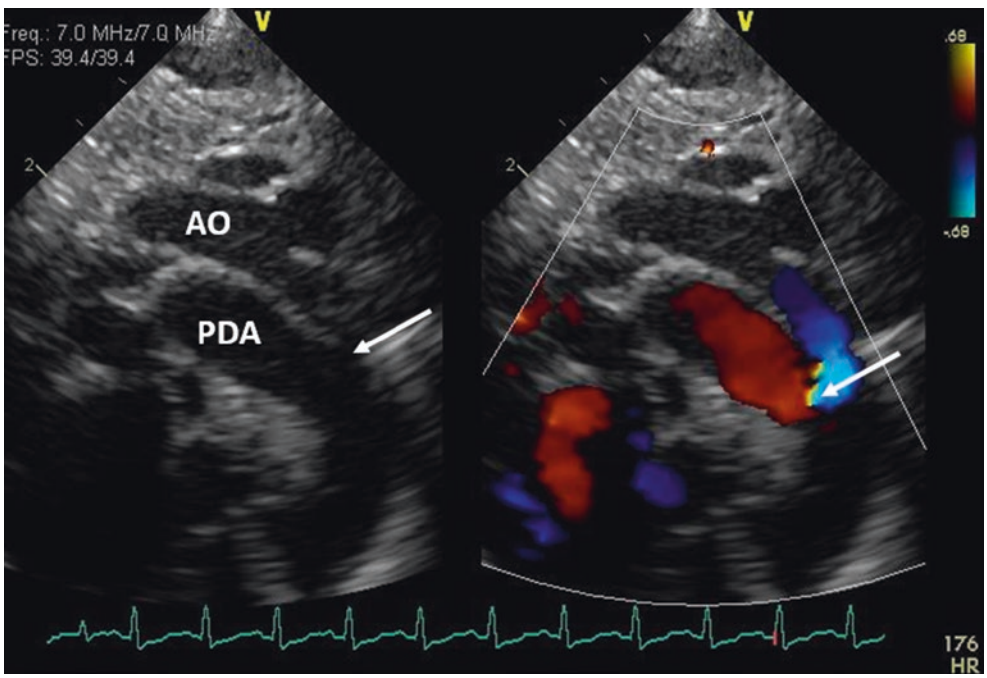

Fig. 32.8 Suprasternal view (2D and color compare) demonstrating hypoplastic aortic arch (AO) inserting into a large patent ductus arteriosus (PDA). Arrows point to the area of coarctation

Unstable neonates must have the ABC of resuscitation completed along with a brief echocardiogram for diagnosis, assessment of ventricular function, and evaluation of patency of ductus arteriosus and foramen ovale. A more detailed echocardiogram should be completed once the infant is stable. PGE1 must be initiated (0.03–0.1 mg/kg/min, dose could be adjusted according to the clinical picture) and inotropic support and fluid and bicarbonate administration should be titrated according to the acid-base status, ventricular function, and hemodynamic status. Some of these patients require "generous" fluid administration to maintain appropriate mixing. The fundamental cause of the cardiovascular instability is insufficient mixing due to PDA closure or restrictive foramen ovale. If the constricting PDA is the only problem, prostaglandin infusion should rapidly compensate the infant. If a restrictive PFO is the main cause of insufficient mixing, an emergent balloon atrial septostomy (BAS) must be done (Fig. 32.9). This procedure can be completed at the bedside, in the intensive care unit [25] or in the cardiac catheterization laboratory (Fig. 32.10). In our experience (Children's Hospital of Pittsburgh of UPMC), the intensive care unit is the place of choice, especially if there is an umbilical catheter placed reaching the heart. However, if the echocardiogram is not able to clearly define the coronary artery anatomy and the surgeon needs that information prior to intervention, angiography of the aortic root is needed to define the coronary anatomy. In such case, it is preferred to take the patient to the Cath Lab and perform both the septostomy and angiography during the same procedure. If a patient is being transferred for an emergent balloon septostomy, it is best directly to have the patient go to the Cath Lab, as, if there were any access problems, fluoroscopy can be helpful. In addition, if any difficulties were encountered with the balloon procedure, alternative options would be readily available (static balloon dilation, ASD creation, etc.). In addition, if the umbilical venous line cannot be advanced into the heart, it is best to perform the procedure in the Cath Lab, as catheter manipulation and visualization with echocardiography is easier in the short catheter course from the umbilicus, while it can be quite difficult from the groin without fluoroscopy.

Prior to starting the BAS, blood must be available and a stable airway must be guaranteed (not necessarily all neonates must be intubated for the procedure). The preferred approach is the umbilical access, although the procedure can be easily done via the femoral vein. If the child has an umbilical vein line in place, and it reaches the heart, then it can be safely exchanged in the ICU over a wire (J tipped or floppy tipped are preferred). If instead the line ends in the liver, it is best to either go to the Cath Lab and perform a venogram of the hepatic vein to assure the ductus venosus is open, after that the catheter can be advanced through it into the heart, or a floppy tip 0.018″ wire can be used to facilitate reaching the heart, under fluoroscopic guidance. A sheath can then be placed from the umbilical vein into the right atrium, and the septostomy catheter advanced.

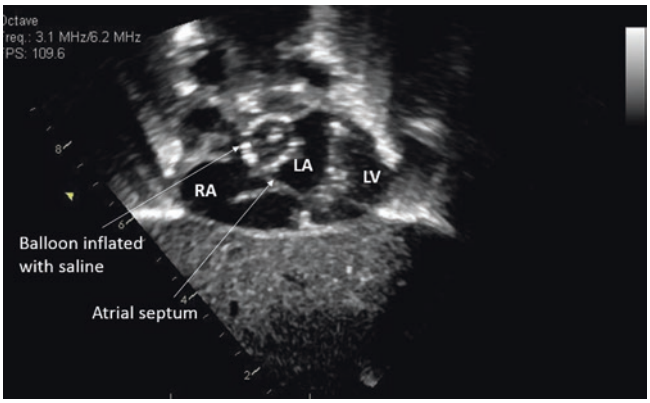

Fig. 32.9 *Balloon atrial septostomy under echocardiographic guidance.* The image demonstrates echocardiographic frame obtained during bedside balloon atrial septostomy, in a modified subcostal four-chamber view. The balloon is inflated in the left atrium, away from the mitral valve. After the septostomy is performed, the balloon will then be seen in the right atrium (RA). (LA left atrium, LV left ventricle)

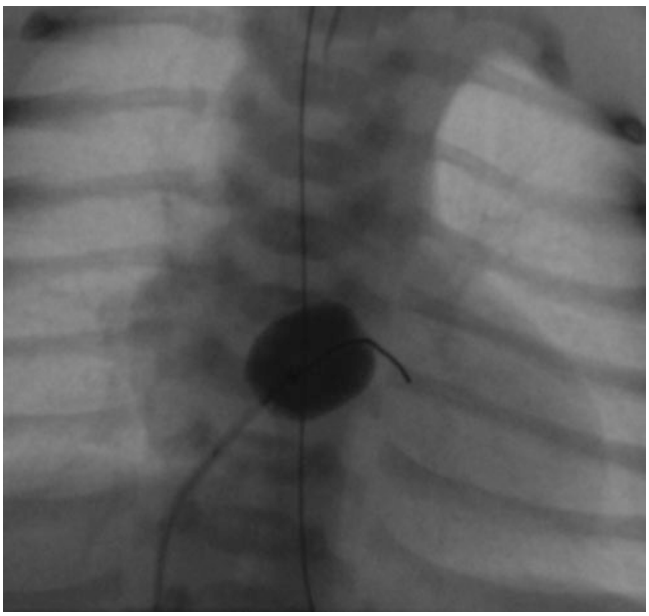

Fig. 32.10 *Balloon atrial septostomy under fluoroscopic guidance.* The image demonstrates the inflated balloon crossing the atrial septum

The setup for a septostomy includes the following:

1. Umbilical catheter (if the umbilical vein is to be accessed).
2. 0.018″ 40–60 cm floppy tip wire.
3. 6F and 7F sheaths.
4. Septostomy catheter (either of the following, or two different ones ideally available):

(a) Braun septostomy catheter (fits via a 6F sheath and has an end-hole which allows to draw back and inject saline): This is the preferred one for bedside septostomies, since it allows for sampling to help assure the tip is in the left atrium and also allows injection of saline which can be visualized by echocardiography. Takes up to 2.5 cc.
(b) Miller–Edwards balloon (Baxter) (fits via a 7F sheath): can take up to 4 cc, although 2.5–3 cc is all that is needed for a term baby.
(c) Traditional Rashkind balloon (fits via a 6F sheath).

The echocardiographer is positioned on the left side of the patient, while the interventional cardiologist is on the right side and feet of the patient. All septostomy catheters have a "hockey stick" type of curve that facilitates reaching the left atrium via the patent foramen ovale. If there is an intact septum, the patient has to go to the Cath Lab where a transeptal puncture can be performed, although this instance is extremely rare in TGA.

If angiography is indicated for definition of coronary arteries, the best approach is using the "laid-back" view, as described by Mandell et al. [26], which involves extreme caudal angulation in the AP camera (Fig. 32.11). A Berman 5F catheter is advanced antegrade into the ascending aorta and angiography is performed in this biplane (extreme caudal in the AP and straight lateral in the lateral cameras) with transient balloon occlusion of the flow. Transient complete heart block can occur as a complication associated with catheter manipulation out the right ventricular outflow tract in these patients, such that if at all possible it is best to avoid angiography and delineate the coronary anatomy by echocardiography. For many surgeons, perfect definition of coronary anatomy is not essential, as this can be determined in the operating room, and an ASO is performed for almost every anomaly anyway.

Once the BAS is completed, prostaglandin E_1 can be stopped, although some neonates may need to have the medication re-started due to poor mixing and persisting significant hypoxemia (pO_2 < 30 mmHg and academia). Prior to reinitiating the prostaglandins in these cases, an echocardiogram must be requested to assess the atrial communication and ductus arteriosus, as well as to determine the presence and degree of pulmonary hypertension. The diagnosis of pulmonary hypertension is usually confirmed by echocardiography and the incidence of persistent pulmonary hypertension in neonates with TGA is 12.5% and is more common in TGA with intact ventricular septum [27, 28]. Management strategies for this has included sedation, paralysis, and hyperventilation, medications such as inhaled nitric oxide, sildenafil, and bosentan along with extracorporeal life support alone or in combination with the prognosis remaining poor in these patients [29]. The goal is to optimize the patient's volume status and to discontinue inotropic support as soon as the infant is hemodynamically stable after BAS. Stable patients after BAS can be fed until surgical repair. Cultures are obtained and antibiotics started when sepsis is suspected. In addition, head ultrasound, renal ultrasound, and genetic tests may be routinely done prior to surgical intervention. Tissue perfusion monitoring may be followed by serial testing for blood lactate levels and near-infrared spectroscopy (NIRS) in the decompensated phase.

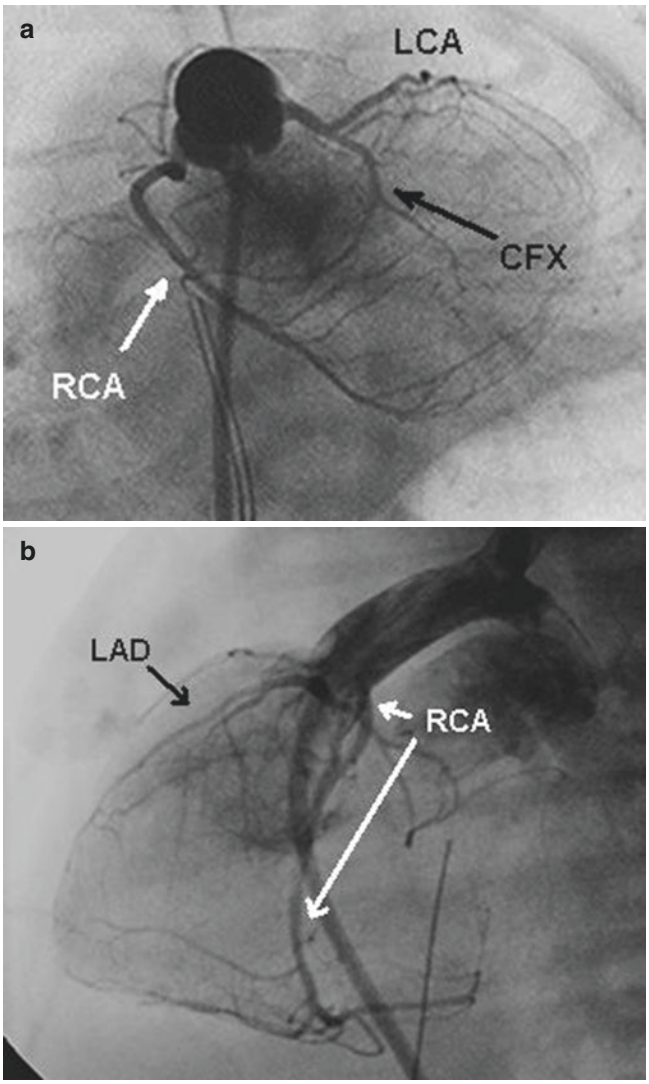

Fig. 32.11 *Aortography for coronary artery definition.* Laid-back aortogram performed in anteroposterior (**a**) and lateral projection (**b**) demonstrates normal coronary anatomy. The balloon is inflated transiently to force contrast into the coronary arteries and deflated toward the end of the injection. (RCA right coronary artery, LCA left coronary artery, CFX circumflex coronary artery, LAD left anterior descending coronary artery)

Patients with arch hypoplasia, coarctation of the aorta, or interrupted aortic arch along with VSD and D-TGA deserve special attention to avoid pulmonary over-circulation syndrome and systemic hypoperfusion with resultant multiorgan failure (refer to these conditions' specific chapters in the section titled "Preoperative Management"). Patients with

D-TGA, interrupted aortic arch, and pulmonary hypertension (concomitant lung disease) will present as critically ill with severe cyanosis [30]. ECMO may be required until pulmonary hypertension improves. The caregiver should be aware that during ECMO the left ventricle may "de-condition" and may cause complications in the postoperative care of the arterial switch operation (ASO) [31].

Associated medical problems such as respiratory distress, meconium aspiration syndrome, and CNS ischemic and hemorrhagic events should be identified and addressed appropriately. If the patient is extremely premature or other associated conditions are present, an early ASO should be delayed. If intracranial hemorrhage is present, it is advisable to wait for 2 weeks before the ASO. As a consequence of the delay of the procedure, the left ventricle needs to be re-trained to handle the high systemic vascular resistance after the ASO. Retraining the LV implies placement of a pulmonary band +/− a shunt (if patient continues to be very cyanotic). In addition, daily echocardiograms must be done to evaluate the left ventricular mass (if greater than 35 g/m^2, the patient is likely to be suitable for ASO) [32]. The LV training process should not take more than 1–2 weeks, especially in infants. During the training period, patients may require a fair amount of inotropic support due to LV failure and low cardiac output syndrome [33, 34].

32.7 Surgical Management of TGA

The arterial switch operation is the procedure of choice for the surgical management of transposition of the great arteries. It is performed via a median sternotomy incision with cardiopulmonary bypass and moderate-to-severe hypothermia. A period of deep hypothermic circulatory arrest is frequently utilized for the closure of the atrial and/or ventricular septal defects. Technically (Fig. 32.12), it involves the transection of both great vessels, the translocation of the pulmonary arteries ante-

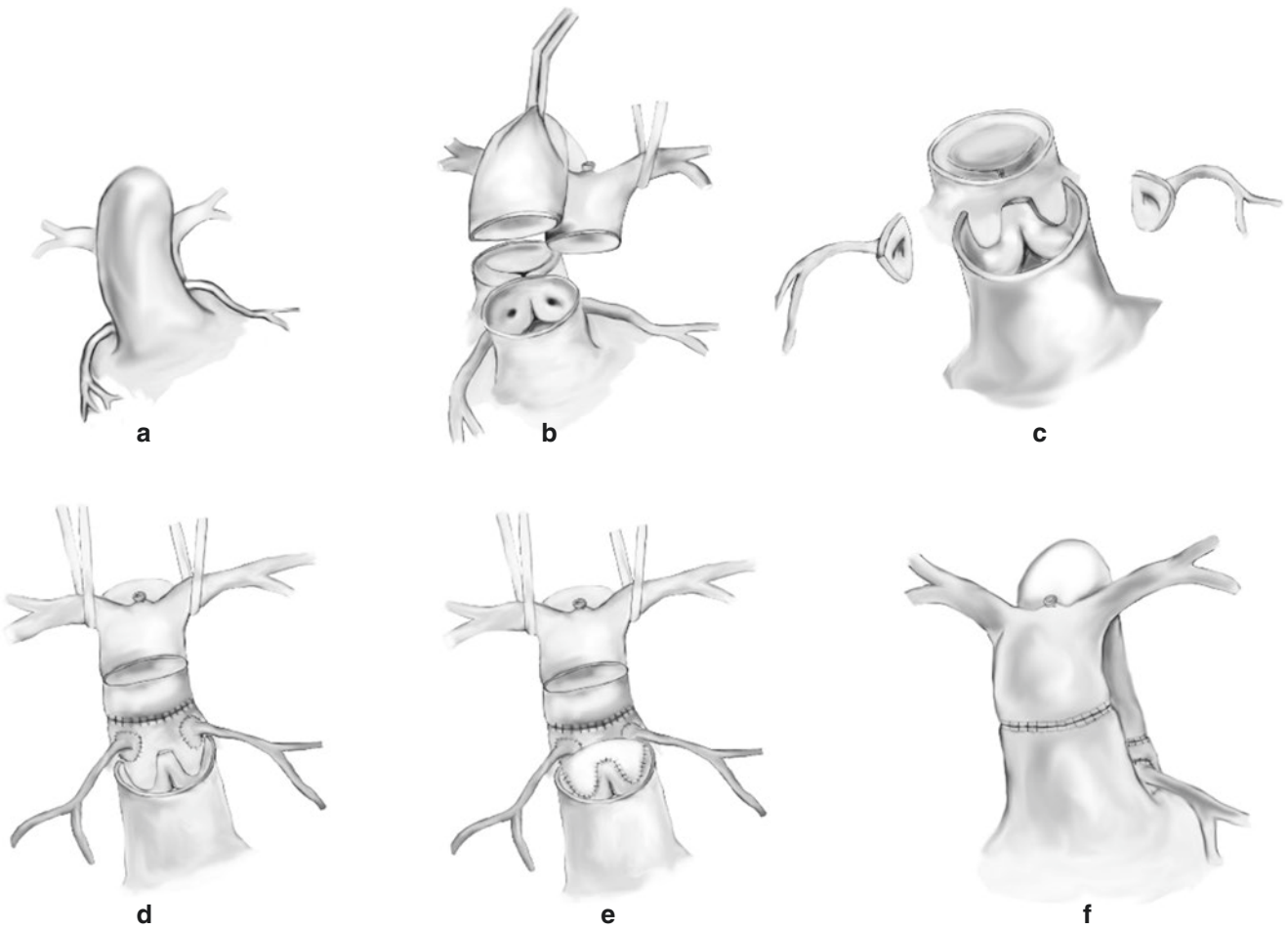

Fig. 32.12 *The Arterial Switch Operation*. (**a**) The ascending aorta is anterior to the main pulmonary artery in transposition of the great arteries. (**b**) Both great vessels are transected. (**c**) The coronary buttons are harvested from the native aorta. (**d**) After performing the Lecompte maneuver, the distal aorta is anastomosed to the neoaortic root and the coronary arteries are reimplanted. (**e**) The neopulmonary root is reconstructed with a pericardial patch. (**f**) The pulmonary artery anastomosis is performed

rior to the aorta (Lecompte maneuver), and the suturing of the distal aspect of both great vessels to the proximal arterial roots attached to the "correct ventricles," the distal ascending aorta to the arterial root attached to the left ventricle (neoaortic root, native pulmonary root), and the distal main pulmonary artery to the arterial root attached to the right ventricle (neopulmonary root, native aortic root). Very importantly, the coronary arteries need to be harvested from the native aorta and reimplanted in the neoaorta. The neopulmonary root is reconstructed with a patch of pericardium. When present, the atrial septal defect and/or the ventricular septal defect are closed through a right atriotomy. The operative mortality associated with the arterial switch operation is approximately 5%.

In cases with delayed diagnosis (greater than 6–8 weeks of age), a *two-stage* approached has been recommended. It consists of an initial pulmonary artery band (to train the left ventricle) followed by an arterial switch operation. Occasionally, a systemic to pulmonary artery shunt is needed if the patient developed significant cyanosis after pulmonary artery banding. Frequently, the left ventricle can be trained in a relatively short period of time (days) allowing for a complete repair within the same hospitalization [35, 36].

For complex TGA with left ventricular outflow tract obstruction and a ventricular septal defect, there are three surgical options. The *Rastelli repair* is frequently utilized and involves the creation of an interventricular tunnel, funneling the left ventricular blood into the anterior aorta; a conduit is used to establish right ventricle to pulmonary artery continuity (Fig. 32.13). Another alternative is the *REV procedure*; it involves the enlargement of the ventricular septal defect to create a more direct communication between the left ventricle and the aorta and a direct anastomosis between the right ventricle and the pulmonary arteries, avoiding the use of a conduit (Fig. 32.14). Finally, in the *Aortic Translocation procedure (Nikaidoh procedure)*, the aortic root is moved into the pulmonary position, closer to the left ventricle, avoiding the creation of an interventricular tunnel (Fig. 32.15). The right ventricular outflow tract can be repaired with or without a conduit. This procedure results in a more "normal" anatomic result which could result in better long-term outcomes. Patients who present later in life with an infra-systemic left ventricle may also be candidates, in some circumstance, to an atrial switch operation (a Mustard or a Senning procedure).

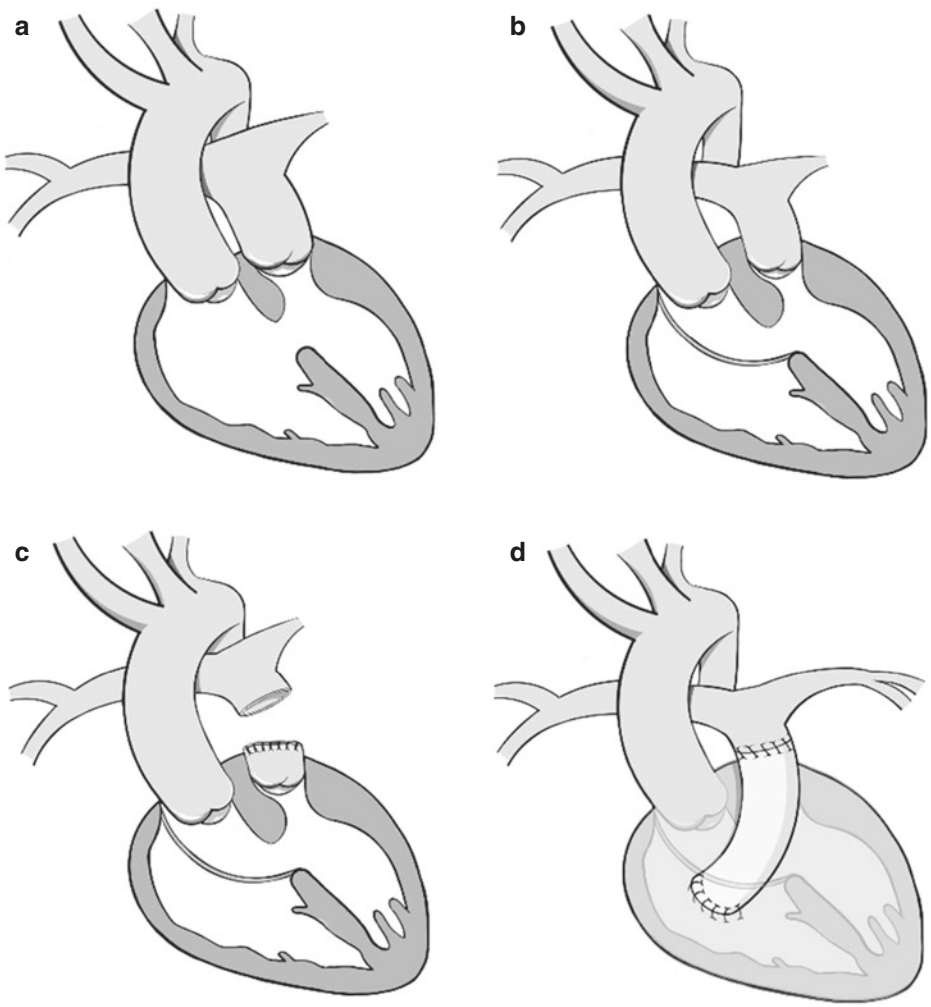

Fig. 32.13 *Rastelli Repair.* (**a**) Transposition with a ventricular septal defect and pulmonary stenosis. (**b**) The interventricular tunnel is created with a prosthetic patch, funneling the left ventricular blood into the aorta. (**c**) The main pulmonary artery is transected. (**d**) After performing a right ventriculotomy, a conduit is placed between the right ventricle and the pulmonary arteries

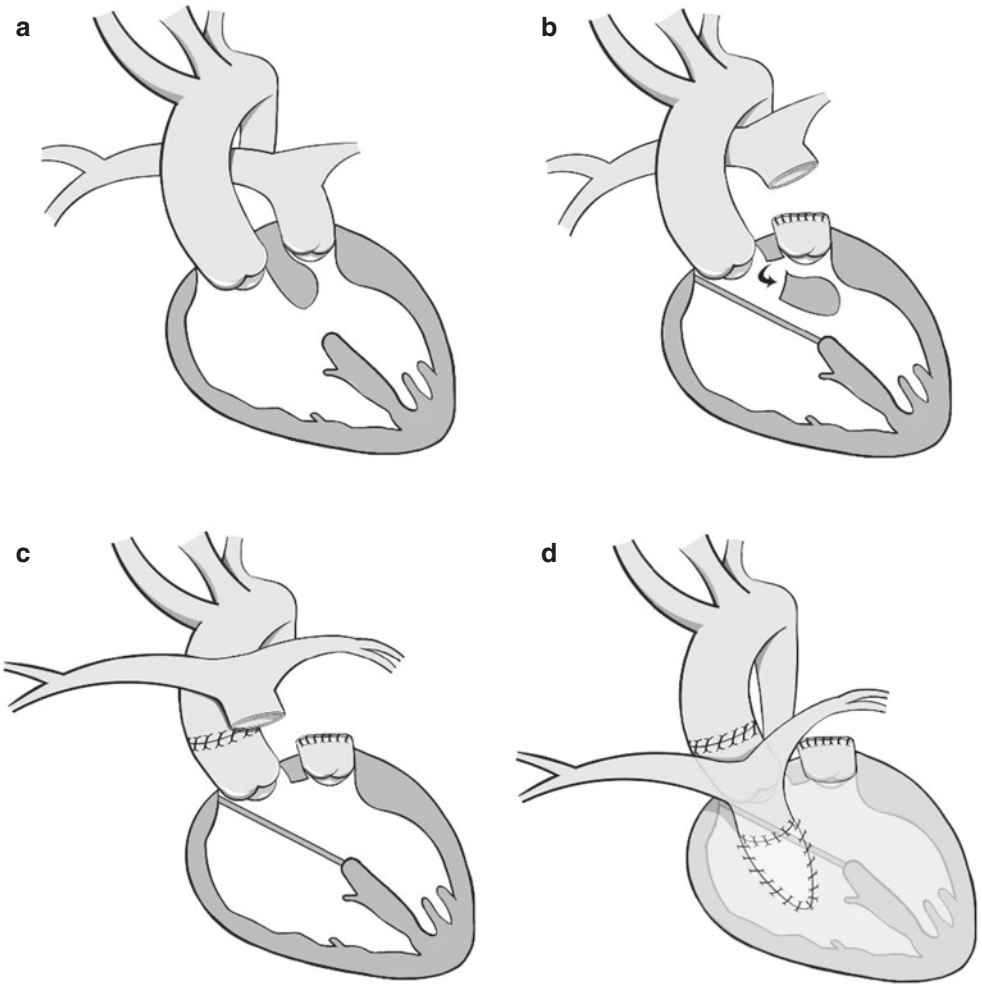

Fig. 32.14 *REV Procedure.* (**a**) Transposition with a ventricular septal defect and pulmonary stenosis. (**b**) The outlet septum is resected, enlarging the VSD, and the interventricular tunnel patch is placed; it results in a more direct communication between the left ventricle and the aorta. (**c**) The main pulmonary artery is transected and the Lecompte maneuver performed. (**d**) A direct anastomosis between the right ventricle and the pulmonary arteries is created

32.8 Postoperative Management

32.8.1 D-TGA and Intact Ventricular Septum

The corrective surgical procedure of this constellation includes ASO and Post Balloon ASD closure. The complications following the ASO include low cardiac output syndrome, mitral regurgitation, coronary insufficiency and/or ischemia, supravalvar AS and PS, and bleeding along multiple sutures lines [37]. To better organize the postoperative management in a more didactic manner, it is divided by system:

32.8.1.1 Cardiovascular

The infant may or may not arrive with the chest open into the intensive care unit. The current trend is chest closure in an uncomplicated ASO. Details of TEE must be immediately available to the intensive care physician. Typical inotropic support includes low-dose dopamine (3–5 μg/kg/min), low-dose epinephrine (0.05–1 μg/kg/min), milrinone (0.25–1 μg/kg/min), and sodium nitroprusside (1–3 μg/kg/min). The doses will be titrated according to the clinical condition and patient hemodynamic status. It is of paramount importance that the intensivist avoids high inotropic support. If a particular infant requires high inotropic support to maintain borderline hemodynamics, the best approach is to use ECMO until the ventricular function recovers. Likewise, it is important to remember that ECMO is only a transient support and an exhaustive search for potential underlying pathology to rule out residual surgical lesions, suboptimal myocardial preservation, and/or excessive tissue stretching/damage during the repair must be completed. After repair, the echocardiogram, CVP, and left atrial pressure are monitored routinely. In addition, lactate levels, mixed venous saturations, and NIRS values as well as basic physical exam findings are checked to assure sufficient cardiac output.

The electrocardiogram is crucial for monitoring potential arrhythmias, coronary insufficiency, and/or infarct. The EKG must be compared to the pre-operative EKG. If coronary

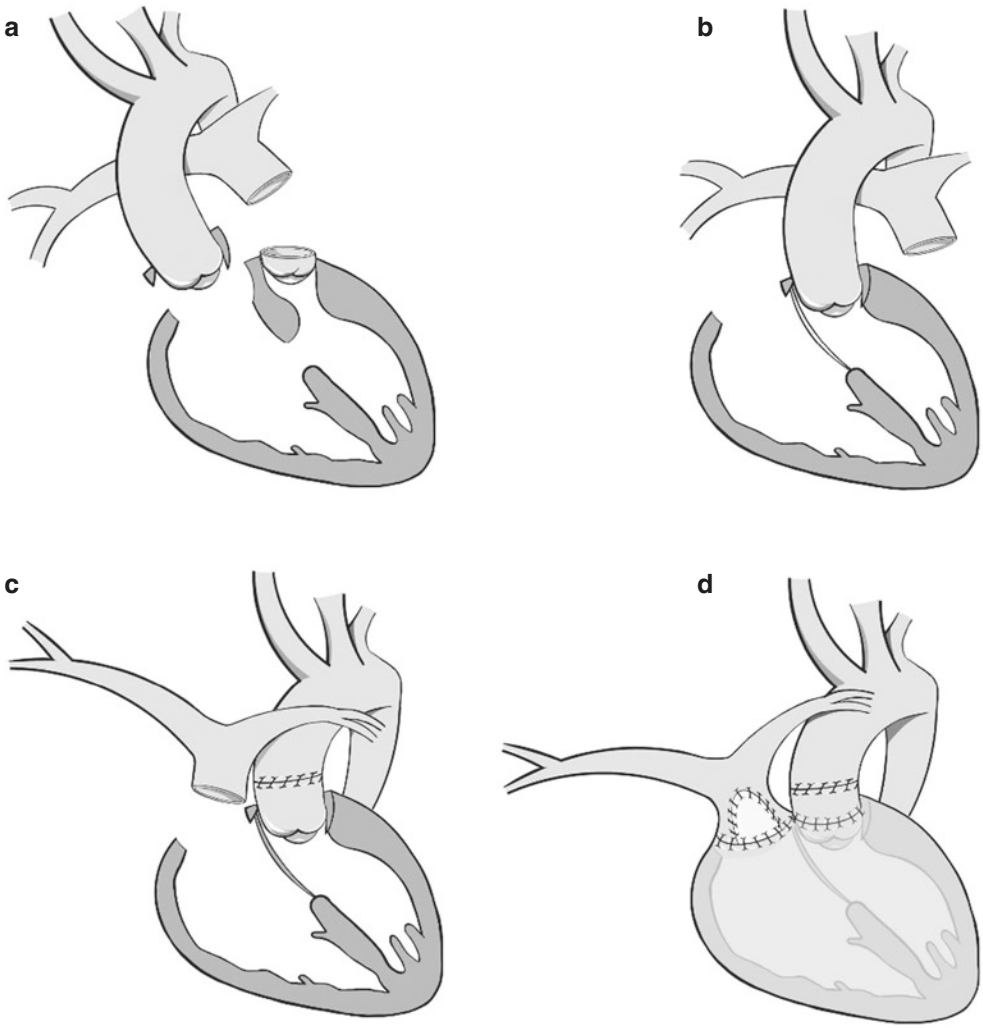

Fig. 32.15 Aortic Translocation Procedure (Nikaidoh procedure). (**a**) The aortic root is harvested from the right ventricle, with or without the coronary arteries attached, and the proximal main pulmonary artery is transected. (**b**) After dividing the outlet septum, the aortic root is moved and sutured in the pulmonary position and the ventricular septal defect is closed. (**c**) The Lecompte maneuver is performed. (**d**) A direct right ventricle to pulmonary artery anastomosis is performed; a patch of pericardium is used to augment the usually hypoplastic main pulmonary artery

insufficiency is suspected, IV nitroglycerine drip may be started. Atrial arrhythmias can be seen due to ASD closure; however, ventricular arrhythmias should alert the intensivist to coronary anastomosis problems. At this time, a diagnostic echocardiogram (looking for regional wall motion abnormalities) and a cardiac catheterization must be requested as soon as possible.

High left atrial pressure usually is indicative of LV dysfunction and mitral regurgitation. Atrial waveform should be analyzed; prominent V wave is most likely consistent with significant mitral regurgitation (MR). Additionally, the pulmonary venous pressure and pulmonary pressure will be elevated secondary to LV dysfunction. Nitric oxide is contraindicated in this setting and, thus, patients may benefit from a generous afterload reduction, low atrial "tolerable" rates for age, and careful fluid administration. In general, once ventricular dilation and function improves, the mitral regurgitation improves. In cases of MR, the left ventricular systolic function may be overestimated by echocardiography due to the unloaded ventricle.

32.8.1.2 Respiratory

Once patients are hemodynamically stable without significant residual anatomic lesions, extubation should be promptly administered following the universal ICU criteria. Extubation failure in the setting of no residual heart disease and no significant lung disease should alert the clinician to the presence of diaphragmatic paralysis. During chest closure, the intensive care physician must closely monitor lung volumes, compliance, and flow ventilator curves as, not infrequently, surgeons may press on the ETT during surgical intervention and respiratory deterioration may occur following cardiovascular collapse. Prior to chest closure, patients must have the endotracheal tube suctioned and a pacemaker must be at the bedside with the pacing wires connected. If the infant has the chest closed after the ASO, patient should be ventilated with tidal volumes of 10–12 cc/kg, peak pressure sufficient to expand the lungs (avoid over-distention and collapse), PEEP 5–6 cm/H_2O, and FIO2 to maintain saturations of 98–100% in patients without intracardiac shunts.

32.8.1.3 Fluid, Electrolytes and Nutrition

Twenty-four hours after surgical repair, parenteral nutrition is begun with Dextrose concentration between 20–25%, protein intake ~ 3 g/day, and fat intake ~3–3.5 g/kg/day. Enteral nutrition is commenced once the infant reaches hemodynamic stability.

32.8.1.4 Hematology

Bleeding is a common complication after ASO and occurs more commonly when the procedure involves a long CPB time and cross-clamp time. In addition, the ASO procedure involves placement of multiple suture lines which are potential sources of bleeding. One method which could possibly be used to treat this complication includes transfusion of either platelets, fresh frozen plasma, or cryoprecipitate. If bleeding persists above 7–10 ml/kg/hour, chest re-exploration should be considered at the bedside. It is not unusual that blood clots may compress some coronary branches causing ischemia and cardiovascular collapse.

32.8.1.5 Gastrointestinal

Liver and pancreatic function tests such as amylase and lipase should be monitored. PO intake is encouraged after 24 hours of extubation. Careful attention must be paid to changes in the quality and quantity of the chest and peritoneal drainage after enteral feeds are started (chylothorax and chyloperitoneum).

32.8.1.6 Renal

Furosemide and thiazides are the most common diuretics used. Furosemide is frequently started within 6–12 hours after repair (dose 0.1–0.4 mg/kg/hour). The aim is to achieve negative balance within 24–48 hours after repair; this will facilitate chest closure and extubation process. It is frequently observed that as the peritoneal drainage decreases, urine output reaches its maximal volume.

32.8.1.7 Neurology

Some centers routinely perform EEG 12–24 hours post repair to detect seizure activity. Although this practice is controversial (low yield), it may be advisable to request an EEG at least 1–2 hours post repair, and, if abnormalities are seen, the test is extended as long as it is clinically necessary. The most important issue for this practice is to select a group at risk that deserves close follow-up. Following the same principle, complete head ultrasounds may be performed post repair.

32.8.1.8 Infectious Disease

At Children's Hospital of Pittsburgh, vancomycin and third-generation cephalosporins are routinely used until the chest is closed. Following closure, a first-generation cephalosporin is used until the chest tubes are removed. The incidence of mediastinatis is almost nonexistent in this institution. Central lines must be discontinued as soon as possible to decrease nosocomial infections. If patients need long-term intravenous access, a Broviac catheter or a peripherally inserted central catheter (PICC) may be placed [37].

32.8.2 D-TGA and Ventricular Septal Defect

In addition to the postoperative care issues mentioned in D-TGA with intact ventricular septum, VSD closure represents an additional challenge [38]. Patients in this category are at higher risk for ventricular dysfunction including low cardiac output syndrome, conduction abnormalities, and other co-morbidities (related to CPB time) than patients with simple transposition. Transesophageal or trans-thoracic echocardiogram must be completed to assess function, AV valve regurgitation, and residual VSD. Transient/complete heart block and/or junctional ectopic tachycardia can be seen as complications of VSD closure (see specific chapters for management).

32.8.2.1 D-TGA With Ventricular Septal Defect and Pulmonic Stenosis

Rastelli Repair

In this repair, an intraventricular baffle across the VSD is used to connect the left ventricle with the aorta. To connect the right ventricle to the pulmonary artery, a conduit is placed between the two structures. Potential complications during the postoperative period include low cardiac output syndrome, biventricular dysfunction, conduction abnormalities, arrhythmias, baffle obstruction (murmur, decreased systemic perfusion, weak pulses, renal failure, etc.), baffle leak, and/or RV-PA conduit obstruction/compression by the sternum (murmur, RV hypertension, cyanosis, and RV dysfunction).

Nikaidoh Operation

The Nikaidoh operation and its modifications involve harvesting the aortic root (separating it from the RV), extensive dissection and individual transfer of the coronary arteries, and reconstruction of the right ventricular outflow tract establishing an anatomic connection between the RV and the

pulmonary tree. This operation allows a better alignment of the right and left ventricular outflow tracts. It is especially useful in the presence of an inlet or restrictive ventricular septal defect, a hypoplastic right ventricle, a straddling atrioventricular valve, and an anomalous coronary artery course interfering with the right ventricular outflow tract. The postoperative period can be complicated by low cardiac out syndrome, ventricular dysfunction, and coronary ischemia.

Physiologic Correction: Senning and Mustard Procedure

The objective of atrial switch operations involving either a Senning (use of the atrial wall and septum tissue) or Mustard (use of the autologous pericardial tissue) procedure is to create an atrial arterial concordance and atrio-ventricular concordance (physiologically corrected transposition of the great arteries). Currently, these procedures are performed as part of the double-switch operation for l-TGA, and they are not the procedures of choice for D-TGA. There are two intracardiac baffles to reroute the systemic venous blood across the mitral valve and the pulmonary venous return across the tricuspid valve. A number of short- and long-term complications have been published including systemic and pulmonary venous baffle obstruction and leaks, tricuspid and mitral valve regurgitation, right ventricular dysfunction, and dysrhythmia [39]. Obstruction of the systemic venous pathway is manifested by upper extremity plethora, chylothorax, anasarca, and low cardiac output syndrome. Pulmonary venous baffle obstruction is manifested by white-out lungs, air-space disease, pulmonary hypertension, and left ventricular dysfunction. Baffle leak from the pulmonary venous blood to the pulmonary ventricle would cause a left-to-right shunt with ventricular overload. Conversely, baffle leak from the systemic venous blood to the systemic right ventricle would result in right-to-left shunt with oxygen desaturation and ventricular volume overload.

32.9 Long Term Outcome

The long term outcome after the arterial switch procedure has been satisfactory in most patients; however, results are strongly influenced by the surgical learning curve of each institution [40, 41]. The overall and arrhythmia-free survival rates were 96.7 ± 1.8% and 96.6 ± 0.1%, respectively, at 25 years. 75.5 ± 2.5% were free of surgical or catheter-based intervention, and 92.9 ± 1.9% were free from adverse cardiovascular events at 25 years. Independent predictors were a single right coronary artery and postoperative heart failure [42].

The re-operation free survival rate including late death in another study was 82.2% at 10 years and 75.7% at 15 years in patients who had the arterial switch procedure. Several publications have documented evidence of neurologic abnormalities after the ASO; [43, 44] nevertheless, this is a moving target and the future care of these patients implies not only an improvement in survival in simple and complex TGA, but also ensures that these infants have a good quality of life [45, 46]. Abnormal CNS has been documented in patients with congenital heart disease even prior to surgery. Regarding the Nikaidoh operation, since 1996, 21 patients have undergone aortic translocation at Children's Hospital of Pittsburgh and at the Congenital Heart Institute of Florida. There was only one early death and one patient required heart transplantation due to left ventricular dysfunction [47].

Late complications of the D-TGA after repair include supravalvar aortic stenosis, supravalvar pulmonary stenosis, development of neo-aortic root dilation and neo-aortic regurgitation, sinus node dysfunction, arrhythmias, coronary artery abnormalities, and, rarely, sudden death. As more and more children are surviving to adulthood, the need for continued monitoring lifelong needs to be emphasized. A recent study of adults with repaired transposition revealed increased risk of cognitive deficits and psychiatric disorders such as anxiety and depression [48].

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Chapter 33
Congenitally Corrected Transposition of the Great Arteries (ccTGA) or Levo-Transposition of the Great Arteries (l-TGA)

Rukmini Komarlu, Victor O. Morell, Ricardo A. Munoz, and Michael D. Tsifansky

Abstract Congenitally corrected transposition of the great arteries (ccTGA) is an uncommon lesion with a prevalence of approximately 0.03/1000 live births. In this condition, there is both atrioventricular and ventriculoarterial discordance which results in physiologically corrected blood flow. It is commonly associated with other cardiovascular anomalies; although extracardiac and chromosomal anomalies are less common. Many cases are discovered incidentally in adulthood, and while mid-term outcomes are favorable, outcomes of surgical repair continue to evolve. Lifelong follow-up is advised both in view of long-term complications such as tricuspid regurgitation and right ventricular dysfunction but also due to increased risk of complete heart block.

33.1 Introduction

Congenitally corrected aortopulmonary transposition (ccTGA) also called l-TGA is characterized by atrioventricular discordance and ventriculoarterial discordance (Fig. 33.1). The right atrium is connected to the morphologic left ventricle which opens into the pulmonary artery. The morphologic left atrium is connected to a morphologic right ventricle, which pumps blood into the aorta. The aorta is anterior and leftward of the pulmonary artery. Therefore, in ccTGA deoxygenated blood passes from the right atrium into the pulmonary artery and the oxygenated blood returns to the left atrium and is ultimately distributed to the body through the aorta [1, 2], and, in contrast with D-TGA results in normal physiology of blood flow. It is an extremely rare anomaly and comprises 0.6–1.4% of all congenital heart defects with male to female ratio of 1.3:1 [3].

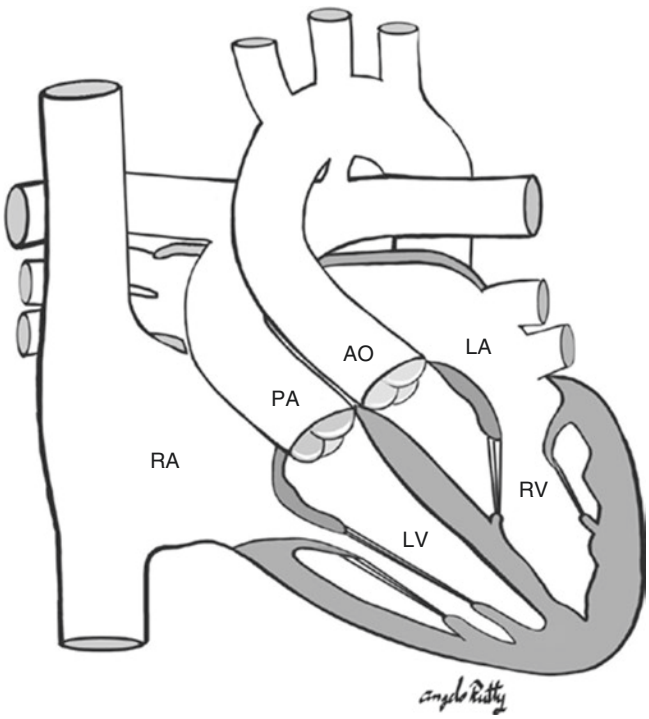

Fig. 33.1 Congenitally corrected transposition of the great arteries

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33.2 Coexisting Anomalies

About 94% of ccTGA cases are associated with other cardiovascular lesions [1], with the most common abnormalities involving the tricuspid valve (in up to 86–91% of patients) [4]. When ccTGA and Ebstein's anomaly coexist, the tricuspid valve and right atrial morphology is different from the "classical" Ebstein's in that the anterior leaflet is not sail-like, and the atrialized part of the right ventricle is relatively small. A ventricular septal defect, usually perimembranous, is found in up to 79% of patients and in some of them, the tricuspid valve straddles the ventricular septum, posing a challenge for biventricular repair. Some patients may have a common ventricle [1, 4] and in them an associated aortic outflow obstruction is common [1]. Pulmonary outflow tract obstruction occurs in up to 44% of cases [4] and is often due to subvalvar obstruction caused by fibrous tissue tags (57%) [2], but valvular pulmonary stenosis or atresia can also occur. In the presence of a VSD, the degree of cyanosis is directly proportional to the amount of pulmonary stenosis. Abnormalities of the AV node, including dual AV node with an abnormal His bundle, are quite common in patients with ccTGA, and many ultimately develop complete heart block, with increased risk in the presence of intact ventricular septum [5], which can occur spontaneously at any point during intra- or extra-uterine life. The risk of natural onset AV block is approximately 2% per year after diagnosis [7]. The AV node is more anterior and an anomalous AV bundle is usually found on the anterior margin of any accompanying VSD. Tricuspid valve or VSD surgery can also precipitate complete heart block with surgical risk between 3% and 16%, higher with arterial switch procedure [6]. The mitral valve is abnormal in 39–55% of patients [1, 8], showing more than two cups, abnormal chordae and papillary muscles, dysplasia, or a cleft [8]. The coronary arteries show the so-called "mirror image distribution." The right coronary artery distributes like the morphologic left coronary artery, giving rise to the circumflex and anterior descending branches. A larger arterial branch crosses the morphological right ventricular outflow tract in 61% of cases which is important for planning of the right ventriculotomy and a main coronary arterial branch crosses the pulmonary artery in 96% of cases [9]. A single coronary artery was noted in 9% of cases [9]. Other cardiac anomalies in patients with ccTGA include dextrocardia (24–32%), mesocardia, situs inversus (3%) [1, 4], right aortic arch, anomalous pulmonary venous return, atrial septal defects (46%), complete AV canal, and patent ductus arteriosus. Patients with Ebstein's anomaly and ccTGA can also have coarctation of the aorta (1.4%) or aortic atresia [10].

33.2.1 Embryology

Corrected transposition in visceral-atrial situs solitus develops when the primitive heart tube loops to the left instead of to the right, resulting in the lack of spiral rotation of the conotruncal septum. Therefore, the aorta is connected to the morphologic right ventricle, and the pulmonary artery is connected to the morphologic left ventricle. The ventricles are attached to the normally positioned atria, making this abnormality physiologically corrected. Based on fetal diagnosis and follow-up, survival from in utero diagnosis to birth is 75–80% [11, 12].

33.2.2 Clinical Presentation

Patients with ccTGA may seek medical advice at any age, depending on the presence and severity of associated cardiac anomalies. Infants with a large ventricular septal defect, severe tricuspid regurgitation, aortic coarctation, or aortic arch defects are early to experience congestive heart failure. They may be cyanotic if the pulmonary blood flow is decreased. Atrial and ventricular arrhythmias and varying degrees of AV block can bring these patients to medical attention [3]. In the absence of associated cardiac anomalies, some patients may remain functional and seek medical advice only as adults [13]. The condition may go undiagnosed until late adulthood, when it is found on echocardiogram done for an abnormal ECG, atypical chest pain, or signs of RV failure [14]. The initial diagnosis was made in 66% of patients after the age of 18 years and 17% were 60 years or older at diagnosis [18, 19].

On physical exam, left parasternal lift and a systolic murmur, akin to mitral regurgitation can be heard at the low left sternal border in the presence of tricuspid regurgitation. A systolic impulse can be felt in the second or third left intercostal space with a loud single second sound. A murmur of pulmonic stenosis may be heard at the mid-sternal border. The cardiac impulse may be maximal on the right side of the chest in the presence of dextrocardia.

33.2.3 Chest X-ray

Chest X-ray may show mesocardia (Fig. 33.2), dextrocardia, or levocardia (Fig. 33.3); the vascular pedicle may be narrow, due to the loss of normal arterial relationship. Cardiomegaly may be evident. The convexity of the descending aorta and pulmonary artery are absent on the left side and hence the left ventricular border may appear more vertical than usual.

33.2.4 ECG

Electrocardiographically, the presence of Q waves in the right but not the left precordial leads suggests the diagnosis of ccTGA. Because of the ventricular inversion, the right and left bundles are inverted, resulting in septal activation from right to left. Varying degrees of AV block can occur.

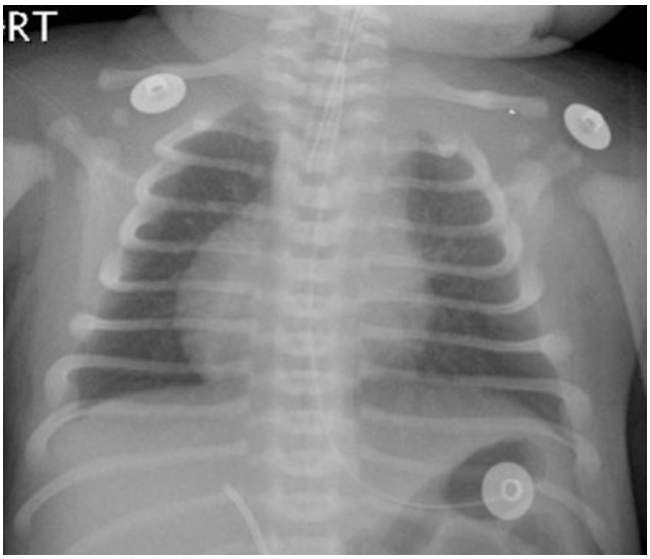

Fig. 33.2 Chest X-ray demonstrating mesocardia and narrowed vascular pedicle

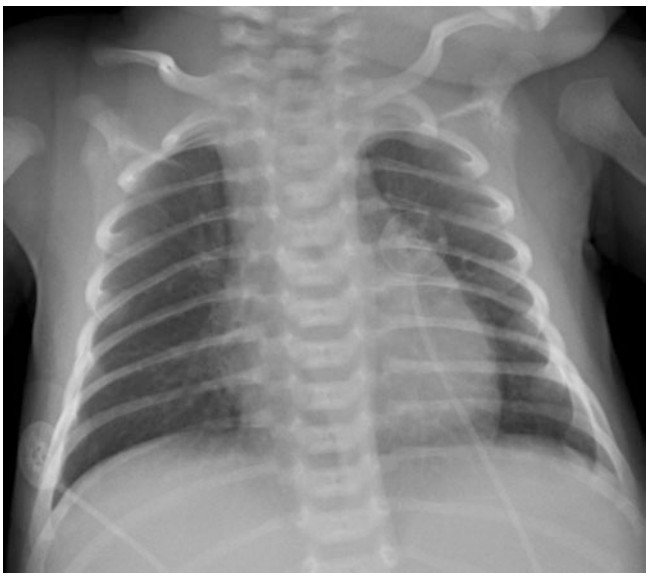

Fig. 33.3 Chest X-ray demonstrating levocardia and narrow vascular pedicle

33.2.5 Echocardiography

Echocardiography allows an easy assessment of the interatrial and interventricular septa, the atrioventricular, aortic and pulmonary valves, and the global biventricular function, although the presence of dextrocardia may make structure identification challenging (Fig. 33.4). Subcostal views demonstrate the atrial situs and the position of the cardiac apex. Short-axis and apical four-chamber views show the ventricular morphology (Fig. 33.5) and function, mitral-pulmonary fibrous continuity, and ventriculoarterial discordance. High parasternal short-axis view demonstrates the abnormal arterial relationship with the aorta anterior and leftward of the pulmonary artery (Fig. 33.6). The aortic arch should be interrogated for the presence of coarctation, interruption, or PDA. Coronary artery anatomy should be identified, although it is often easier to do by cardiac MRI or high-resolution CT scan. Transesophageal echocardiography is extremely helpful in making the diagnosis in adults, especially for the determination of atrial situs and presence of tricuspid regurgitation [15].

33.2.6 Cardiac Catheterization

Cardiac catheterization can assess systemic AV valve regurgitation, systemic ventricular function, the hemodynamics of any associated anomalies, the left and the right heart pressures, and the pulmonary vascular resistance [33]. Transient or complete heart block can occur due to catheter manipulation during the procedure. In older patients, coronary angiography is important prior to surgical intervention.

33.3 Preoperative Management

Congestive heart failure in patients of any age is managed with diuretics, inodilators or other afterload reducers, and sodium restriction. Often, complete heart block is common, but placement of an endocardial pacemaker can precipitate deterioration in RV function and worsening of tricuspid regurgitation.

Cyanotic neonates with severe PS, right ventricular outflow tract obstruction, or pulmonary atresia benefit from PGE_1 infusion and optimization of Q_p/Q_s in preparation for a systemic-to-pulmonary artery shunt. Cyanotic infants and children with ccTGA beyond the neonatal period tend to be more stable, and their surgical outcomes are less compromised by poor preoperative status [16]. Patients should always receive prophylaxis for bacterial endocarditis.

33.4 Timing of Surgery

Patients in need of surgery usually have either significant cyanosis or significant pulmonary overcirculation. Cyanotic neonates and small infants commonly undergo a systemic-to-pulmonary artery shunt before proceeding with a complete repair. At our institution, we prefer to perform the double switch procedure at about 1 year of age. Patients with low LV (subpulmonary) pressures and "deconditioned" LV may need "retraining" prior to the double switch procedure via a process of progressive PA banding to increase LV afterload and promote LV hypertrophy. To proceed with double switch,

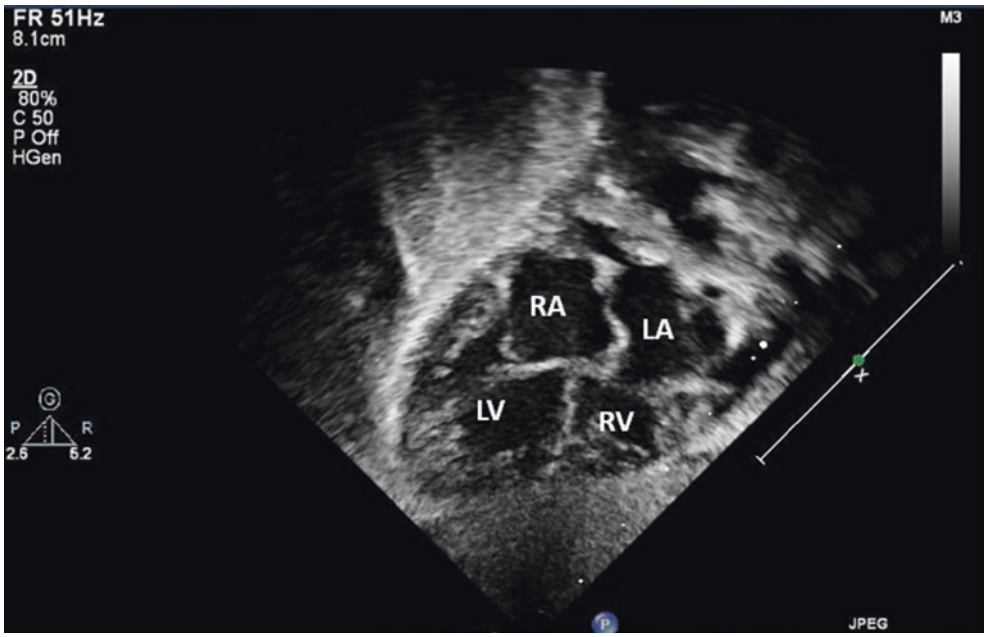

Fig. 33.4 Subcostal long axis view demonstrating dextrocardia with morphologic l-looped ventricles; left ventricle (LV) on the right side (RA right atrium, LA left atrium, RV right ventricle)

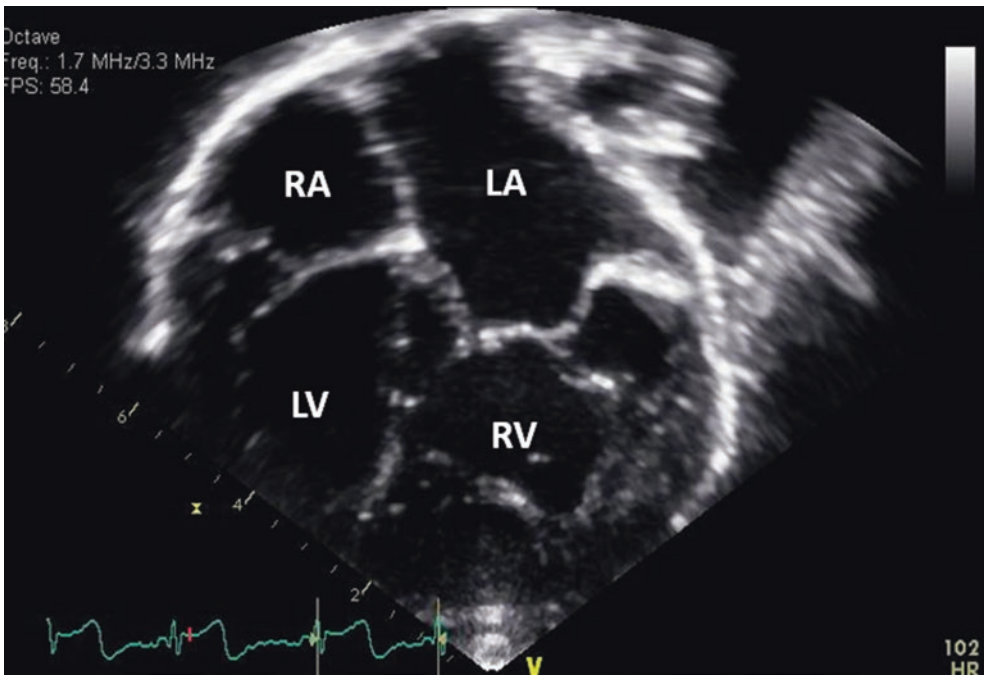

Fig. 33.5 Apical 4 chamber view demonstrating morphologic left ventricle (LV) on the right side (RA right atrium, LA left atrium, RV right ventricle)

LV pressure ≥ 90%, systemic LV mass/LV volume ratio > 1.5, normal LV systolic function, and mitral valve function are important criteria to assess; some patients may not tolerate banding and develop significant LV dysfunction [17–19].

The timing of tricuspid valve repair or replacement in these patients remains uncertain. The mid- and long-term outcomes may improve if tricuspid valve replacement is performed in patients with right ventricular ejection fraction greater than 44% and can halt deterioration of RV function [14, 20]. An exercise stress test may help assess impaired exercise tolerance even before functional limitations occur indicating the need for a tricuspid valve procedure. Patients with significant tricuspid regurgitation may benefit from a pulmonary artery banding that would decrease the regurgitation by increasing the LV (subpulmonary ventricle) pressure with associated septal shift, therefore partially compressing the RV (systemic ventricle) inducing remodeling and a decrease of the tricuspid annulus size with better coaptation of the leaflets, with some advocating this as a long-term palliation [21, 22].

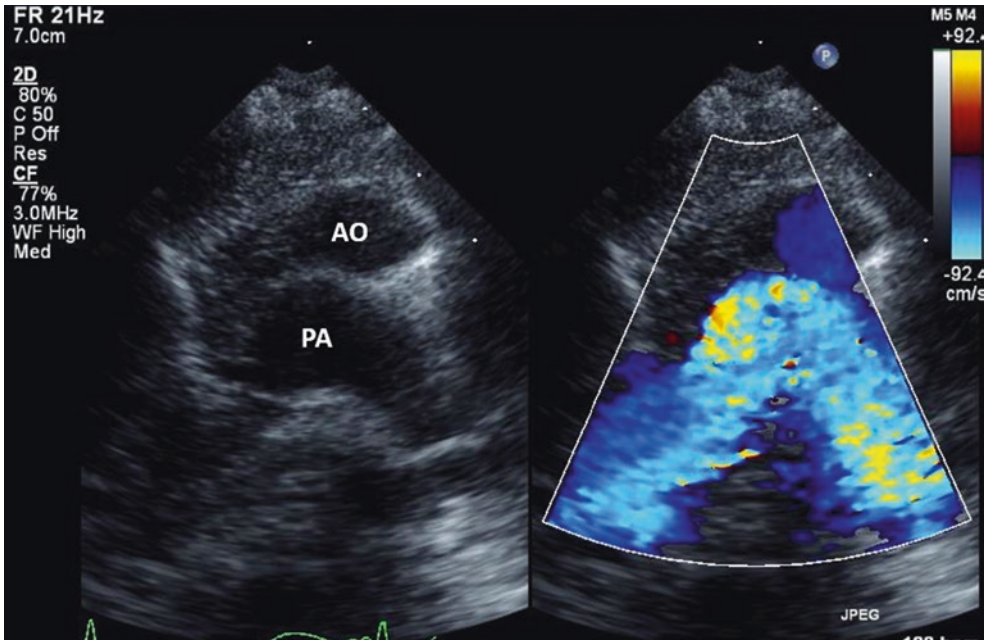

Fig. 33.6 High right parasternal short axis view showing aorta anterior and to the left of the pulmonary artery (Ao aorta, PA pulmonary artery)

33.4.1 Surgical Techniques

The approaches to surgical management of patients with ccTGA can be grouped into two options: a *physiologic repair* and an *anatomic repair*.

After physiologic repair, the right ventricle remains the systemic ventricle and any other associated lesion is repaired. Although simpler, this approach results in a right ventricle-dependent systemic circulation, which has negative long-term implications, mainly RV failure and tricuspid regurgitation [23]. Patients are at high risk of reoperation for systemic AV valve repair/replacement and conduit replacement [24–26].

After anatomic repair, the left ventricle becomes the systemic ventricle and the outcomes should be better. Nevertheless, the repair involves some form of a technically challenging double switch procedure.

33.4.1.1 The Double Switch Procedure

The "double switch operation" encompasses several techniques depending on the associated lesions, including:

1. An atrial switch with an arterial switch
2. An atrial switch with a Rastelli procedure
3. An atrial switch with an aortic translocation

All of these require cardiopulmonary bypass and cardioplegic arrest. Figures 33.7 and 33.8 depict the two atrial switch procedures, the Mustard and the Senning interventions. The arterial switch, the aortic translocation, and the Rastelli procedure have been described in the chapter related to D-TGA. The operative mortality of the double switch is reported around 10% [27, 28].

33.4.2 VSD Closure

It is important to recognize that in patients with atrioventricular and ventriculoarterial discordance, the conduction tissue runs anterior and cephalad to the pulmonary valve and then descends along the anterior margin of the VSD before diverging into the bundle branches [3]. Division of the outlet septum (required during the aortic translocation procedure) does not result in complete heart block, but closure of the VSD may injure the conduction tissue (Fig. 33.9). Not surprisingly, a significant number of patients will develop postoperative or spontaneous heart block and require pacemaker placement.

33.4.3 Single Ventricle Repair

Patients with straddling atrioventricular valves, multiple ventricular septal defects or associated ventricular hypoplasia should be considered for univentricular palliation [25].

33.5 Postoperative Management

The postoperative management depends on the repair of the associated lesions, including pacemaker placement, relief of right ventricular outflow tract obstruction, Blalock-Taussig shunt placement, tricuspid valve repair, ventricular septal

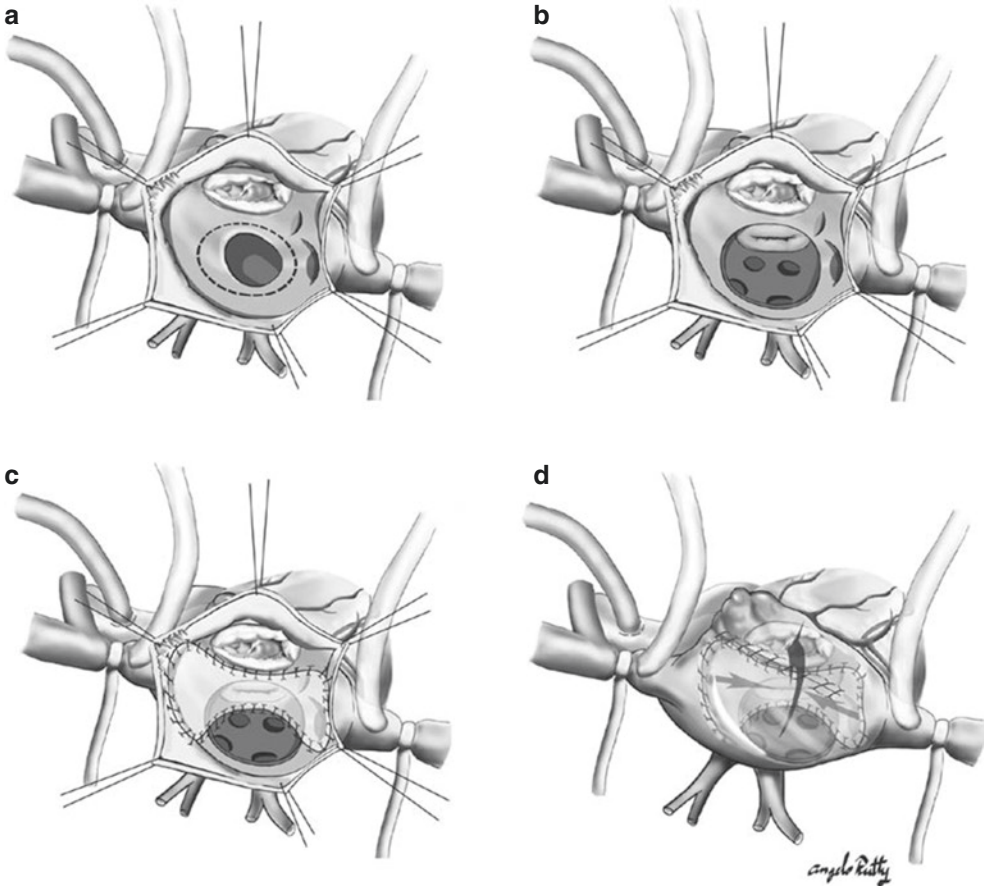

Fig. 33.7 The Mustard procedure (**a, b**) A right longitudinal atriotomy is made, and the atrial septum is aggressively resected, preserving the medial ridge. (**c**) A dumbbell-shaped patch of autologous pericardium is used to redirect the systemic venous return into the right ventricle via the posteriorly located tricuspid valve. (**d**) The right atriotomy is closed; now the pulmonary venous return drains into the left ventricle via the anteriorly located mitral valve

defect closure, conventional Rastelli, double switch operation, atrial switch and intraventricular rerouting, and Fontan-type surgery [28]. With the exception of the double switch, specific postoperative care of associated lesions is described in their respective chapters.

33.5.1 Double Switch Operation (Atrial and Arterial Switch)

The postoperative care addresses the potential complications of the atrial switch (Senning or Mustard operations) and the arterial switch operations.

33.5.2 Complications of the Atrial Switch

- Systemic venous baffle obstruction: These patients can have SVC syndrome, plethora, anasarca, and low cardiac output syndrome. Rapid bedside echocardiographic diagnosis of the obstruction must be made and the decision taken to proceed with cardiac catheterization or surgical reintervention.
- Pulmonary venous baffle obstruction: These patients how clear signs of pulmonary edema. Gas exchange worsens and high ventilatory settings are often needed (increased PEEP, tidal volumes and FiO2). Pulmonary venous return falls leading to a decrease in systemic cardiac output. Echocardiogram, cardiac catheterization, and/or surgical reintervention may be indicated.
- Baffle leaks may lead to ventricular volume overload and systemic desaturation may be present and may, depending on the severity, require interventional cardiac catheterization or surgical reintervention.
- Atrial arrhythmias, conduction disturbances, or sick sinus syndrome are managed according to the specific electrophysiologic disturbance [29].

Postoperative management and outcomes of the arterial switch operation has been described elsewhere, in the chapter dedicated to D-TGA [30]. It is noteworthy, however, that patients after a double switch operation are at risk of significant ventricular dysfunction requiring generous inotropic support or ECMO. Risk factors for ventricular dysfunction are older age at repair (> 10 years), weight > 20 kg, pacemaker implantation, and severe neo-aortic regurgitation [17, 31, 32].

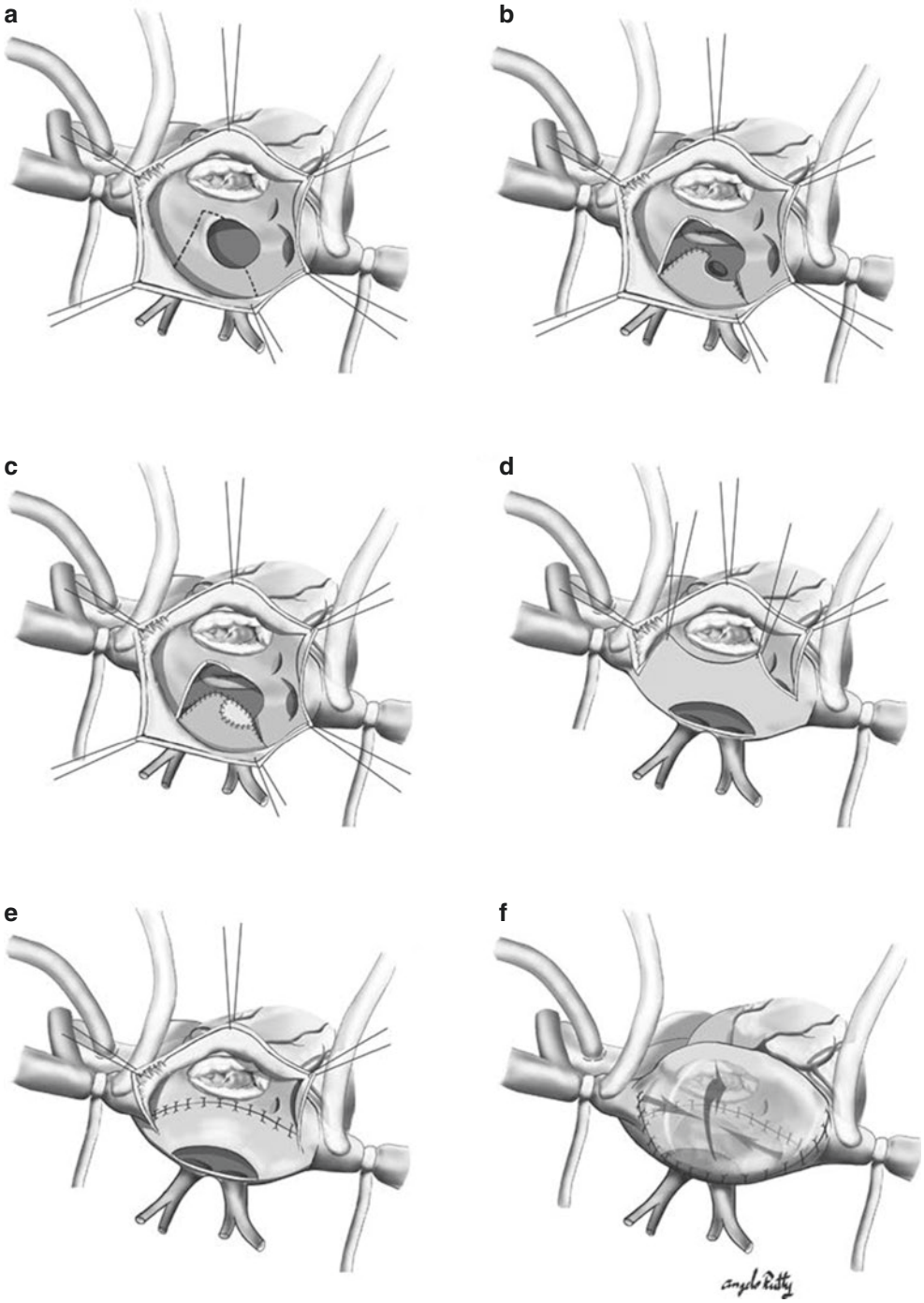

Fig. 33.8 The Senning procedure (**a, b**) via a right atriotomy, a laterally based flap of atrial septum is created and moved posteriorly, over the orifices of the pulmonary veins, becoming the roof of the pulmonary venous baffle. (**c**) Frequently, a segment of pericardium is needed to augment the flap. (**d**) A separate incision is made in the left atrium, just anterior to the right-sided pulmonary veins. (**e**) The systemic venous baffle is created by suturing the posterior edge of the right atrial incision to the medial rim of the atrial septum. (**f**) The pulmonary venous channel is created by suturing the anterior edge of the right atrial incision along the external surface of the systemic venous baffle (around the superior and inferior vena cava) and to the lateral edge of the left atrial incision

33.6 Long-Term Outcomes

The main long-term complication of ccTGA is failure of the systemic right ventricle, especially in the presence of tricuspid regurgitation. RV dysfunction usually becomes clinically significant by 17 years of age [25]. About 50% of patients with associated defects and about 30% without them develop RV dysfunction by 45 years of age [34]. The prevalence of complete heart block and tricuspid regurgitation also increases with age.

Historically, patients undergoing conventional repair (physiologic repair) have shown survival rates of 61% at 15 years [24] and 48% at 20 years [23] after the initial repair. Slightly more than half of the patients required re-operation within 16 years and 35% required placement of a pacemaker. Nearly half the cohort required tricuspid valve surgery by the age of 40 years. The most common causes of death were re-operation (from myocardial failure) in 36%; other causes being sudden explained death, progressive myocardial failure, and documented arrhythmias [23]. Risk

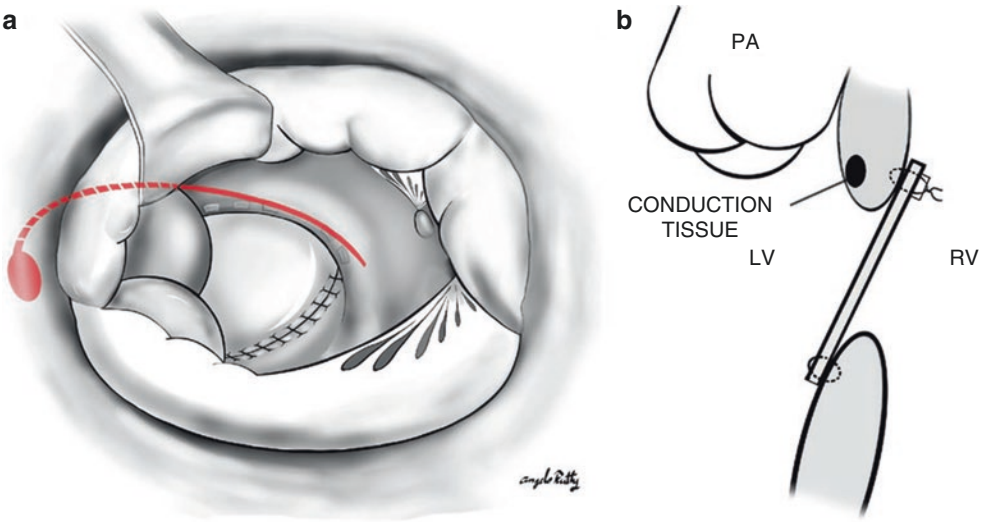

Fig. 33.9 (**a**) The atrioventricular conduction bundle (in red) runs in the anterosuperior margin of the defect. (**b**) Along the anterosuperior margin of the VSD, interrupted sutures are placed along the RV site in order to avoid injuring the conduction system

factors for death included RV end diastolic pressure > 17 mm Hg before surgery, complete heart block after surgery, subvalvular pulmonary stenosis, Ebstein malformation of tricuspid valve, and preoperative RV dysfunction [24]. The double switch procedure was associated with nearly 75% survival at 15 years [28]. A meta-analysis of 11 nonrandomized studies totaling 124 patients revealed that Rastelli-type repair had significantly lower hospital mortality, likely due to lower incidence of heart block and systemic AV valve regurgitation. Operative era before 1995 was also associated with increased mortality [35].

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Chapter 34
Truncus Arteriosus

Eduardo M. da Cruz, Harma K. Turbendian, and Victor O. Morell

Abstract Truncus arteriosus is a rare congenital cardiac malformation with a reported incidence between 0.006 and 0.043 per 1000 live births. It accounts for 0.7% of all congenital cardiac malformations and for 1–2% of congenital heart diseases identified at autopsies. This malformation has been defined as an anomaly in which the aorta, the coronary arteries, and the pulmonary arteries arise from a single vessel (common truncus) originated from the cardiac chambers. There is no remnant or rudimentary pulmonary artery arising separately from the heart. This chapter reviews the diagnosis and management of this entity.

34.1 Introduction

Truncus arteriosus (TA) is a rare congenital cardiac malformation, firstly described by Wilson in 1798 and reported with an incidence between 0.006 and 0.043 per 1000 live births. It accounts for 0.7% of all congenital cardiac malformations [1] and for 1–2% of congenital heart diseases identified at autopsies. This disease occurs with equal frequency in male and female gender and it has no racial preference.

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This cardiac malformation has been defined as an anomaly in which the aorta, the coronary arteries, and the pulmonary arteries arise from a single vessel (common truncus) originated from the cardiac chambers. There is no remnant or rudimentary pulmonary artery arising separately from the heart.

TA may be an isolated anomaly or associated with chromosomal anomalies. The most commonly associated condition is the 22q11^{-} deletion [2, 3]. This deletion may have an impact on the complications associated with the surgical correction of the TA as well as on the long-term prognosis.

34.2 Anatomy

Persistent truncus arteriosus is a conotruncal anomaly that consists of a unique arterial trunk that leaves the heart giving rise to the coronary arteries, the pulmonary and the systemic arteries. This anomaly is usually diagnosed in a context of situs solitus with a ventricular D-loop.

The truncal valve is located in the expected aortic valve position, with a fibrous continuity between truncal and mitral valves, but it presents a larger annulus. Leaflets are most often dystrophic resulting in stenosis and/or regurgitation. This unique semilunar truncal valve is in most cases tricuspid (69%), but may also be quadricuspid (22%) or bicuspid (9%). Uni, penta, and hexacuspid valves have been rarely described [4]. No other semilunar valve is found in these cases. The function of this valve has to be precisely analyzed before surgery to decide if it can be preserved or not. Usually, the truncal valve overrides equally the ventricular septal defect over right and left ventricle, but quite often the truncal valve is deviated on the right and may result in a narrowing of the left ventricle outflow after repair of the ventricular septal defect.

The partial or complete failure of the aortopulmonary septation results in the common arterial trunk, and the absence of infundibular septum results in the ventricular septal defect under the truncal valve. The ventricular septal defect is large and juxta truncal. Its inferior part is usually muscular (poste-

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rior limb of the trabecula septomarginalis) and remote from the tricuspid valve. Occasionally, this muscular part does not exist or is very thin and the lower limit of the ventricular septal defect can be very near the tricuspid valve and the conduction system, which can be injured during repair.

The pulmonary arteries arise from the common trunk, close to the truncal valve, from a short posterior pulmonary trunk, separately from the posterior wall or in a random fashion often associated with an interrupted aortic arch.

Many associated anomalies have been reported:

- There is a left superior vena cava in 4–12% of patients.
- In most cases, coronary artery distribution is normal, but anomalies that may occur include [4–6]:
  - A large infundibular artery or a left descending artery originating from the right coronary artery can cross the infundibulum (prominent conus branch of the right coronary artery supplying the right ventricular outflow tract) and have to be preserved during the infundibulotomy
  - A small leftward-displaced left anterior descending coronary artery
  - An origin of the posterior descending artery from the circumflex artery may be seen in 27% of patients
  - Anomalies of coronary ostial origin are documented in 37–49% of patients
  - Some coronary arteries may also arise from variable levels of the TA and have to be identified so as not to be injured during surgery
- A right aortic arch in 21–36% of patients [4, 5, 7].
- In 11–19% of patients, there is an interrupted aortic arch, most commonly a type B (in Van Praagh's type 4 truncus arteriosus) [4, 5, 7, 8].
- Hypoplasia of the aortic arch with or without coarctation occurs in 3% of patients [8].
- In 16% of patients, one pulmonary artery is absent on the side of the aortic arch [9].
- The mitral valve may be dysplastic.
- Other associations:
  - A secundum atrial septal defect in 9–20% of patients.
  - An aberrant subclavian artery in 4–10% of cases.
  - Mild tricuspid stenosis in 6% of cases.
  - Partial anomalous pulmonary venous connection, tricuspid atresia, mitral atresia, ventricular inversion, and an asplenia complex [9–13] have been described as rare.

Patients with TA may also have extracardiac anomalies in 21–30% of cases. The most common association is the 22q11^{-} deletion or DiGeorge sequence. This anomaly has been documented in one-third of all TA cases and in two-thirds of patients with a type B interrupted aortic arch and may have a significant impact in the postoperative course and in the long-term prognosis of these patients. Other described associated anomalies include skeletal deformities, hydroureter, bowel malrotation, and multiple complex anomalies [6].

34.3 Classifications

Two classifications are commonly used. The classification from *Collett and Edwards,* described in 1949 [14], is based on the origin of the pulmonary arteries (Fig. 34.1). *Type I* is defined by the presence of a main pulmonary trunk, arising from the ascending aorta giving the two pulmonary arteries. In *Type II*, the pulmonary arteries arise from close but separated ostia on the common arterial trunk, whereas these ostia are widely separated in *Type III*. *Type IV*, where pulmonary arteries are coming from the descending aorta, is now considered like a form of tetralogy of Fallot with pulmonary atresia in which pulmonary blood supply is achieved by aortopulmonary arteries (pseudo TA).

In the *Van Praagh* classification, defined in 1965 [4], differences in the types of TA are based on the embryological septation (Fig. 34.2). *Type A* is defined by the presence of a ventricular septal defect and *Type B* by its absence. These types are completed by four extracardiac patterns for the aorta and pulmonary arteries:

- *Type 1* presents a partially formed aortopulmonary septum resulting in a segment of a main pulmonary trunk. It is the most frequent type (about 60%) and corresponds to Collett's Type I.
- *Type 2* has no aortopulmonary septum and thus no main pulmonary trunk, pulmonary arteries originating directly from the TA (about 30%, corresponding to Collett's types II and III).
- *Type 3* is very rare and defined by a unique pulmonary artery originating from the TA, the second one coming from the ductus arteriosus or from an aortopulmonary artery (hemitruncus).
- *Type 4* corresponds to an aortic arch interruption downstream the left common carotid artery. After the pulmonary bifurcation, a large patent ductus arteriosus supplies the descending aorta and the left subclavian artery.

34.4 Pathophysiology

Since the common trunk receives blood from both ventricles, a VSD is almost always present [15, 16]. This ventricular septal defect is usually large. The predominant physiological characteristic of this disease is therefore a significant left-to-

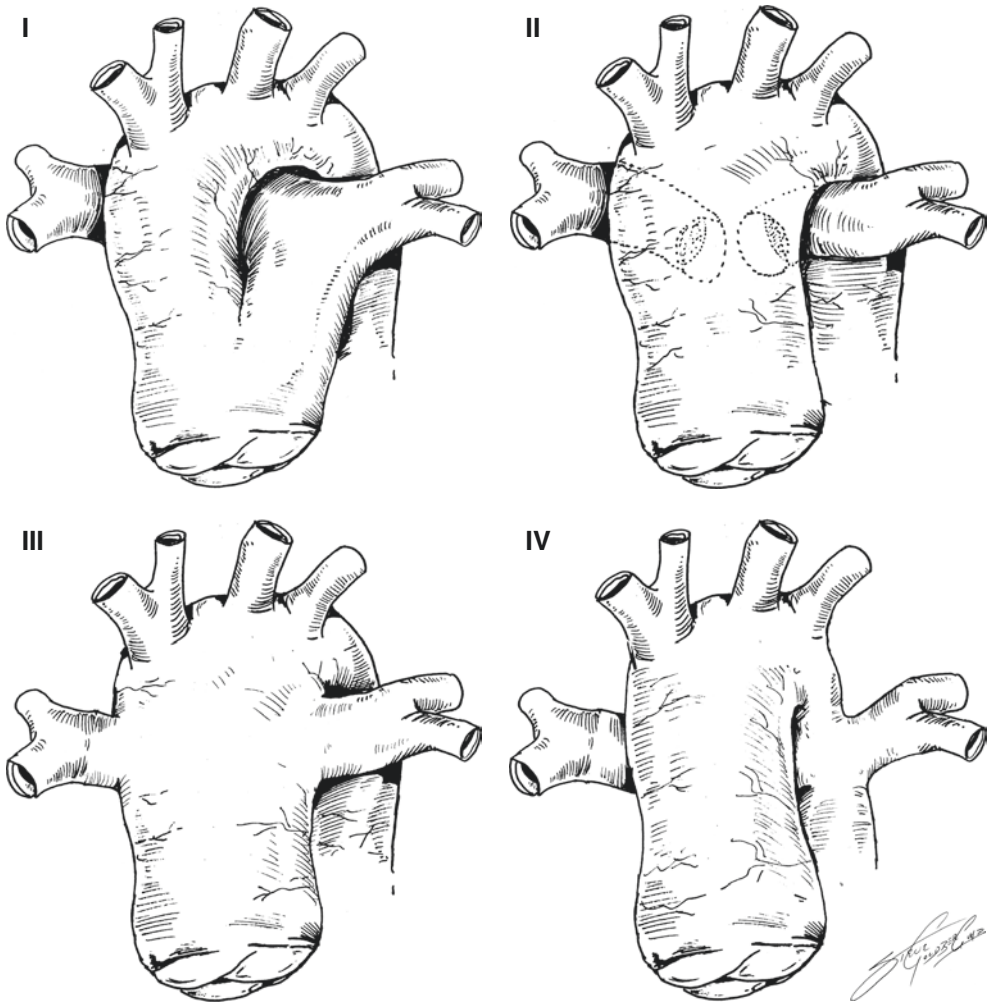

Fig. 34.1 Truncus arteriosus, classification of Collett and Edwards

right shunt, unless the pulmonary arteries are hypoplastic or stenotic or the pulmonary vascular resistances are elevated. The degree of shunting depends to a great extent on the ratio of resistances between the systemic and the pulmonary circulations. As pulmonary vascular resistances decrease over the first few weeks of life, patients develop signs of cardiac failure.

Truncal valve regurgitation and stenosis are seen in 10–15% of patients respectively. If truncal insufficiency is severe, signs and symptoms of heart failure may appear shortly after birth.

In the uncommon situation in which infants have stenosis of the pulmonary arteries, obvious cyanosis may be present at birth and intensify with age [6], although these patients have less cardiac failure.

If an interrupted aortic arch is associated, patients become very symptomatic early in life, associating pulmonary overcirculation with pulmonary hypertension and cardiac failure, with signs of low cardiac output and left-sided obstruction. Nevertheless, in type 4 TA, often the pulmonary arteries are stenotic, protecting the patients against overcirculation.

34.5 Diagnosis

34.5.1 Clinical Presentation

Most patients present in the neonatal period, if not diagnosed in utero. Clinical presentation depends on the Qp/Qs, hence, patients with stenosis of the pulmonary arteries are essentially cyanotic, whereas patients without pulmonary protection develop signs of cardiac failure and failure to thrive over the first 2–4 weeks of life. Neonates may also appear mildly cyanotic because of high pulmonary vascular resistances. Feeding difficulties may be secondary to the TA, but caregivers must pay attention to the association with 22q11^{-} deletion that may also have an impact on the feeding capabilities. Patients with very high Qp/Qs may ultimately associate some degree of cyanosis to the signs of cardiac failure, due to pulmonary interstitial edema.

Patients with excessive pulmonary flow present with clinical signs of cardiac failure and of diastolic steal from the truncal vessel toward the lungs, namely, failure to thrive, tachycardia, tachypnea, excessive sweating, bounding pulses,

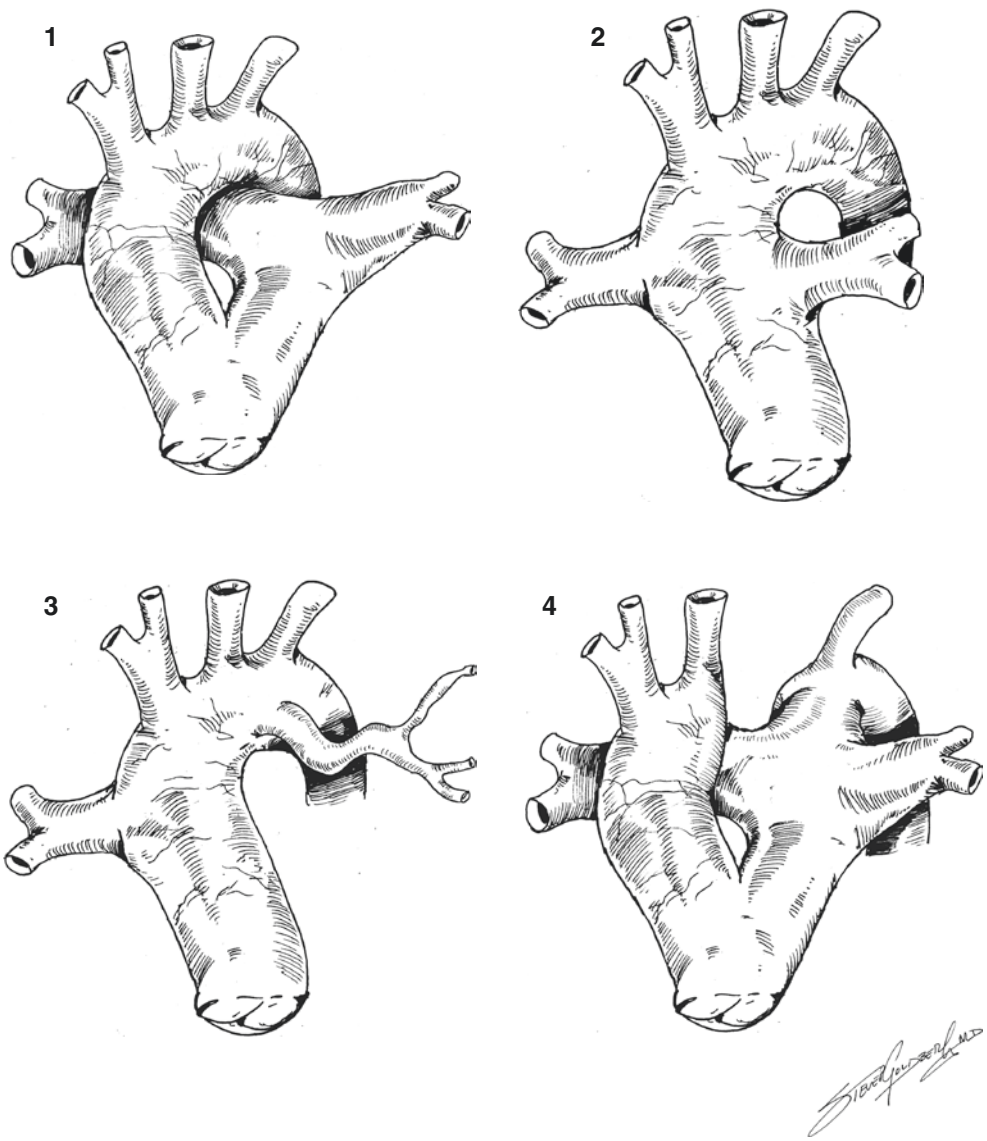

Fig. 34.2 Truncus arteriosus, classification of Van Praagh

and significant systemic systolo-diastolic pressure differential. These patients also have a hyperdynamic precordium, a left precordial bulge and cardiac auscultation may reveal a gallop rhythm and the presence of murmurs. A dysplastic and stenotic truncal valve may be the source of a pansystolic murmur, and also of a diastolic high-pitched murmur, directly proportional to the degree of the associated regurgitation, if any. Stenotic pulmonary arteries will explain the presence of a systolic murmur, irradiated toward the side of the affected artery. A thrill is present in patients with increased Qp/Qs. The first sound is normal and the second sound may be unique and loud. An ejection click may also be heard.

34.5.2 ECG

The ECG findings in the neonate may be varied and even normal. It usually shows a sinus rhythm and signs of biventricular hypertrophy. ECG is useful to rule-out the exceptional scenario of myocardial ischemia and as a baseline study for any eventual postoperative event.

34.5.3 Chest X-ray

Chest radiography shows cardiomegaly frequently present since birth. The aortic arch may be right-sided. In patients with high Qp/Qs, as the pulmonary vascular resistances decrease, cardiomegaly as well as pulmonary vascular markings will increase progressively, reflecting the excessive blood flow. With the increased venous return to the left heart, the left atrium may be enlarged and compress the left bronchus. Venous congestion may also be noted as the left ventricle dilates—with both the increased left-sided return and the truncal valve regurgitation—and fails in older patients. In patients with stenotic pulmonary arteries or in late survivors with elevated pulmonary

resistances, pulmonary vascular markings will be normal or decreased and the cardiomegaly is mild unless induced by severe truncal regurgitation. The absence of thymus suggests the association with 22q11⁻ deletion.

34.5.4 Echocardiography

Echocardiography is the cornerstone reference for diagnosis and follow-up of patients with truncus arteriosus (Figs. 34.3, 34.4, 34.5, and 34.6). It has significantly reduced the need for cardiac catheterization for diagnostic purposes, since it comprehensively shows:

- The conotruncal anomaly, with the ventricular balance, the ventricular function and the interventricular septal defect.
- The origin and configuration of the pulmonary arteries allowing the definition of the type of TA.
- The anatomic and functional characteristics of the truncal valve.
- The origin and distribution of the coronary arteries.
- The anatomy of the aortic arch; elucidates the association with interrupted aortic arch and aberrant retroesophageal right subclavian artery.
- Any other associated anomaly.

Echocardiography also facilitates the immediate perioperative evaluation of the surgical repair using trans-esophageal techniques. The main differential diagnosis prior to intervention is tetralogy of Fallot and pulmonary atresia with ventricular septal defect.

34.5.5 Cardiac Catheterization

Cardiac catheterization may be needed to confirm anatomic and physiologic details whenever the echocardiography is not conclusive or if there is suspicion of multiple ventricular septal defects or complex associated anomalies. It is particularly useful in late survivors who present with severe pulmonary arterial hypertension and in whom there is a need to study pulmonary vascular resistances and their responsiveness to therapy. Patients with TA who have pulmonary artery resistances above 8 Wood units/m^2 have higher operative and postoperative mortality [9, 17].

In patients who have been previously operated upon and who require re-intervention (i.e., right ventricle to pulmonary artery conduit replacement), cardiac catheterization may be useful in identifying coronary artery anatomy that can be obscured by the presence of pericardial adhesions when assessed by echocardiography.

34.5.6 Other Studies

34.5.6.1 MRI

Cardiac MRI (cMRI) is a useful noninvasive method that enables a noninvasive anatomic diagnosis of TA and can in some cases replace cardiac catheterization, particularly in older patients. cMRI is currently recognized by pediatric cardiologists and cardiac surgeons as an important technique for the preoperative and postoperative evaluation of some heart diseases [18]. It provides information about the anatomic

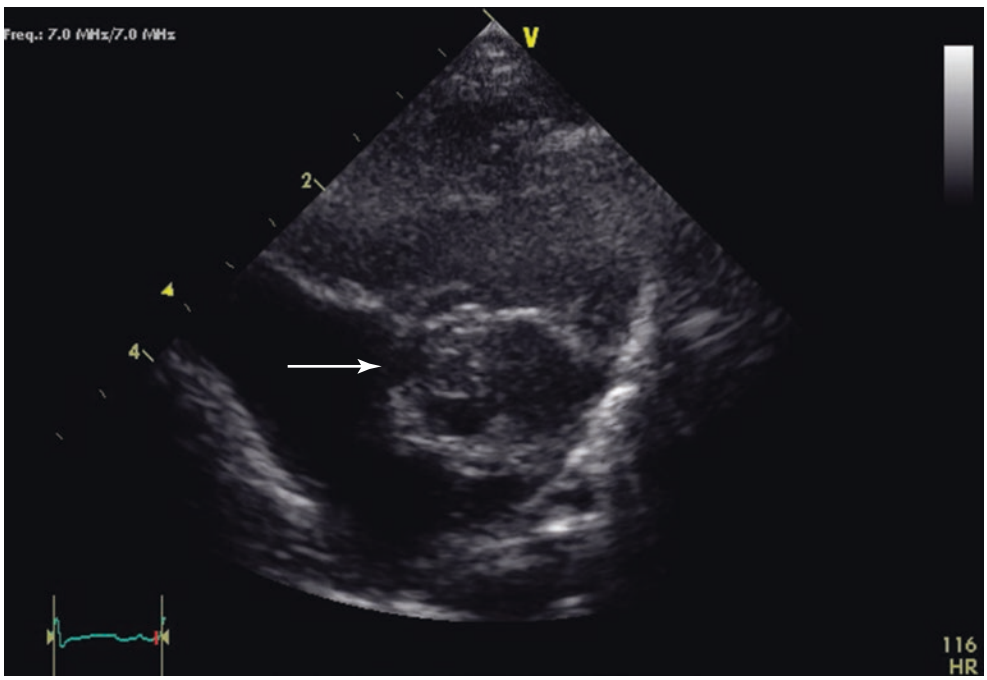

Fig. 34.3 Echocardiography showing a truncus arteriosus with a dysplastic truncal valve (arrow)

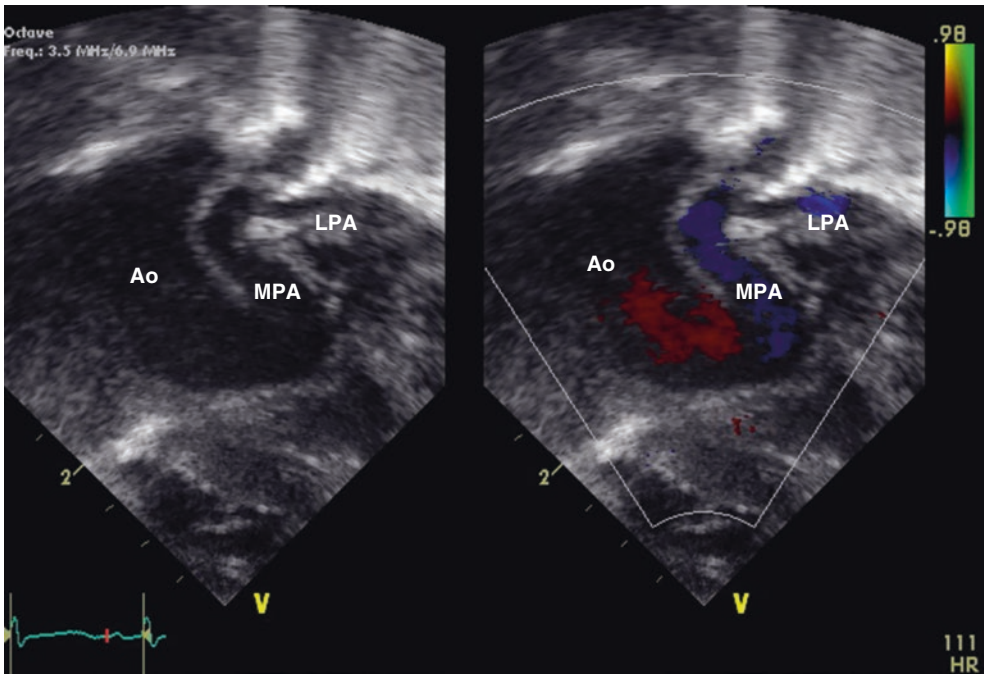

Fig. 34.4 Echocardiography showing a type 1 truncus arteriosus (Ao aorta, MPA main pulmonary artery, LPA left pulmonary artery)

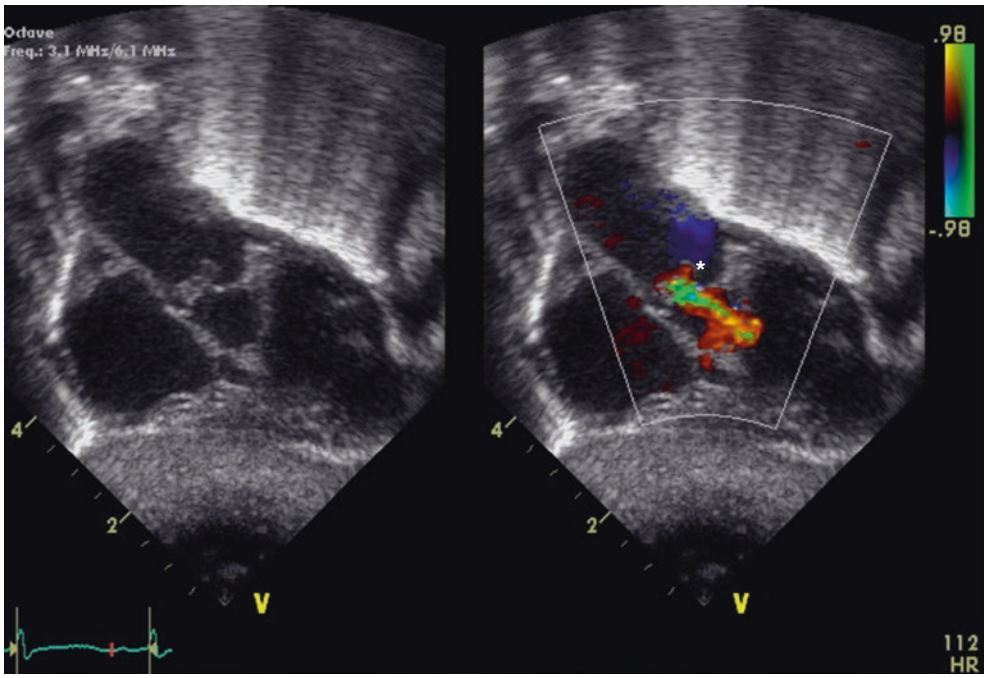

Fig. 34.5 Echocardiography showing a truncus arteriosus with a moderate regurgitation of the truncal valve (∗)

characteristics of the vascular anomalies and their relation to the bronchial system. It also allows a reliable functional evaluation of the ventricular performance and provides flow information determining the degree of truncal valve stenosis or regurgitation.

34.5.6.2 CT Scan

CT scans are useful for the evaluation of anomalies of the aortic arch and major vessels such as the aberrant origin of the right subclavian artery. It may also help define systemic and pulmonary venous connections, anomalies of the origin and course of the coronary arteries and the spatial relationship between vascular and airway structures.

34.6 Management

Total repair of TA should be performed in early life unless contraindicated by prematurity or extracardiac comorbidities. However, some patients require preoperative management of

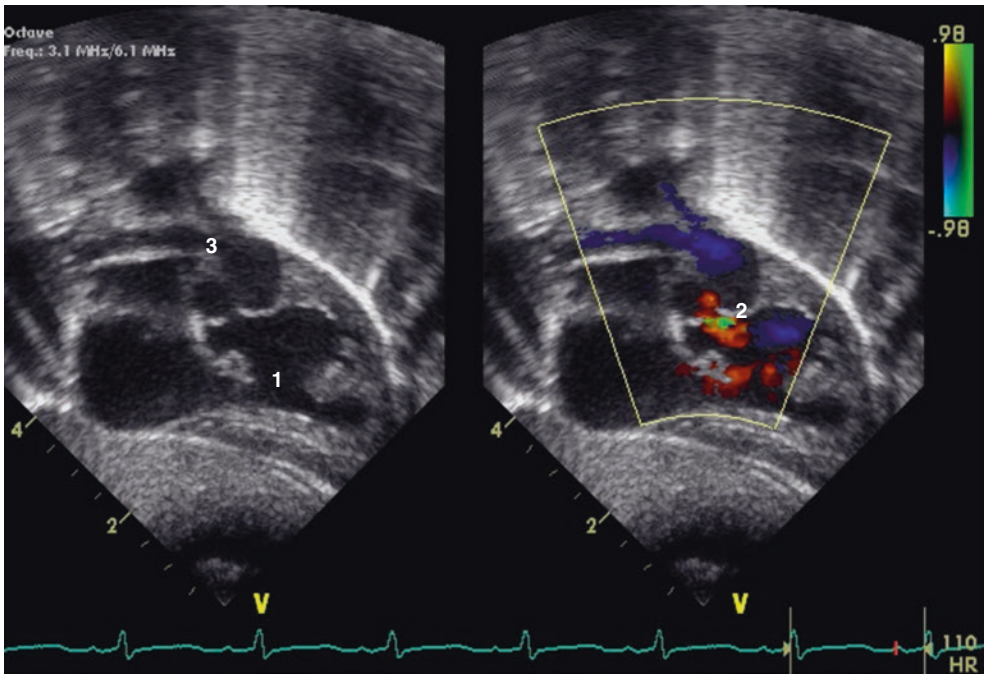

Fig. 34.6 Echocardiography showing a type 1 truncus arteriosus (1 ventricular septal defect; 2 mild to moderate regurgitation of the truncal valve; 3 pulmonary artery bifurcation)

specific problems to optimize conditions for the surgical procedure.

34.7 Preoperative Medical Management

34.7.1 Cardiovascular Management

Patients with significant truncal valve regurgitation or cyanosis due to pulmonary edema may benefit a milrinone infusion until surgery. Milrinone improves myocardial contractility, reduces the afterload of the ventricular mass and the left atrial pressure. Nevertheless, particular care must be taken with excessive systemic vasodilation that might compromise coronary perfusion.

In patients with elevated Qp/Qs, inspired oxygen must be carefully administered since, by inducing pulmonary vasodilation, it may facilitate further pulmonary overcirculation and pulmonary edema with low systemic cardiac output. In exceptional cases, sub-atmospheric therapy may be needed.

Diuretics are indicated in these patients to decrease the preload and the degree of pulmonary edema. Loop-diuretics may be administered in boluses or as a continuous infusion.

Fluid restriction should be avoided because of the impact on the caloric input.

34.7.2 Respiratory Management

Symptomatic patients may require noninvasive positive pressure in the form of CPAP or BiPAP. It improves pulmonary edema and reduces systemic afterload, hence improving the stroke volume. When mechanical ventilation is required, caregivers should provide conditions to reduce or limit pulmonary vascular flow. Hyperventilation should therefore be avoided. The objective is to provide low respiratory rate, tidal volume, peak pressures and FiO_2, keeping oxygen saturations in the range of 75–85%. When the excessive Qp/Qs is refractory to these measures, patients may need deep sedation, the use of muscle relaxants and sub-atmospheric gases.

34.7.3 Nutritional Management

Preoperative nutrition is crucial and may have an impact on the postoperative course. Early enteral feeding is therefore recommended. Patients in whom enteral feeding is contraindicated or limited should be started on parenteral feeding as soon as possible.

34.7.4 Other

Patients with excessive Qp/Qs improve with measures that optimize systemic flow. This includes, other than the use of systemic vasodilators, diuretics, adequate ventilation, and increased blood viscosity with transfusion of red blood cells.

Considering the high incidence of $22q11^-$ deletion, a sample for genetic analysis should be systematically sent to the laboratory.

34.8 Surgical Management

As previously discussed, truncus arteriosus induces cyanosis due to blood mixing at the level of the VSD, as well as a left to right shunt at the arterial level, resulting in heart failure and rapid development of severe pulmonary vascular obstructive disease by 6 months of age. Survival after surgical repair has greatly improved with early repair, and most authors recommend treating these children before 1 month of age. Surgical repair is always indicated excepted for late survivors with high pulmonary vascular resistances (Eisenmenger's syndrome).

For the large majority of TA (about 90%), in the absence of truncal valve dysfunction or aortic arch interruption, surgical repair consists in the separation of the pulmonary arteries from the truncal vessel, the closure of the ventricular septal defect, and the reconstruction of the right ventricular outflow tract with the placement of a valved conduit toward the pulmonary arteries. In cases with truncal valve dysfunction, although techniques of repair have been described, replacement by a homograft is often indicated. TA with aortic arch interruption necessitates reconstruction of the aorta as well.

The type of surgical repair depends on the anatomic form:

34.8.1 Repair of Isolated TA

Isolated forms of TA (nearly 90% of cases) correspond to Van Praagh's types A1 and A2 and to Collett's types I, II, and III.

After sternotomy and fixation of a pericardium patch in glutaraldehyde, cardiopulmonary bypass is established between the distal ascending aorta and both vena cava. The procedure may be achieved under continuous high flow, high hematocrit normothermic cardiopulmonary bypass. After pulmonary artery control, aortic cross-clamping, and cardioplegia, the common TA is opened, and a pulmonary trunk or an aortic patch including the two pulmonary arteries is harvested. This defect on the ascending aorta is generally repaired by an end-to-end anastomosis between the aortic root and the distal ascending aorta. Both pulmonary branches are well mobilized. Through a right ventriculotomy starting immediately under the truncal valve, the ventricular septal defect is exposed and closed by a pericardial or prosthetic patch. The patch must be large to avoid narrowing of the left ventricular outflow and its lower fixation has to preserve the conduction system. The right ventricle outflow tract is then reconstructed with a small size pulmonary or aortic homograft or with a valved prosthetic conduit, placed between the pulmonary bifurcation and the right ventriculotomy (Fig. 34.7). All these materials are unable to grow and will undergo degradation requiring iterative replacement.

To avoid such material, surgical techniques have been developed using autologous tissues [19]. These techniques consist in a mobilization of the pulmonary trunk or bifurcation toward the right ventriculotomy and the anastomosis of its posterior wall to the top of the ventriculotomy, directly or using the left atrial appendage. An anterior hood is made of pericardium to complete the anterior part of the right outflow tract. To avoid consequences of postoperative pulmonary hypertension, a monocuspid valve is implanted in the right outflow tract, but ultimately pulmonary regurgitation appears as the main drawback of this technique.

Finally, although it is not the author's policy, some surgeons may preserve a small (5 mm) atrial septal defect as a security in case of pulmonary hypertensive crisis or right ventricular failure [20].

34.8.2 Repair of TA with Truncal Valve Dysfunction

Truncal valve stenosis is rare and often overestimated preoperatively because of the increased blood flow. Intraoperative commisurotomy is sufficient in most cases and must be conservative to avoid postoperative regurgitation.

Preoperative regurgitation is frequent, due to the dystrophic truncal valve leaflets. Mild to moderate regurgitation may be accepted. For severe regurgitation though, a valvuloplasty should be attempted (Fig. 34.8).

If a valvuloplasty is not possible, the truncal valve is replaced by a cryopreserved aortic homograft. The truncal valve is removed, the ventriculotomy is extended through the truncal annulus, and the superior edge of the patch used for the ventricular septal defect closure becomes the anterior part of the new annulus where the homograft is sutured. Coronary arteries are [21] then reimplanted in the homograft before distal anastomosis to the distal ascending aorta.

34.8.3 Repair of TA with Aortic Arch Interruption

TA with aortic arch interruption corresponds to Van Praagh's type A4 truncus arteriosus. For this repair, cardiopulmonary bypass is modified to avoid circulatory arrest. These authors use a PTFE prosthetic tube anastomosed to the brachio-cephalic arterial trunk for the arterial cannulation in order to achieve a continuous anterograde cerebral perfusion during partial circulatory arrest necessary for the reconstruction of the aortic arch.

After removing the pulmonary trunk from the TA, all the ductal tissue is resected. The descending aorta is extensively mobilized and in most cases its posterior wall can be sutured to the longitudinal incision of the ascending aorta. The large anterior and inferior defect of the ascending aorta and aortic arch is reconstructed with a patch of autologous aorta or vas-

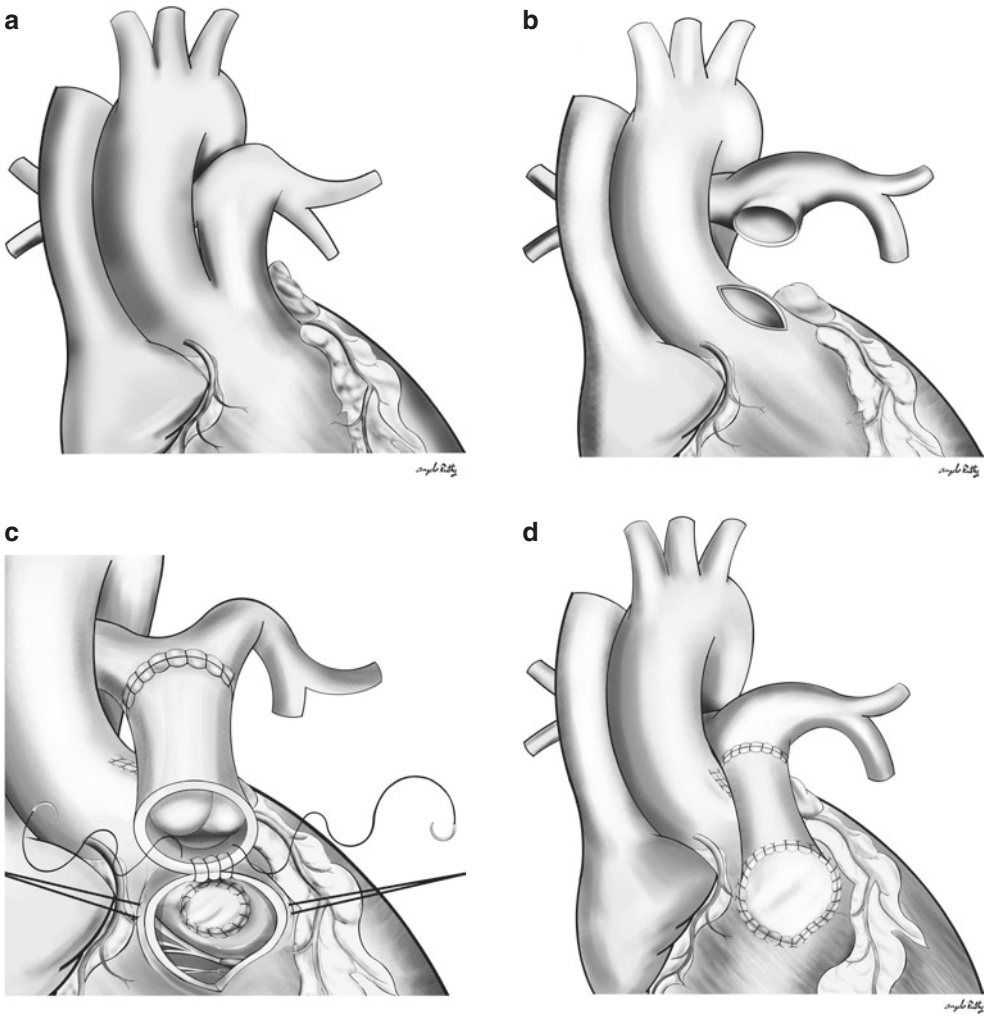

Fig. 34.7 *Truncus arteriosus Type I Repair.* (**a**) Type I truncus arteriosus. (**b**) First, the pulmonary trunk is separated from the truncus. (**c**) Then through a right ventriculotomy the VSD is closed and a valved conduit is used to establish RV to PA continuity. (**d**) The completed repair

cular homograft. Cerebral perfusion is then converted to total and conventional cardiopulmonary bypass is initiated. The VSD is closed, followed by the RV to PA conduit as described for other types of TA (Fig. 34.9).

34.8.4 Repair of Hemitruncus

For hemitruncus repair, the pulmonary artery originating from the ductus arteriosus or the descending aorta is detached and then branched on the pulmonary arterial tract forming a new pulmonary bifurcation.

34.9 Postoperative Management

Postoperative management after TA repair varies with the anatomic form and may be impacted by the duration of cardiopulmonary bypass, the aortic cross-clamp, and the circulatory arrest time. Residual lesions will also complicate the postoperative course and must absolutely be ruled-out in patients who do not progress uneventfully. Most of the potential complications develop during the peak of the inflammatory process throughout the first 48 hours. The main complications to be anticipated and prevented if possible are pulmonary hypertensive spells and low cardiac output syndrome (LCOS), in addition to those related to co-morbidities.

34.9.1 Monitoring

Although institutional preferences may vary, most patients require indwelling pulmonary and left atrial catheters, as a complement to the central venous and arterial lines. Noninvasive monitoring is based on heart rate with ECG, respiratory rate, and peripheral oxygen saturation, as a minimal requirement. Transcutaneous CO_2 and NIRS are also important tools to use. The most important hemodynamic markers to follow concern tissue perfusion.

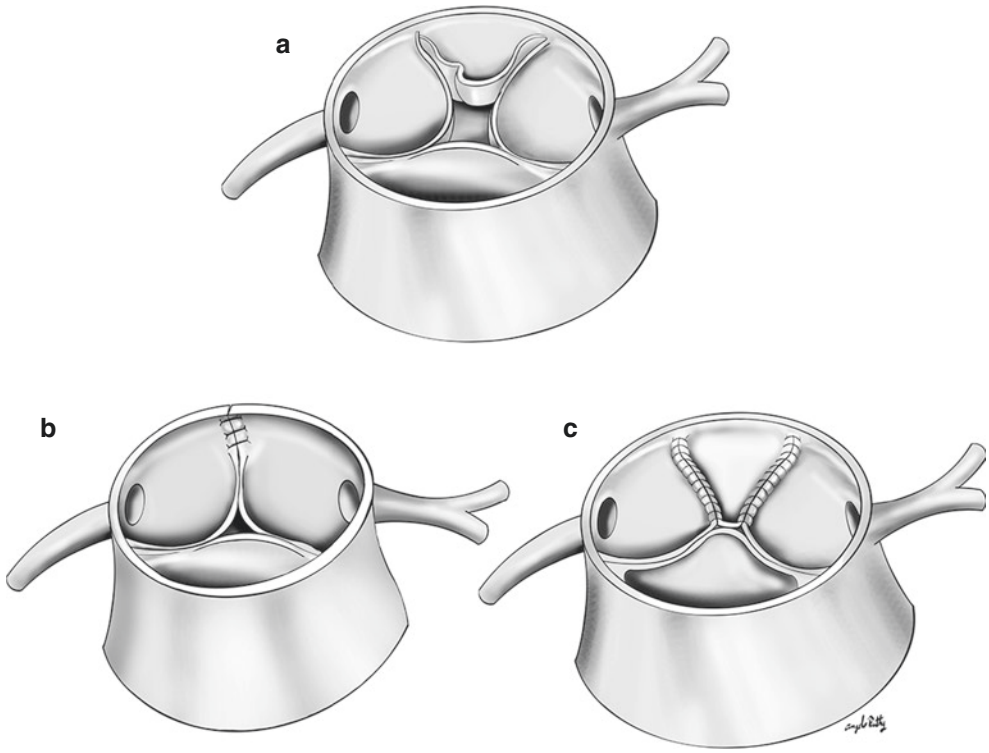

Fig. 34.8 *Truncal valve repair.* (**a**) Options for valve repair in the presence of a quadricusp truncal valve with a prolapsing leaflet include: (**b**) leaflet and aortic sinus resection or (**c**) commissural closure

34.9.2 General Measures

During the acute phase, patients should be mobilized and manipulated as minimum to decrease the risks for pulmonary hypertensive spells. With the same goal, potential triggers for pulmonary hypertension ought to be prevented. These include volume overload, pain or agitation, fever, metabolic or respiratory acidosis, hypoxia and anemia to mention some.

Patients should be kept in an anabolic status for which early nutrition is crucial.

Caregivers must pay attention to risks related to the presence of a 22q11$^-$ deletion, particularly with regard to metabolic disturbances, airway complications, and sepsis.

34.9.3 Fluid Management

After total repair of TA on cardiopulmonary bypass, patients must be restricted to 50% of their requirements on day 1, followed by 75% on day 2, and 100% from day 3. Obviously, these recommendations must be individualized and adapted to the patient's hemodynamic, respiratory, and metabolic status.

34.9.4 Sedation and Pain Control

After total repair of a TA, patients are under the risk of developing pulmonary hypertensive crisis and should be maintained well sedated and under analgesia for at least 12–24 hours or until there is confirmation of a consistent hemodynamic stability, with a combination of opioids and benzodiazepines to be titrated to the minimal efficient dose. Titration and length of treatment with these drugs also depend on the type of intervention and patients' characteristics. Infants with 22q11$^-$ deletion are often more difficult to wean from the ventilator due to associated anatomic or functional airway anomalies. Delayed chest closure is also a factor that might determine the length and strength of sedation and analgesia. Muscle relaxants may be required in patients who remain unstable and who have refractory pulmonary hypertensive crisis; however, these should not be used systematically. Dexmedetomidine is a very useful agent that does not inhibit the respiratory drive. Propofol, ketamine, or clonidine drips may be used in specific cases.

34.9.5 Respiratory Management

These patients are very sensitive to cardiopulmonary interactions. Provided adequate and consistent hemodynamic stability, and in the absence of bleeding, neurologic, respiratory, or metabolic concerns, patients should progress toward spontaneous breathing and extubation as soon as possible, with serious consideration taken for the risks of pulmonary hypertension. This later factor is more prevalent in patients repaired later in life or who have had a complex repair. Sometimes, extubation is deferred by a systematic delayed sternal closure. All respiratory collateral complications (pleural efusion, atelectasis, or pneumothorax) should be aggressively managed.

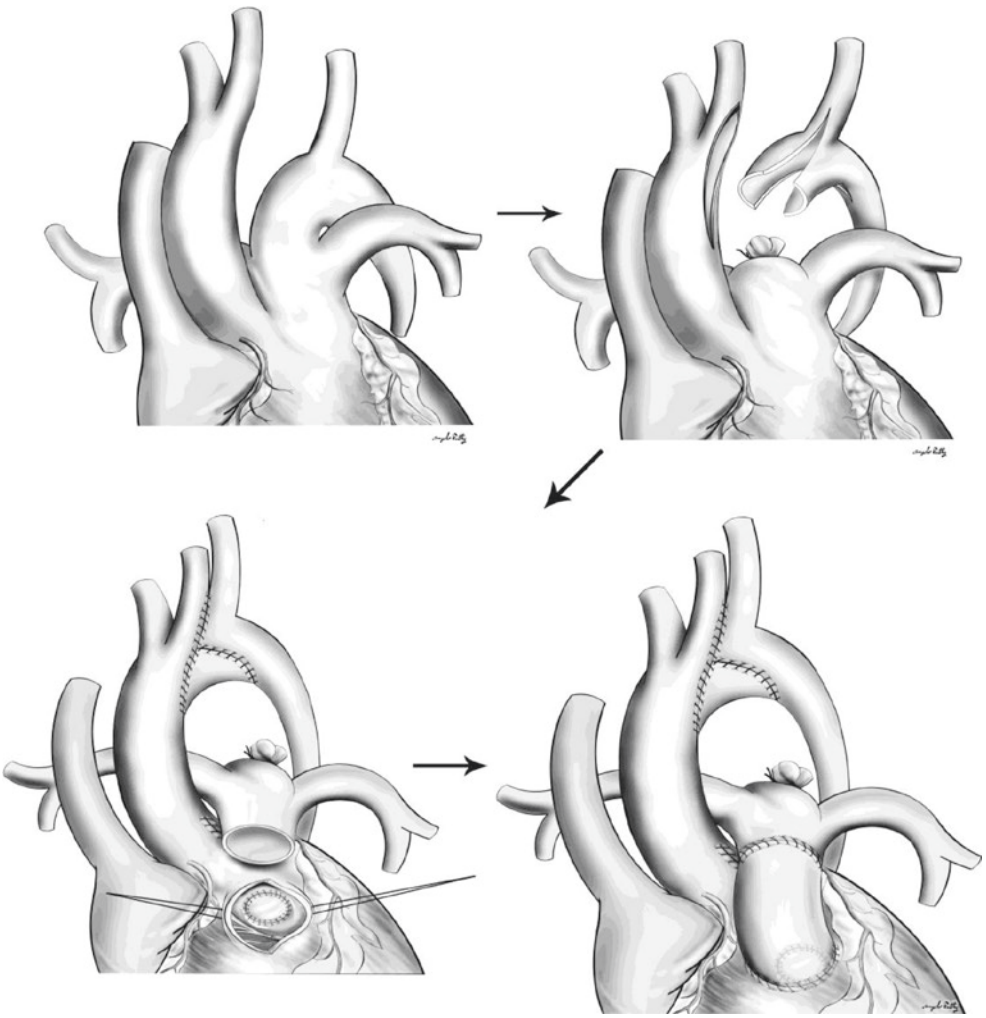

Fig. 34.9 *Repair of truncus arteriosus with aortic interruption.* The technique utilized to repair the aortic interruption involves a direct anastomosis (superiorly) with patch augmentation (inferiorly). After separating the pulmonary trunk from the truncus and closing the VSD, a valved conduit is used to establish RV to PA continuity

Minimal manipulation of the airways is also essential to prevent pulmonary hypertension. It is important to ensure adequate oxygenation and to maintain pH levels between 7.40 and 7.45, with pCO_2 around 30–35 mm Hg.

During pulmonary hypertensive crisis, patients may be managed with hyperoxygenation and hyperventilation, and often require a supplemental dose of sedation, analgesia, and muscle relaxants.

The use of inhaled nitric oxide is an outstanding resource to manage these patients. Some institutions promote the use of preventive nitric oxide, although there is no evidence-based data supporting this practice. Patients who require long-term pulmonary vasodilation or remain nitric oxide-dependent may be candidates for the use of sildenafil.

34.9.6 Cardiovascular Management

Hemodynamic management also depends on the type of repair. The most common drug combination seeks both an inotropic effect (milrinone, dopamine, epinephrine) and systemic vasodilation (milrinone, phentolamine, phenoxybenzamine, sodium nitroprusside, nitroglycerine). Milrinone is the most common choice, owing to its inotropic, lusitropic, and vasodilator effects, sometimes in combination with low-dose epinephrine. In patients with significant vasoplegia, the association of low-dose vasoconstrictors (vasopressine, norepinephrine) may be useful.

If the right ventricle is hypertrophic and poorly compliant, higher filling pressures may be required and beta-blockers may be useful in order to decrease the cardiac rate therefore optimizing the ventricular filling (diastolic) time. Esmolol is a reasonable option since it is easy to titrate and its short half-life offers an advantage in patients who poorly tolerate it.

Loop diuretics are usually initiated throughout the first postoperative day.

After total repair of a TA, a number of scenarios may occur, requiring more specific or aggressive hemodynamic management:

34.9.6.1 Right Ventricular Dysfunction

Right ventricular dysfunction, both systolic and diastolic, may be secondary to multiple causes: elevated pulmonary pressures, residual left-to-right shunts, coronary compression by the conduit, and also the impact of the ventriculotomy. The consequence of this is an inadequate forward flow and the development of right-sided failure with venous congestion, hepatomegaly, and ascites. This will also result in increased afterload for vital organs like the kidneys and the gastrointestinal tract. Echocardiography is essential to rule-out residual shunts, assess the ventricular function and also to define the anatomy of the reconstructed outflow tract and pulmonary arteries. Significant obstruction and/or regurgitation may be documented and require re-intervention. Nevertheless, in most cases of right-sided dysfunction, progressive improvement is observed over time. If the etiology is not apparent by echocardiography alone, a cardiac catheterization is indicated and may also allow percutaneous intervention.

These patients require higher right-sided filling pressures and the use of lusitropic drugs. Ventilatory measures and eventually inhaled nitric oxide may be used to try to reduce the right ventricular afterload to promote an increase in the stroke volume and the reduction of the conduit regurgitation.

34.9.6.2 Left Ventricular Dysfunction

Left ventricular dysfunction and its immediate consequence, LCOS, is one of the most common occurrences after TA repair. It may be secondary to pulmonary hypertension, right ventricular failure, the presence of residual defects or the intrinsic changes induced by the cardiopulmonary bypass, the stress-response, and the inflammatory syndrome. Patients may persist with relatively adequate blood pressure, but their stroke volume and tissue oxygen delivery will be sub-optimal. The consequence will be the progressive development of low peripheral perfusion, reduced urine output, metabolic or lactic acidosis, decreased sVO_2 and decreased NIRS values.

Management is based upon the use of milrinone, low dose of dopamine and epinephrine, and correction of all identified metabolic disturbances. Particular attention must be paid to the calcium, magnesium, potassium, and sodium levels in these patients. The presence of LCOS widely justifies the search for residual defects (see below).

Refractory cases may need ECMO and this strategy should be utilized sooner than later when the trend does not show an adequate response to the medical treatment.

34.9.6.3 Residual Lesions

Patients who do not progress well need to be evaluated for residual lesions. Clinical examination remains important to develop a pathophysiological assessment. Echocardiography is the main tool utilized for this purpose but complementary investigations may be required. In patients with a pulmonary catheter, a Qp/Qs estimation may also reveal important data.

The main lesions to rule-out are:

(a) Residual ventricular septal defects
(b) Residual aortic arch obstruction
(c) Residual stenosis or significant regurgitation of the truncal valve
(d) Right ventricular outflow tract obstructions
(e) Pulmonary obstructions or conduit regurgitation
(f) Coronary compression
(g) Poor ventricular function

Prognosis in these patients depends on anticipation. Early identification and correction of these problems by medical or surgical measures is essential.

34.9.7 Management of Arrhythmias and Conductive Disorders

Arrhythmias are not uncommon after total repair of a TA. The most common disturbances are supraventricular tachycardias and junctional ectopic tachycardia. Ventricular arrhythmia should induce urgent assessment of the coronary arteries and myocardial perfusion.

Conductive disorders may also be identified. The incidence of complete heart block for this anomaly is around 3–5%.

Right bundle brunch block is common after TA repair.

34.9.8 Management of Electrolytic and Acid–Base Status

Acidosis is a potential trigger for pulmonary hypertensive crisis and should be avoided. Although the mostly appropriate treatment of the acidosis is to correct its cause, meticulous correction of metabolic acidosis with sodium bicarbonate or with THAM is common practice. Ventilatory parameters must also be adapted to the blood gases in order to preserve an adequate acid-base status. Electrolytic disturbances should also be systematically compensated. Calcium chloride may be required on a regular basis as a bolus or as a continuous infusion in patients with $22q11^{-}$ deletion.

34.9.9 Management of Renal Function

Urine output may remain marginal during the first 48–72 hours and caregivers need to be cognizant of the risks of acute kidney

injury. The early use of loop-diuretics as boluses or as a continuous infusion is recommended, provided that an adequate renal preload and circulatory volume is ensured. It is common to insert a peritoneal catheter in the perioperative period to facilitate diuresis. Some teams recommend the systematic replacement of fluid losses through the peritoneal catheter with albumin during the first 24 hours. Peritoneal catheters should be removed as soon as possible, when patients are deemed to have normal urine productivity.

34.9.10 Neurologic Management

A preoperative brain ultrasound is recommended as a baseline evaluation and should be controlled after the intervention. Management of neurologic complications is discussed in a specific chapter in this book.

34.9.11 Management of Infectious Issues

Protocols related to antibiotic prophylaxis vary within countries and even institutions. Cefazolin remains probably the most widely used antibiotic for this purpose, and vancomycin replaces the later in MRSA-positive patients.

Patients with $22q11^{-}$ deletion, those with an open chest and on ECMO, require close monitoring of the infectious markers. Early broad-spectrum antibiotics are indicated in case of suspected sepsis.

34.9.12 Management of Gastrointestinal Issues

Early enteral feeding, at least for trophic stimulation is not contraindicated, unless patients have low cardiac output syndrome that predisposes to splanchnic hypoperfusion and increases the theoretical risk for necrotizing enterocolitis. NIRS may be a useful tool to assess risks and tolerance to feeding in these neonates and infants. Patients who cannot be enterally fed should be started on early total parenteral nutrition. H_2-antagonists or proton-pump inhibitors are recommended during the acute phase. Hepatic and pancreatic function should be carefully monitored, particularly once feeding is resumed.

34.10 Outcomes

Reported perioperative mortality for children operated for TA in the neonatal period varies from 10% to 15% [22–29]. Mortality rate is higher for older children with augmented pulmonary vascular resistances, interruption of the aortic arch or truncal valve insufficiency.

All patients with a valved conduit will need reoperation for stenosis and/or pulmonary regurgitation. Age for these reoperations is variable according to the size of the first conduit or homograft and its alteration. Recipients of larger conduits may become candidates for percutaneous valve implantations in later life.

The evolution of a truncal valve dysfunction may also lead to reoperation for truncal valve replacement.

Long term-survival is about 80–85% at 20 years [30], with, for most patients a close-to-normal quality of life, in the absence of co-morbidities and syndromic features. Without treatment, the natural history is primarily fatal, with a survival reported around 20% at 1 year of age. Nevertheless, some patients have been reported to survive until their third, fourth, or fifth decade of life [31, 32].

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Chapter 35
Double Outlet Right Ventricle

Uyen Truong, Eduardo M. da Cruz, Jason P. Weinman, and James Jaggers

Abstract Double outlet right ventricle is a type of anomalous ventriculoarterial connection that represents 0.5–1.5% of congenital cardiac defects and can express several "phenotypes." This conotruncal anomaly presents with a wide spectrum of anatomical forms depending on the location of the ventricular septal defect, the relationship between the great vessels and the ventricular cavities, and the presence of a pulmonary flow obstruction. Furthermore, DORV may or may not be associated with hypoplasia of one ventricle. This chapter provides an overview of the facets related to diagnosis and medical and surgical management of this cardiac malformation.

35.1 Introduction

Double outlet right ventricle (DORV) is one of the most fascinating and difficult congenital heart diseases to be classified. Six decades since the initial description by Witham [1], controversies remain. DORV is a type of anomalous ventriculoarterial connection that can express several "phenotypes." This conotruncal anomaly represents 0.5–1.5% of congenital cardiac defects and presents with a wide spectrum of anatomical forms depending on the location of the ventricular septal defect, the relationship between the great vessels and the ventricular cavities, and the presence of a pulmonary flow obstruction. Furthermore, DORV may or may not be associated with hypoplasia of one ventricle, thus adding the potential of a single ventricle physiology to the complexity. It is exactly this wide variation that has led to ongoing discussions about anatomical definition and optimal surgical management.

35.2 Genetic Association

The two most common genetic disorders with which DORV has been associated are 22q11 deletion [2, 3] and heterotaxy syndrome. The prevalence of 22q11 has been reported to be between 0.05% and 8% [3, 4] of DORV cases. In a recent study of 117 DORV cases from a single center, the authors found that only those patients with aortic arch anomalies had 22q11 deletion [2], similar to findings reported 30 years prior, which also noted higher prevalence in anomalies of the pulmonary arteries in 22q11 deletion [3]. In addition, deletions involving the development of neural crest cells such as MESP1 loss-of-function mutation [5], HAND1 loss-of-function mutation [6], and Fibulin-1 [7], development of the second heart field (Tbx1 [8]), or development of laterality, including CFC1 mutations [9] and NPHP4 mutations [10], have also been identified with DORV. Chromosomal abnormalities as well as associated extracardiac anomalies may influence the management decision and postoperative course of DORV.

35.3 Anatomical Definition

DORV is defined as a heart in which the trunks of both great vessels arise predominantly from the right ventricle. Initial description of DORV came from a practical need to distin-

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guish it from tetralogy of Fallot. It subsequently became clear that DORV spans a morphologic spectrum from tetralogy of Fallot at one end and transposition of the great arteries at the other, depending on the relationship of the great vessels to one another and to the interventricular septal defect.

Beyond an academic discourse, an accurate definition of this lesion allows for appropriate medical management and surgical planning, as well as a common language to study epidemiology and establish the basis for research. DORV has been morphologically characterized by prominent pathologists, cardiologists, and cardiovascular surgeons. One of the more popular definitions of DORV is the presence of bilateral complete infundibula [11]. Richard Van Praagh [13] defined DORV as essentially a mitro-aortic discontinuity in relation to the persistence of the subaortic conus, again emphasizing the role of the conus in DORV. However, it has since been shown that DORV can exist in the absence of bilateral conus. The Society of Thoracic Surgeons and the European Society for Cardio-thoracic Surgery [1, 17] stated that bilateral infundibula is not a prerequisite for a DORV heart, and that instead DORV should be defined as a heart in which at least 50% of the arterial trunks arise from the right ventricle. This "50% rule" was first used by Robert H. Anderson [12] and is currently the most frequently used definition.

35.4 Pathophysiology and Functional Classification

The pathophysiology of DORV depends on the anatomical associations, namely, the position of the VSD relative to the great vessels and the presence or absence of right ventricular outflow tract obstruction. The spatial relation of the VSD with the arterial outlets and the association with stenosis of one of the outflow tracts and/or semilunar valves allow the distinction of various *functional types*, which share common clinical presentations and more importantly, similar surgical repair.

The *functional classification* (Fig. 35.1) that follows has been adopted as the nomenclatures of the Association for European Paediatric and Congenital Cardiology (AEPC), the European Association for Cardio-Thoracic Surgery (EACTS), and the Society of Thoracic Surgeons (STS) [17–19]:

35.4.1 VSD-Type DORV

This variant represents 24% of cases and includes DORV with subaortic or doubly committed VSD and no pulmonary stenosis. The pathophysiology of this association is that of a VSD with a large left-to-right shunt with excessive pulmonary blood flow and risks of pulmonary vascular occlusive disease and pulmonary hypertension. In more than one-third of the cases [15, 16, 20, 21], the VSD is restrictive.

35.4.1.1 Fallot-Type DORV

This anatomic form that represents 64% of cases includes DORV with subaortic or doubly committed VSD with RV outflow tract obstruction. The pathophysiology is the equivalent of tetralogy of Fallot. It is often quite difficult to differentiate these forms from a true tetralogy of Fallot as the overriding of the aorta may be partial. In more than one-third of these cases [15, 16, 20], the VSD is restrictive.

35.4.1.2 DORV with Atrioventricular Septal Defect, Pulmonary Stenosis, and Heterotaxy

The pathophysiology of this association is the same as in an atrioventricular septal defect (AVSD) with tetralogy of Fallot. Clinical progression may be complicated by anomalies present in heterotaxy, usually a right isomerism. Varying degrees of outflow tract and pulmonary valvar stenosis occur, with pulmonary atresia being most extreme. The AVSD anatomy is usually a Rastelli type C. In most cases, the VSD is an AVSD-Fallot type, with a large superior component, close to the aortic valve [15, 16, 20]. Total anomalous pulmonary venous return is a frequent association. Most cases are not associated with Down syndrome. Intestinal malrotation is common and should be evaluated with an upper gastrointestinal study.

35.4.2 TGA-/VSD-Type DORV (Taussig-Bing Anomaly)

The pathophysiology of this anomaly is similar to that of transposition of the great arteries (TGA) with VSD. There is no pulmonic stenosis and the VSD is sub-pulmonary. In some cases, the VSD is restrictive and associated with aortic arch obstruction and subaortic obstruction. In this case, the aorta is often significantly smaller than the pulmonary artery. The right ventricle is usually slightly small but not hypoplastic, unless there is associated tricuspid valve stenosis.

35.4.3 DORV with a Noncommitted VSD

In this anatomic form, the VSD is distant from the arterial valves by a distance greater than the diameter of the aortic

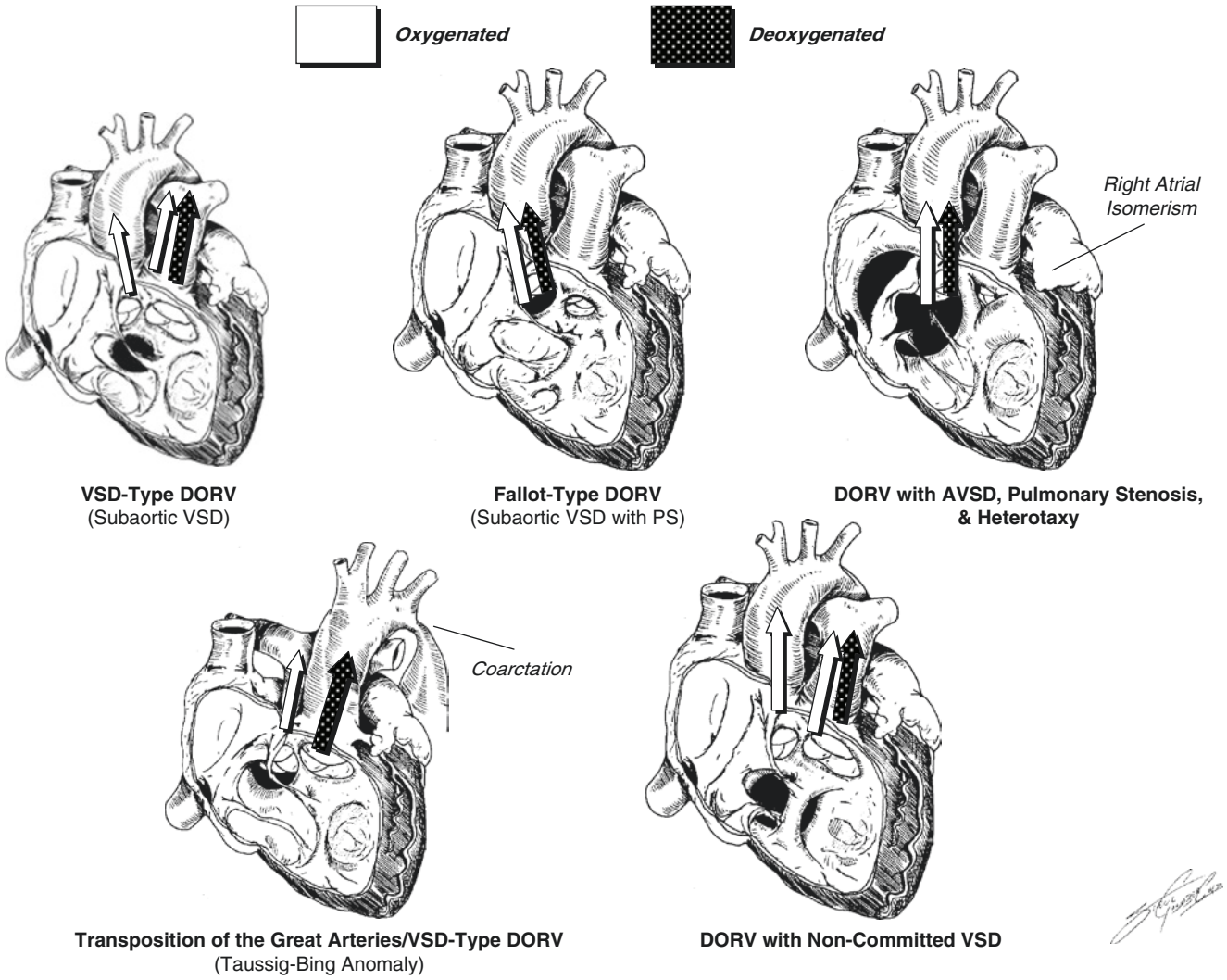

Fig. 35.1 Functional classification of the DORV

annulus [22]. The VSD is located below the trabecula septomarginalis [23], and is in contact with the tricuspid annulus [20]. In the absence of pulmonary stenosis, the pathophysiology is that of a large VSD with unrestricted pulmonary blood flow. In the presence of pulmonary stenosis, the pathophysiology is that of a VSD with restricted pulmonary blood flow.

35.5 Coronary Artery Anomalies

Although a normal coronary artery pattern is most common in DORV [24], anomalies of the origin and the course of the coronary arteries do occur. Anomalous patterns can include a left anterior descending coronary artery from the right coronary artery, circumflex from the right coronary artery, single coronary artery, and intramural coronary arteries. Preoperative, accurate delineation of the coronary artery pattern is critical to surgical planning.

35.6 Clinical Presentation

The clinical presentation of the DORV depends upon four critical anatomic traits:

(a) The position of the VSD with regards to the great vessels
(b) The position of the great vessels
(c) The presence or the absence of pulmonary obstruction
(d) The presence or the absence of anomalies of the aortic arch

If the VSD is sub-pulmonary, patients usually present in the neonatal period with cyanosis and signs of cardiac failure secondary to an elevated Qp/Qs (pulmonary overcirculation). This includes failure to thrive, breathlessness on feeding, tachycardia, tachypnea, and diaphoresis. Clinical examination reveals a cyanotic patient with a hyperdynamic precordium, a thrill on palpation, a gallop on auscultation, and hepatosplenomegaly. When the lesion is associated with an aortic arch obstruction

with ductal-dependent systemic blood flow, the child may become critically ill once the ductus arteriosus closes.

Patients with a subaortic VSD and no RV outflow tract obstruction present with predominant signs of cardiac failure and excessive pulmonary flow after the pulmonary vascular resistance drops in the first few weeks of life. In patients with predominant cardiac failure and no pulmonary protection, a thrill and a S3 will be present.

On the other hand, patients with sub-aortic VSD and RVOT obstruction present with decreased pulmonary blood flow and cyanosis that is proportional to the severity of the obstruction. The cardiac murmur also depends on this factor and tends to increase in intensity as the degree of obstruction increases.

When the VSD is doubly committed, the signs of cardiac failure will depend on the VSD size.

35.7 Chest X-Ray

Chest X-ray demonstrates cardiomegaly and plethoric lungs in case of subaortic VSD or sub-pulmonary VSD without pulmonary stenosis. In the case of pulmonary obstruction, cardiomegaly is mild or absent, and lung vascularity may be normal or decreased depending on the severity of the stenosis.

35.8 Echocardiography

Echocardiography is the cornerstone of diagnosis allowing a detailed delineation of the anatomic associations (Figs. 35.2 and 35.3) and is instrumental for follow-up. Advances in fetal echocardiogram have allowed for accurate prenatal diagnosis for conotruncal abnormalities, although determination of the spatial relationship of the great arteries in DORV remains challenging [25]. Planning for postnatal management of infants with DORV has also become more common as more complex cardiac lesions are identified in-utero. A single center study showed that prognosis for fetuses diagnosed with DORV was poor, with many of these fetuses having chromosomal and extracardiac anomalies [26]. Presence of associated cardiac and extracardiac anomalies, as well as abnormal karyotype, predicts outcomes [27]. In DORV cases without heterotaxy, whether the diagnosis was made pre- or postnatally, the major determinant of outcomes was the morphologic subtype [28].

3D echo is an evolving technique for noninvasive diagnosis and surgical planning. 3D echocardiography is becoming useful for assessment of valvar morphology and function and can add substantially to the perioperative planning for complex DORV. 3D fetal echocardiogram is in the very infancy stages, although an early report by Zidere et al. suggested 100% prediction of spatial orientation of the great vessels in DORV [30].

35.9 Cardiac Catheterization

Cardiac catheterization (Figs. 35.4 and 35.5) is not routinely performed in the neonatal period although it is sometimes indicated in complex forms to elucidate coronary anatomy and the suspicion of multiple VSDs. In older patients or in patients with significant residual lesions, catheterization is very useful

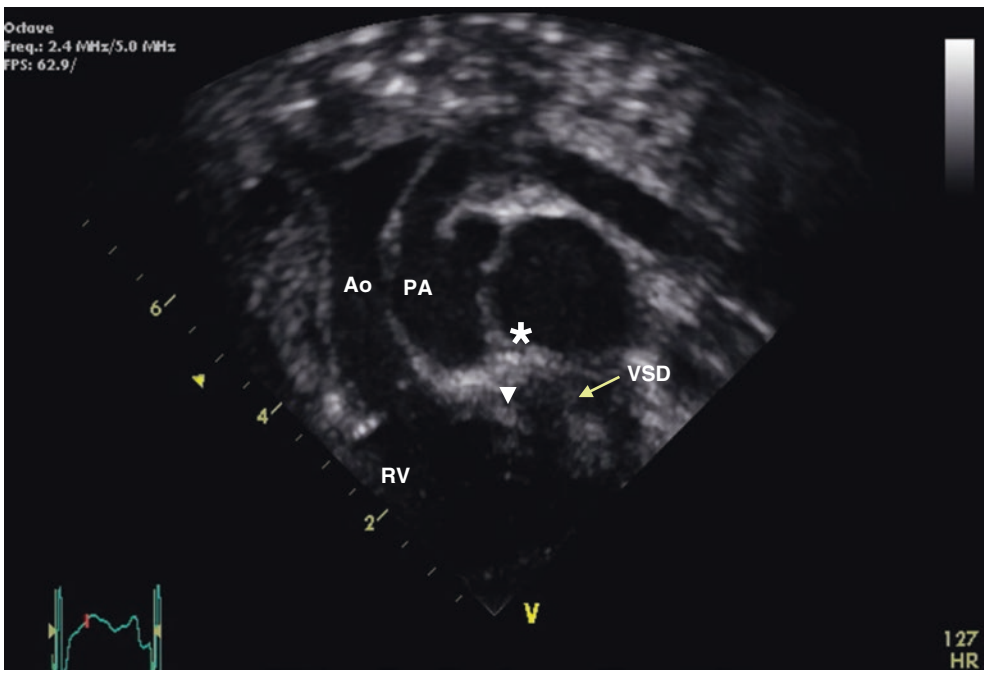

Fig. 35.2 DORV with a noncommitted ventricular septal defect, transposed aorta, pulmonary stenosis (∗), and a large conal septum (▼)

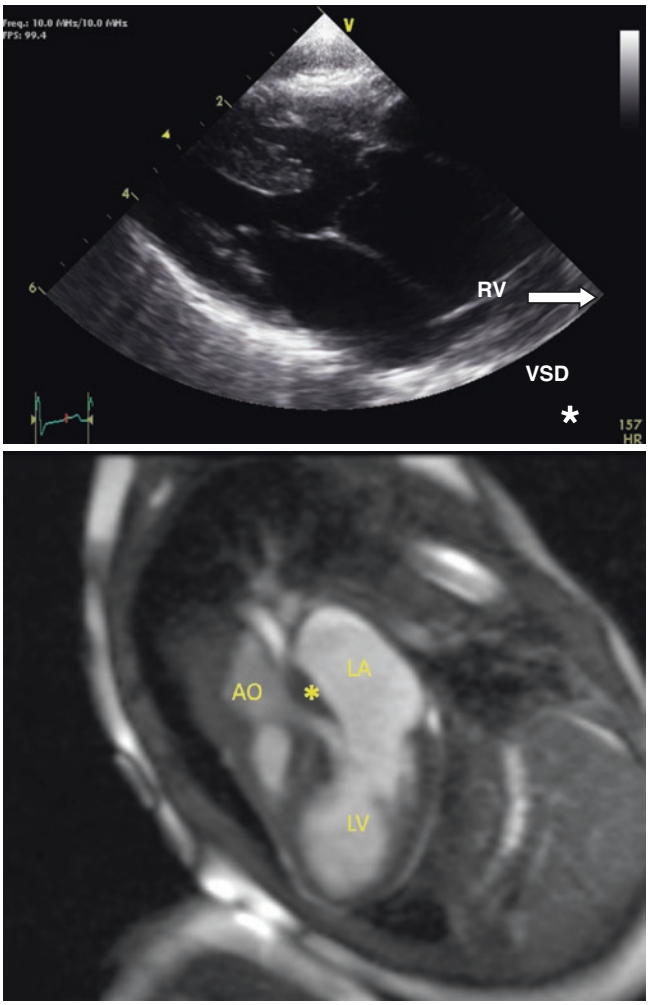

Fig. 35.3 Fallot-type DORV. The ventricular septal defect is subaortic. (**a**) Echocardiographic parasternal long-axis view of the left ventricular outflow tract. Notice that the aorta is not fully arising from the right ventricle and that there is a sub-pulmonary obstruction (full arrow). There is a mitro-aortic discontinuity (∗). (**b**) MRI 3-chamber view showing similar findings. The ∗ clearly shows muscle mass that separates the aortic and mitral annulus, reflecting the presence of a subaortic conus

and often percutaneous intervention can be performed as a complement to cardiac surgery. Cardiac catheterization may be useful to perform palliative percutaneous pulmonary valvulotomy in cases of obstruction, as an alternative to surgical shunts. In cases of ductal-dependent pulmonary circulation, stenting the ductus arteriosus is an option. In patients in whom the intracardiac mixing is inadequate in spite of the VSD, Rashkind atrioseptostomy is performed in the neonatal period.

35.10 MRI

MRI has emerged as a critical noninvasive imaging modality in congenital heart disease [29]. This is the single imaging modality that allows high-resolution anatomic and functional

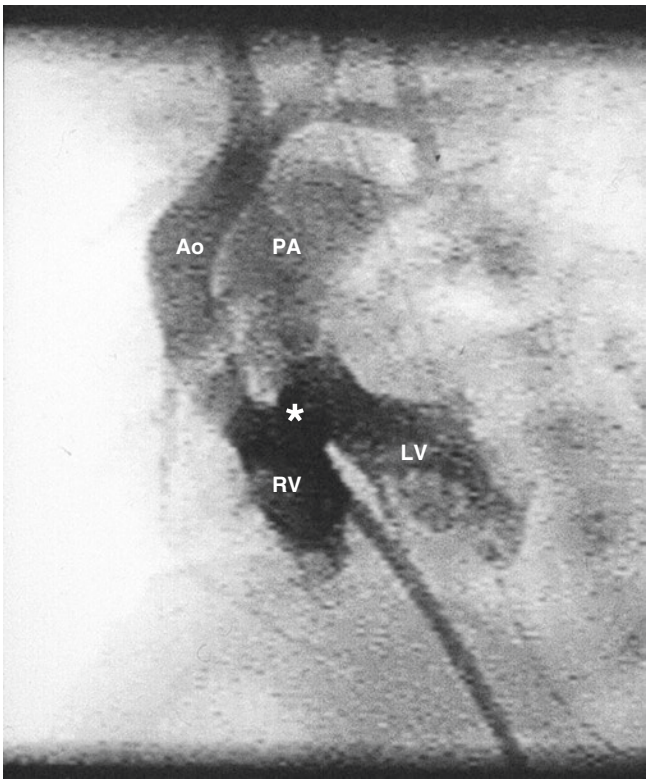

Fig. 35.4 Cardiac angiography documenting a DORV with transposition of the great arteries, subpulmonic ventricular septal defect, and obstructed aortic arch (Taussig-Bing anomaly). PA pulmonary artery, Ao aorta, RV right ventricle, LV left ventricle ∗

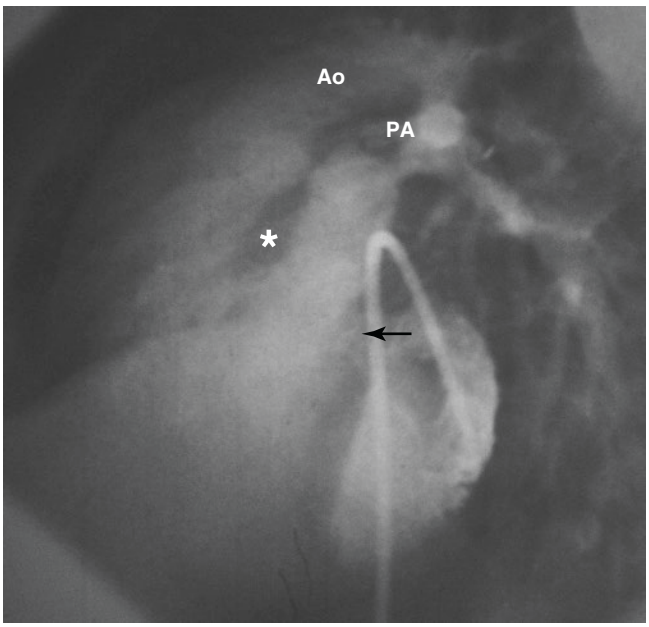

Fig. 35.5 Cardiac catheterization documenting a DORV with a non-committed ventricular septal defect (filled arrow). Both great vessels (PA pulmonary artery, Ao aorta) arise from the right ventricle. Notice that the conal septum (∗) is part of the RV and unrelated to the ventricular septation

assessment of the ventricle and the vasculature, without exposure to ionizing radiation which is critical for patients requiring serial follow-up imaging. MRI is the reference standard for measuring ventricular volume, mass, and ejection fraction. This can be applicable in cases where it is unclear whether a hypoplastic ventricle is of adequate volume to support a biventricular repair (Figs. 35.3 and 35.6). This approach also allows for determination of ventricular volume based on the ultimate position of the intracardiac baffle or patch used to close the VSD to the aorta. MRI also has the ability to assess coronary perfusion and viability of the myocardium.

35.11 Cardiac CT

Cardiac CT has emerged as an important adjunct method of imaging in congenital heart disease. CT offers the advantage of very fast temporal resolution (as fast as 0.075 s) allowing for imaging of tiny structures such as the coronary arteries even in neonatal patients with high heart rates (Fig. 35.7a). Accurate depiction of the coronary artery origins in patients with DORV can have important implications for surgical management. Other associated vascular anomalies such as anomalous pulmonary venous return can be easily depicted by CT, which offers the freedom to rotate the image such that relationships to adjacent structures can be understood (Fig. 35.7b). The total acquisition time for a cardiac CT in a neonatal patient is often less than a second, an important factor in these often critically ill patients. The volumetric acquisitions in CT allow for reconstruction in any plane as well as volume-rendered 3D reconstructions that can help depict both cardiac and extracardiac anatomic relationships that are critical in surgical planning such as total anomalous pulmonary venous return. CT also provides excellent detail of the lungs to evaluate for complicating pulmonary disease. While exposure to ionizing radiation remains an important concern,

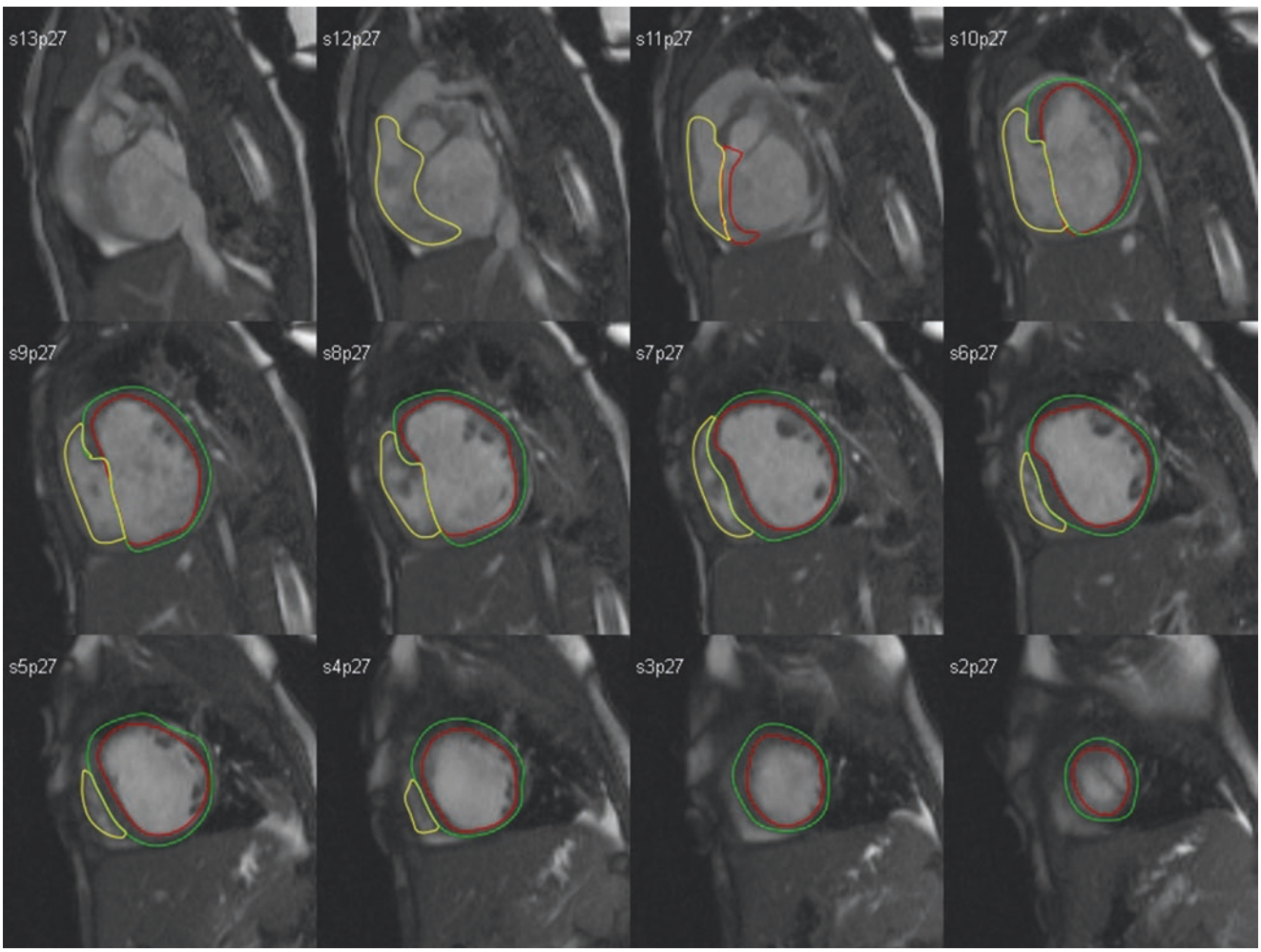

Fig. 35.6 MRI-derived volumetric measurement of an unbalanced atrioventricular septal defect/DORV. Total ventricular volume is determined by the summation of volumes of a series of short-axis stack

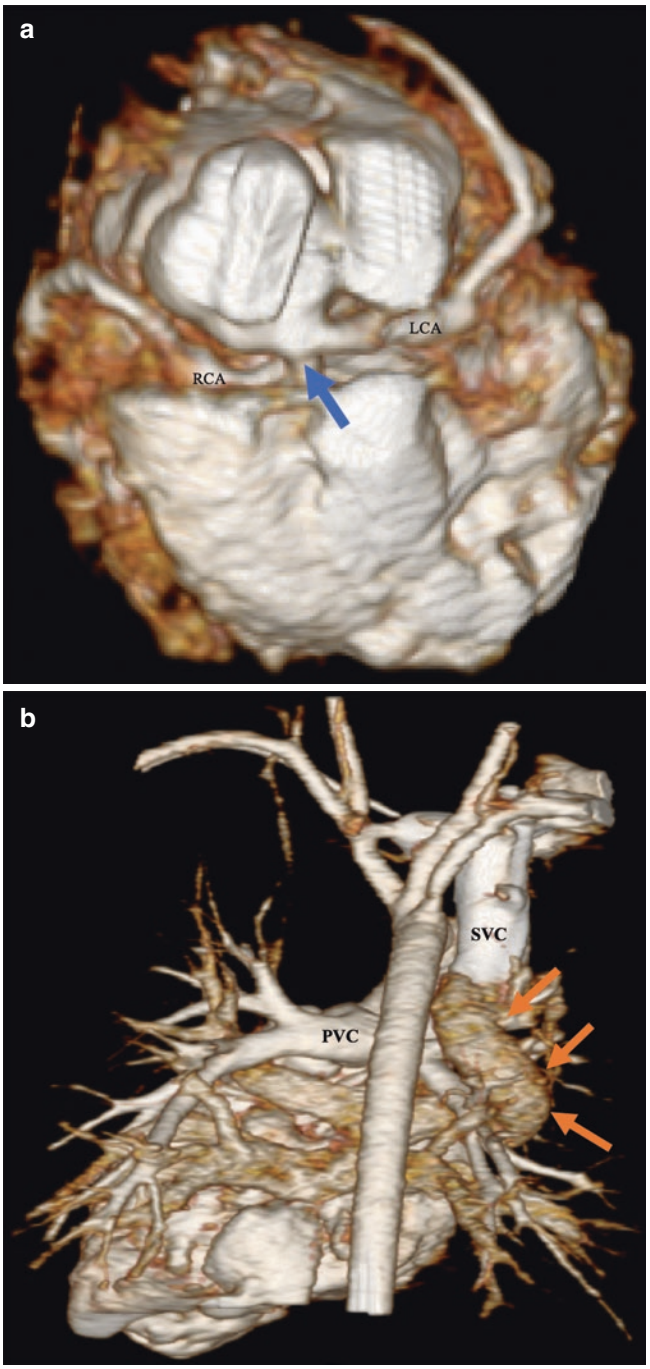

Fig. 35.7 Volume-rendered 3D reconstruction of cardiac CTA in a 5-day-old male with DORV. The high spatial and temporal resolution of cardiac CTA can be used to define coronary anatomy (**a**) such as the anomalous common coronary origin (arrow) originating from the posteriorly directed cusp of a quadricuspid aortic valve before dividing into the right (RCA) and left (LCA) coronary arteries. Additionally, complicating extracardiac anatomy such as total anomalous pulmonary venous return (**b**) vertical vein (orange arrows) connecting the confluence of pulmonary veins (PVC) to SVC can be readily demonstrated

modern CT scanners using pediatric-specific protocols can limit exposure to the equivalent of approximately 6 months of background radiation exposure.

35.12 Neonatal Management

Preoperative medical management depends on the clinical presentation. In the neonatal phase, there are three main scenarios:

1. *In the absence of right ventricular outflow tract obstruction,* neonates present with a large left-to-right interventricular shunt. During this period, patients are relatively asymptomatic. However, as the pulmonary vascular resistance falls, pulmonary overcirculation increases, and by 3–6 weeks of age, the infants will manifest signs of congestive heart failure. First line for medical management of heart failure is diuretics. Anemia should be avoided as it may increase the severity of the left-to-right shunt due to decreased viscosity. Once medical management is shown to be inadequate to control heart failure, surgical intervention is indicated. In patients with excessive pulmonary blood flow, the pulmonary vascular bed must be protected to prevent the development of pulmonary vascular disease which can occur as early as 6 months of age. The surgical therapy may be either palliative with a pulmonary artery band procedure to restrict pulmonary blood flow or with a definitive repair. This decision is based on the associated anomalies, clinical conditions, as well as the surgeon's preference.
2. *In the presence of valvular or subvalvular pulmonary stenosis*, clinical status should be assessed once the ductus arteriosus closes. If the right ventricular outflow tract obstruction is severe, with ductal closure patients will become progressively cyanotic and demonstrate ductal-dependent pulmonary blood flow, requiring administration of E_1 prostaglandins (PGE_1). In some cases, pulmonary blood flow may require augmentation with either a modified Blalock-Taussig shunt or a ductal stent placement in the catheterization laboratory. In some circumstances of favorable anatomy, a primary definitive repair can be considered.
3. *In the case of mild RVOT obstruction,* pulmonary overcirculation may occur with a significant left-to-right shunt, that can be severe enough to warrant surgical intervention or medical therapy. It is possible that the RVOT obstruction will progress, necessitating either augmentation of pulmonary blood flow or a definitive repair. If, however, the RVOT obstruction is adequate, a state of balanced systemic and pulmonary blood flow will exist. In this case the patient can be followed expectantly until definitive repair.
4. Patients with heterotaxy syndrome may have anomalous pulmonary venous return. Surgery is required in the first few days of life if the pulmonary venous system is obstructed. Patients with this complex association of

defects often have significant RVOT obstruction and anomalies of atrial anatomy, requiring BT shunt placement.

35.13 Surgical Management

35.13.1 Biventricular Repair

35.13.1.1 VSD-Type DORV

Patients present with clinical signs of overcirculation due to an unrestrictive VSD and unprotected pulmonary blood flow. For this reason, these children usually require a definitive repair within the first 3 months of life. A pulmonary artery banding may be considered in selected cases, when delayed repair is necessary, such as in a patient with multiple muscular VSDs or a "Swiss cheese" interventricular septum. With complete repair, a baffle or patch is placed in the interventricular septum, directing left ventricular blood to the aorta. Any atrial level defect is repaired at the same time. The repair is accomplished through the tricuspid valve or a right ventriculotomy. In some situations, the VSD is relatively small and requires enlargement to prevent left ventricular outflow tract (LVOT) obstruction [31, 32]. The size of the defect and the relationship to the aortic valve will dictate the size of the baffle. In the case of an inlet extension of the VSD, the baffle is modified to direct flow properly.

35.13.1.2 Fallot-Type DORV

These patients present similar to those with tetralogy of Fallot. Surgical repair is also very similar. Most patients will have adequate pulmonary blood flow at least initially and repair can be electively deferred till 3–6 months of age. If there is evidence of insufficient pulmonary blood flow, then either early repair or a palliative shunt procedure is necessary. A restrictive VSD may need enlargement in nearly one-third of the cases [15, 16, 20].

35.13.1.3 DORV with Atrioventricular Septal Defect, Pulmonary Stenosis, and Heterotaxy

These patients typically have a clinical picture of tetralogy of Fallot associated with an AVSD. The degree of RVOT obstruction can be variable from minimal to pulmonary atresia with ductal-dependent pulmonary blood flow. The AVSD is a Rastelli type C. The VSD has an outlet component close to the aortic annulus [20]. Particularly challenging is the patient with associated heterotaxy and TAPVR as repair of the pulmonary veins in the neonatal period will often be required. Because definitive repair involves repair of the very large VSD with a complex baffle or RV-PA conduit, it is often delayed till 6–9 months of age when patients can better tolerate a more extensive procedure. The patch required to baffle the VSD to the aorta may sometimes reduce the right ventricular size. In this case, a one and a half ventricle repair may be necessary.

35.13.1.4 TGA-/VSD-Type DORV (Taussig-Bing Anomaly)

Helen B. Taussig and Richard J. Bing first described this lesion in 1949, and characterized it by the presence of transposition of the great arteries and a subpulmonic VSD [32]. This defect is most often repaired in the first few weeks of life in a single stage due to associated aortic arch obstruction. If there is any contraindication to neonatal repair, palliation with a PA banding and aortic arch reconstruction can be performed, but this is rarely indicated. Patients may have associated subaortic obstruction especially when there is aortic arch obstruction. This situation requires a right ventriculotomy and sometimes a right ventricle to pulmonary artery conduit. The technical challenge of this neonatal arterial switch is due to the side-by-side relationship of the great vessels, the complex coronary anatomy, the associated subaortic obstruction, and a weight lower than 2.5 kg. Due to the frequent hypoplasia of the neo-pulmonary annulus, these patients are at risk for late RVOT obstruction [35].

35.13.1.5 DORV with Noncommitted VSD

In these patients the VSD is in the septum remote from either great vessel and the two great vessels arise almost entirely over the right ventricle [16, 36]. Importantly, the VSD lies at a distance from both the aortic and pulmonary annulus greater than the aortic diameter [35]. Pulmonary blood flow obstruction and a restrictive VSD may also be present

There are different surgical options for these patients depending on the presence of a pulmonary obstruction and the possibility of constructing a tunnel between the VSD and the aorta:

1. *In the absence of pulmonary obstruction*, repair requires baffling of the left ventricle to the aorta with a large patch or multiple patches [37] and resection of the parietal band. It may additionally require the reimplantation of the conal tricuspid papillary muscle on the baffle patch and a resection of the subaortic conus. When the VSD is very remote from the aorta, it may be better to baffle the LV to the pulmonary artery and perform an arterial switch procedure similar to the repair of a Taussig-Bing anomaly (Fig. 35.8) [35].
2. *The presence of pulmonary obstruction* is a rare anatomical form and raises the most difficult surgical issues. When the RVOT obstruction is purely muscular, an arterial switch with VSD to PA baffle and infundibular patch

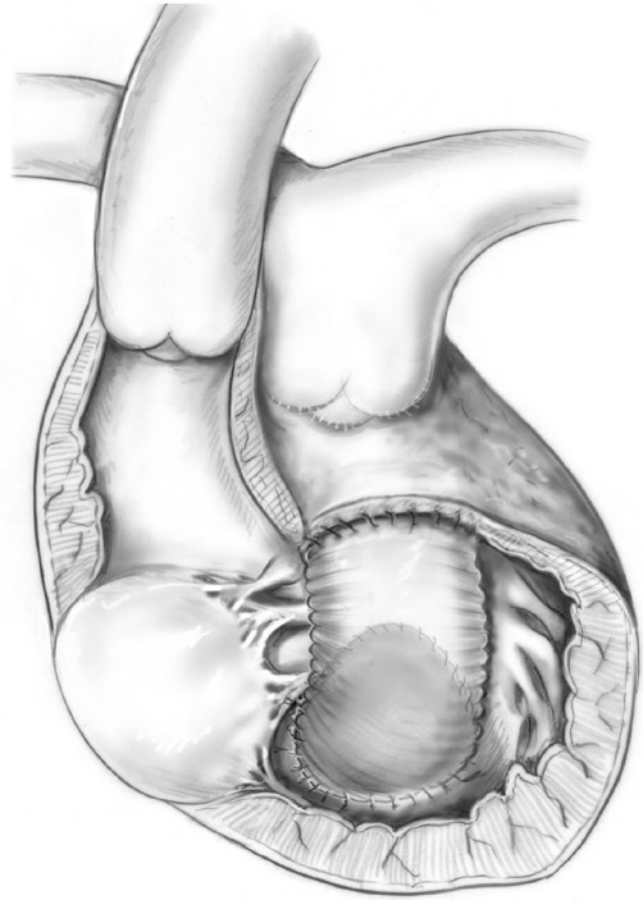

Fig. 35.8 DORV with a noncommitted VSD and a very remote aorta. The patch is tunnelizing the LV toward the pulmonary artery across the VSD. This technique will be complemented with an arterial switch

or RV-to-PA conduit is a good option. If the obstruction is valvular, a Rastelli [38]-type operation or a REV [39, 40] operation (Réparation à l'Etage Ventriculaire or Lecompte intervention) is indicated if the VSD-to-aorta tunnel can be safely performed. This requires closure of the pulmonary outflow and a RV-to-PA conduit (Rastelli) or a Lecompte maneuver (REV). The Nikaidoh [41, 42] operation has also been reported successfully in DORV with noncommitted VSD.

35.13.2 Univentricular Repair

In some situations of remote VSD or associated complex atrial anatomy, a single ventricle palliation may be the best option. Univentricular repair is *mandatory* in specific circumstances:

(a) Significant hypoplasia of one of the ventricles
(b) Severe atrioventricular valve straddling or overriding
(c) Multiple ("Swiss cheese") ventricular septal defects

35.14 Postoperative Management

As with every stage of care of the DORV patient, postoperative management depends on the anatomic and physiologic form and on the type of intervention. Thus, principles discussed in specific chapters dedicated to the management of VSD, tetralogy of Fallot and TGA with VSD are applicable to a great extent (see corresponding chapters elsewhere in this book).

Possible complications to consider in the patient with DORV are rhythm and conductive disturbances (persistent atrial tachycardia, ventricular ectopy, third-degree atrioventricular heart block), myocardial ischemic changes, and persistent subvalvular obstructions (secondary to a prolapse of the VSD patch onto the left ventricular outflow tract or to a VSD with restrictive dimensions).

35.14.1 Monitoring

Invasive monitoring includes an arterial line (to be inserted on the right radial artery in cases of associated arch obstruction) and a central venous catheter. A trans-thoracic pulmonary catheter may be inserted if the patient is considered at risk of developing acute pulmonary hypertensive spells.

Noninvasive monitoring is based on heart rate with ECG, respiratory rate, and peripheral oxygen saturation, as a minimum requirement. Transcutaneous CO_2 and NIRS are also important tools to consider, the latter being a surrogate of the mixed venous saturation.

35.14.2 Sedation

Postoperative sedation after palliative interventions may be superficial, although an adequate pain control is essential. Patients should be kept comfortable and free of pain and yet able to protect their airways and breathe spontaneously, allowing early extubation. This can be achieved by combining non-opioid analgesia with low-dose morphine or fentanyl and benzodiazepines (in boluses or as a continuous infusion).

After definitive repair, patients are sedated and under analgesia until there is consistent hemodynamic stability, with a combination of opioids and benzodiazepines to be titrated to the minimal efficient dose. Titration and length of treatment with these drugs depend on the type of intervention. Usually, a VSD closure or a Rastelli-type intervention progresses more rapidly than an arterial switch with VSD closure and coarctectomy than a REV repair. Delayed chest closure is also a factor that can dictate the length and degree of sedation and analgesia.

Muscle relaxants may be required, however should not be used systematically.

Dexmedetomidine, propofol, ketamine, or clonidine drips may be used in specific cases. Patients with significant right ventricular incisions may be at greater risk of junctional ectopic tachycardia. Dexmedetomidine is a drug that allows effective sedation without depressing the respiratory drive and it may have beneficial effects in prevention of these tachyarrhythmias.

35.14.3 Fluid Management

Fluid management is based upon the type of intervention. Palliative surgery does not require fluid restriction unless the patient is deemed to be volume overloaded. Nevertheless, after total repair on cardiopulmonary bypass, patients must be restricted to 50% of their requirements on day 1, followed by 75% on day 2, and 100% from day 3. Obviously, these recommendations must be individualized and adapted to the patient's hemodynamic, respiratory, and metabolic status.

35.14.4 Respiratory Management

Postoperatively, patients are very sensitive to cardiopulmonary interactions. With documented adequate and consistent hemodynamic stability, without evidence of bleeding, neurologic, respiratory, or metabolic concerns, patients should progress toward spontaneous breathing and extubation as soon as possible. Sometimes, extubation is deferred by delayed sternal closure. All morbid respiratory occurrences (pleural effusion, atelectasis, or pneumothorax) should be aggressively managed.

35.14.5 Hemodynamic Management

Hemodynamic management also depends on the initial defect and on the repair type. Further details are discussed in the chapters related to the management of VSD, TGA with VSD and tetralogy of Fallot.

Inotropic drugs (dopamine, dobutamine, epinephrine) and systemic vasodilators (phentolamine, phenoxybenzamine, sodium nitroprusside, nitroglycerine) or lusitropic drugs—like milrinone—are often combined with low-dose epinephrine as required.

If the right ventricle is hypertrophic with poor compliance, higher filling pressures may be required. Beta-blockers, like esmolol, may be useful to decrease the cardiac rate therefore optimizing the ventricular filling (diastolic) time. Patients with right ventricular failure require RV-protective measures, including judicious volume administration and aggressive RV afterload reduction with pulmonary vasodilators (iNO) and ventilatory strategies associated with lusi- and inotropic support. Extubation of the airways needs to remain a priority whenever deemed safe, as the failing right ventricle is exquisitely sensitive to positive airway pressures.

Vasopressin may also be useful to maintain adequate coronary perfusion pressure and as an attempt to modulate vascular tone.

Loop diuretics are commonly initiated throughout the first postoperative day in an effort to maintain a negative fluid status.

35.14.6 Morbidity and Mortality

Overall long-term survival is estimated between 80 and 95%. However, morbidity and mortality of DORV repair of course depends upon the anatomic associations, the surgical technique, and the general conditions of the patients and interrelated non-cardiac anomalies. For example, patients with 22q11 deletions have a higher incidence of metabolic, respiratory, and infectious complications.

In cases of subaortic VSD, mortality is reported to be 5%, whereas in Fallot-type repair, mortality ranges between 5 and 10%. More complicated cases requiring arterial switch with interventricular repair increase mortality significantly, especially when the VSD is uncommitted, and very distant from the left ventricle. This type of lesion requires a complex and long intraventricular tunnel reconstruction to establish continuity between the left ventricle and the aorta. In 2016, Villemain et al. reported that among 433 patients with biventricular repair of DORV, those with noncommitted VSD and those with intraventricular baffle repair with arterial switch were the two groups with highest risk for reoperation and mortality. Experience at a single center with DORV patients, without atrioventricular septal defect or heterotaxy syndrome, who underwent biventricular repair showed that at mean 3.4-year follow-up, there were 2.1% late deaths and 1% reoperation for subaortic obstruction [42]. Anatomic forms requiring a univentricular repair share the same morbidity and mortality as other anomalies with univentricular physiology.

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Chapter 36
Ebstein's Disease of the Tricuspid Valve

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Abstract Ebstein's disease of the tricuspid valve is a congenital cardiac anomaly that occurs with an incidence of approximately 1–5 in every 200,000 live newborns, therefore representing 1% of congenital cardiac defects. It is the most common etiology for congenital tricuspid regurgitation in the neonatal period as well as later in life. This chapter will summarize the main aspects related to diagnosis and management of the Ebstein's disease of the tricuspid valve.

36.1 Introduction

Ebstein's disease of the tricuspid valve is a congenital cardiac anomaly that occurs with an incidence of approximately 1–5 in every 200,000 live newborns, therefore representing 1% of congenital cardiac defects. It is the most common etiology for congenital tricuspid regurgitation in the neonatal period as well as later in life. The etiology of Ebstein's anomaly is unknown; however, a number of environmental factors have been implicated, namely, maternal exposure to varnishing substances and maternal use of benzodiazepines and lithium ingestion during the first trimester of pregnancy.

Steven P. Goldberg is deceased at the time of publication of this chapter.

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36.2 Anatomy

In Ebstein's disease, there is a displacement of the septal and posterior tricuspid leaflets toward the apex of the right ventricle (Fig. 36.1). These leaflets are usually dysplastic and aberrantly adherent to the ventricular wall by multiple, short, anomalous chordae. There is a redundant anterior leaflet with a sail-like format. The result of this anomalous anatomy is the reduction of the right ventricular volume because the inlet portion between the plane of the annulus and the plane of the valvular closure is integrated onto the right atrium. This so-called atrialized ventricular portion is often thin and dyskinetic. The tricuspid annulus and the right atrium are usually dilated and can become quite large. Depending on the severity of the disease, tricuspid regurgitation will develop, and the right ventricle may be deprived of its inlet portion. Functional right side obstruction is therefore a common finding with an impediment of forward pulmonary flow [1–5].

Ebstein's disease may have various degrees of severity that have been classified in 1988 by Alain Carpentier as follows (Fig. 36.2) [6]:

1. *Type A:* This is a mild form of the disease in which valvular dysplasia is discrete. The leaflet displacement is mild and consequently, the right ventricular volume and functionality are barely affected. Tricuspid regurgitation is usually trivial if not absent.

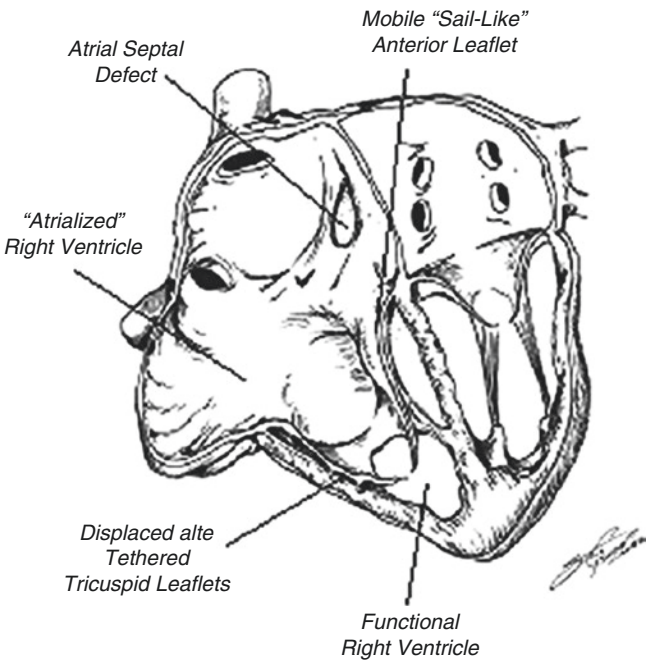

Fig. 36.1 Ebstein's anomaly

2. *Type B:* In this form, leaflet dysplasia and caudal displacement are moderate and the atrialized portion of the right ventricle is larger. The anterior leaflet is redundant and mobile with mild to moderate tricuspid regurgitation. The size of the right ventricle is still adequate, although in the lower acceptable range.
3. *Type C*: The atrialized portion of the right ventricle is large. The anterior tricuspid leaflet is redundant but has limited motion, restricted by the short chordae. Since the volume of the right ventricle is reduced, the anterior leaflet may be a source of right ventricular outflow tract obstruction.
4. *Type D*: The right ventricle is almost completely atrialized; hence, the cavitary volume is confined to the outlet portion. The anterior leaflet, although redundant, is immobile since the aberrant chordae are too short and rigid. The only path between the right atrium and the pulmonary artery, through the small ventricle, is ensured by the tricuspid antero-septal commissure.

An echocardiographic grading score for neonates with Ebstein's disease has been described by Celermajer et al. [7]. The Great Ormond Street Echo (GOSE) score is defined as the ratio of the combined area of the right atrium and atrialized right ventricle is compared with that of the functional right ventricle and left heart.

1. Grade 1: ratio < 0.5
2. Grade 2: ratio of 0.5–0.99
3. Grade 3: ratio of 1–1.49
4. Grade 4: ratio > 1.5

Concomitant anatomic abnormalities are present in 39% of patients with Ebstein's anomaly, and most commonly associated defects are as follows [3, 4, 7–9]:

- Atrial septal defects (ASD) are found in 80–94% of Ebstein's disease; 42–60% of cases have an ASD that plays an important role in the pathophysiology.
- Severe pulmonary stenosis or atresia is also a common association. This obstruction may be functional in approximately half of the cases and anatomical in a fourth of cases. Both types of obstruction significantly increase mortality in these patients.
- Anomalous conduction pathways may be associated with Ebstein's disease. Wolff-Parkinson-White syndrome has been described in 10–25% of patients. The majority of pathways is localized around the malformed tricuspid annulus with multiple aberrant pathways in 6% of cases.
- Ventricular septal defects (VSD), coarctation of aorta, transposition of great arteries, tetralogy of Fallot, and mitral valve abnormalities have also been described as infrequent associations with the disease.

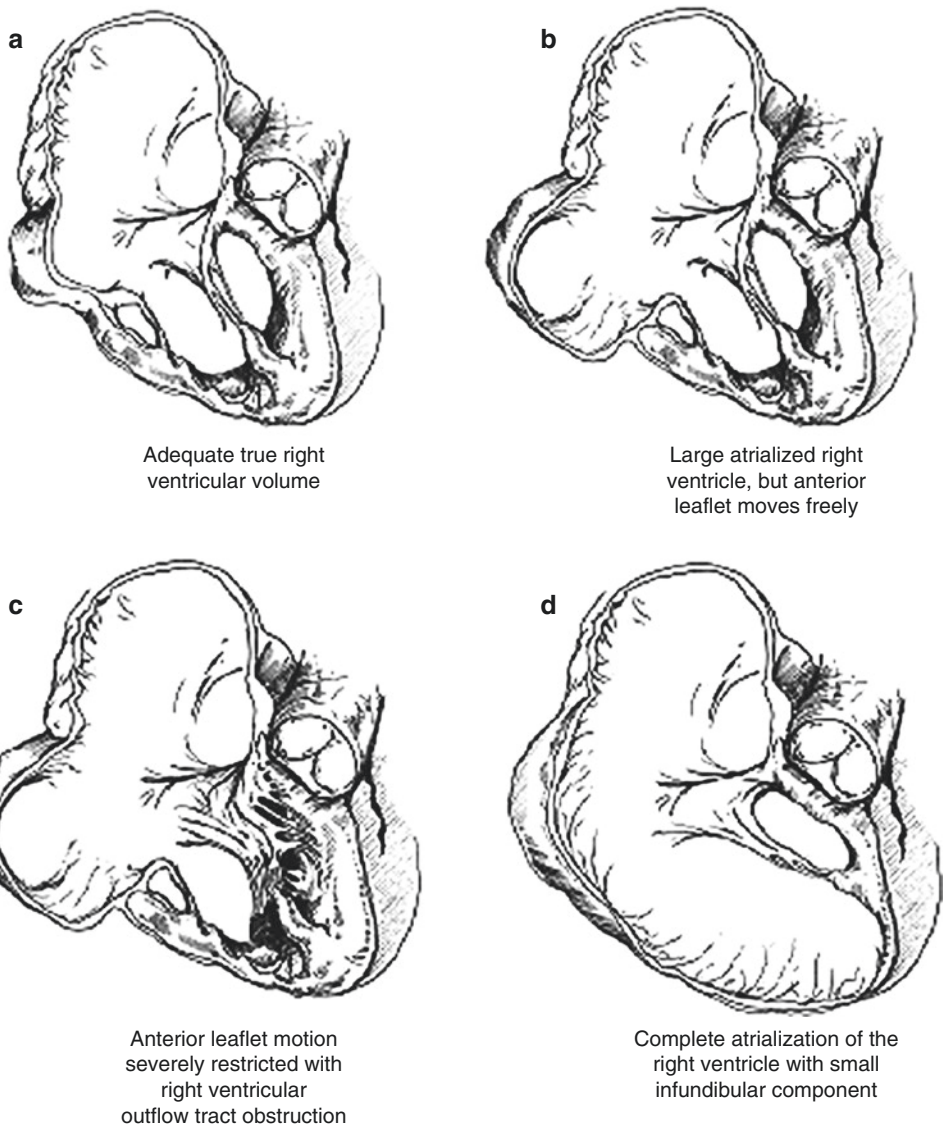

Fig. 36.2 Carpentier's classification of Ebstein's disease. (**a**) Adequate true right ventricular volume. (**b**) Large atrialized right ventricle, but anterior leaflet moves freely. (**c**) Anterior leaflet motion severely restricted with right ventricular outflowtract obstruction. (**d**) Complete atrialization of the right ventricle with small infundibular component

36.3 Pathophysiology

This disease includes a large spectrum of varied grades of valvular dysplasia with caudal displacement of the valvular leaflets, the septal and the posterior leaflet being often adherent to the wall and restricted in their motion.

Hemodynamic consequences of the anomaly are associated with the following factors:

1. The degree of displacement of the tricuspid leaflets and the degree of atrialization of the right ventricle
2. The severity of the tricuspid regurgitation
3. The functional capacity of the reduced right ventricle
4. The degree of functional or anatomic right obstruction
5. The presence of an atrial septal defect and the degree of right-to-left shunt
6. The presence and the nature of arrhythmias
7. The degree of left ventricular compression by the right cavities in older patients

Although the atrialized portion of the right ventricle is anatomically integrated into the right atrium, it contracts with the right ventricle causing a backward flow into the right atrium.

The functional capacity of the right ventricle is affected by the lack of volume and of diastolic preload, the functional or anatomic right ventricular outflow tract obstruction, and significant anomalies of its geometry. The right cavities may also distort the geometry of the left ventricle and have an impact in both the diastolic and the systolic function of the latter.

The presence of an atrial septal defect plays an important pathophysiological role and defines the degree of cyanosis due to a mandatory right-to-left shunt. This shunt may be dependent on the degree of tricuspid regurgitation, right atrial pressure as well as right ventricular size and compliance.

36.4 Diagnosis

36.4.1 Clinical Presentation

There is a large spectrum of clinical signs, ranging from the severe neonatal form to asymptomatic cases that may present in the middle teenage years or in young adulthood. Symptoms in patients with Ebstein's anomaly depend on the anatomical associations, the functional characteristics, and coexisting arrhythmia or conductive disorders.

Ebstein's disease may be diagnosed in-utero and can be the cause for *fetal* cardiomegaly, hydrops and arrhythmia. Doppler analysis of blood flow in the hepatic vein and the ductus venosus may show a reverse-flow pattern, providing an early sign of dysfunction.

Cyanosis is a common feature, secondary to the right-to-left shunt across an atrial septal defect and to the functional right ventricular obstruction. In the *neonate*, increased pulmonary vascular resistances (PVR) are the main cause of a functional right obstruction that, in association with the right-to-left shunting at the atrial level, account for the degree of cyanosis. Clinical signs depend on this factor and evolve with the PVR modifications during the first few weeks of life. Fifty percent of neonates present with cyanosis and a cardiac murmur during the first week of life. As PVR decreases, cyanosis improves and may even disappear unless there is a significant anatomic right obstruction or severe tricuspid regurgitation with a shunt at the atrial level. Nevertheless, patients with severe forms of Ebstein's or with associated right outflow tract obstruction may be persistently cyanotic and develop early signs of cardiac failure. In the absence of an adequate medical or surgical management, 20–40% of these patients may decease in the neonatal period, and less than 50% survive beyond the age of 5 years.

In some neonates, a "circular shunt" may develop in the presence of a patent ductus arteriosus which might be vital if the pulmonary stenosis is significant. This shunt results in a significant retrograde flow from the main pulmonary artery toward the right ventricle and, then, by the tricuspid regurgitation, toward the right atrium. This phenomenon will induce a lack of perfusion toward the peripheral pulmonary arteries and may also be a source of further right cardiac failure and of a massive right-to-left shunt, if there is an associated ASD. It will lead to low cardiac output and then significant heart failure and eventually cardiogenic shock.

Older patients may remain asymptomatic from the cardiovascular standpoint until adolescence or adulthood, albeit with various degrees of failure to thrive. They are usually diagnosed upon the presence of progressive cyanosis, fatigue on exertion and arrhythmia. Cyanosis tends to be progressive and to worsen, particularly when an arrhythmia arises. Progressive right ventricular failure with decreased cardiac output leads to the development of *dyspnea*, *fatigue, ascites,* and *peripheral edema*.

Cardiac arrhythmias and conductive disorders significantly add to the symptoms and may be a cause of cardiac failure, shock, or sudden death. As many as one-third of patients may have paroxysmal supraventricular tachycardia spells. Ventricular arrhythmias, although less frequent, may also occur.

Patients with Ebstein's anomaly and atrial septal defects have an accrued risk of developing paradoxical embolism, brain abscess, and bacterial endocarditis. Potential risks in chronic patients include the following:

1. Paradoxical embolism
2. Transient ischemic spells
3. Stroke
4. Brain abscess, related to chronic cyanosis
5. Infective endocarditis
6. Sudden cardiac death
7. Cardiac arrhythmias

36.4.2 Description of the Main Clinical Signs

Cyanosis has varying degrees of severity, may worsen with arrhythmia, and may induce the development of clubbing in untreated patients.

As cardiomegaly develops, precordial examination may show a significant *asymmetry and right parasternal prominence*.

Right cardiac failure is a common pathophysiological feature. These patients may display *congested jugular veins*, although right atrial pressure may be low in which case this sign is not present. As the right dysfunction increases, caregivers may identify the presence of large *a* and *v waves*.

On auscultation, the *first heart sound is split* and loud on the tricuspid focci and mitral component may be soft or even absent. This is due to the delayed closure of the elongated tricuspid anterior leaflet. The second sound is usually normal but may also be split in the presence of right bundle brunch block. In the presence of cardiac failure and distended right atrium, a *third and fourth sounds* may be present. Tricuspid regurgitation is a source of a *holosystolic murmur, the intensity and duration of* which vary with the severity of the regurgitation and may increase during inspiration.

Arrhythmias, mostly supraventricular tachycardia, atrial fibrillation or flutter, are common: 5–10% of neonates, 10–20% of infants and as high as 50% in grown-up patients.

36.4.3 ECG

Most patients with Ebstein's anomaly have an abnormal ECG, but such findings are not diagnostic. Common ECG patterns are [3, 4, 10, 11]:

1. A normal sinus rhythm
2. Abnormal p waves compatible with right atrial enlargement
3. Prolonged PR interval (first-degree AV block) in 42% of patients. PR may be short in the presence of WPW syndrome (preexcitation)
4. Low QRS voltage
5. Right bundle branch block with RSR in the right precordial leads
6. Presence of arrhythmias:
   (a) Paroxysmal supraventricular tachycardia
   (b) Atrial fibrillation
   (c) Atrial flutter
   (d) Ventricular tachycardia

36.4.4 Chest X-Ray

Chest radiographs can reveal a number of anomalies:

1. In the majority of cases, there is a very significant cardiomegaly. This cardiomegaly is often impressive (Fig. 36.3) and occupies most of the thoracic cavity with associated lung hypoplasia. This is the so-called wall-to-wall heart.
2. The right atrium is distended.
3. Lung vascular markings may be normal or decreased, depending on the presence and the degree of right outflow tract obstruction.
4. The aortic root and the main pulmonary artery shadow may be small.

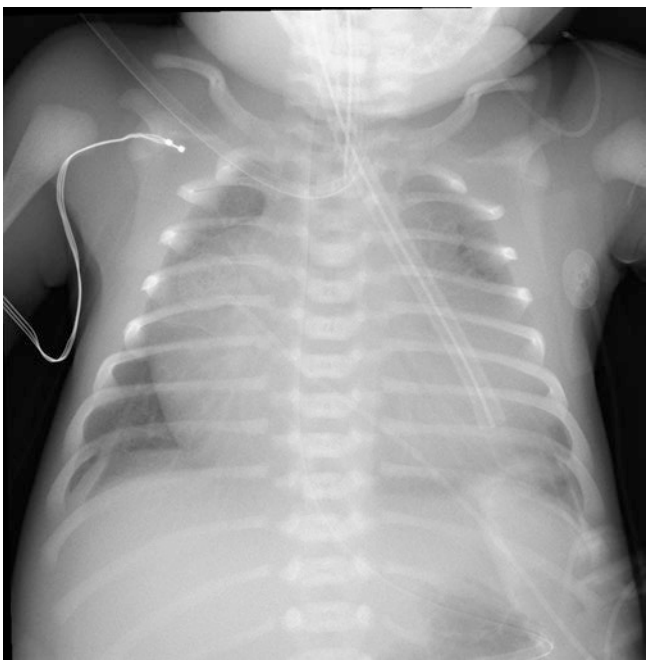

Fig. 36.3 Chest X-ray showing the characteristic massive cardiomegaly in a newborn with Ebstein's anomaly

36.4.5 Echocardiography with Color Doppler

Echocardiography remains the standard method for establishing the diagnosis [5, 12–15], even in the antenatal period (Fig. 36.4). It allows a comprehensive evaluation of the tricuspid anatomy (Figs. 36.5 and 36.6), the ventricular characteristics, the degree of right outflow tract obstruction, and the direction of atrial shunt, if present. Echocardiography also allows categorizing the type of anomaly and help defining the adequate surgical options.

The main echocardiography findings are as follows:

1. An apical displacement of the tricuspid septal leaflet greater than 8 mm/m^2.
2. Anomalous aspect of the leaflets with dysplasia, thickening, redundancy, anomalous motion, and aberrant attachments to the ventricular wall. This anatomy leads to an eccentric or absent coaptation.
3. A dilated right atrium and atrialized portion of the right ventricle. An atrialized to functional right ventricular ratio greater than 0.5 is associated with unfavorable prognosis.
4. A right ventricle with reduced volume and altered contractility. A functional right ventricular area of less than 35% of the total right ventricular area is associated with poor prognosis.
5. Some patients may have an aneurismal dilatation of the right ventricular outflow tract (right ventricular outflow tract/aortic root $\geq$ 2:1).
6. The left ventricle may be distorted and compressed by the right cavities and may have abnormal diastolic and systolic function.
7. Doppler assessment shows varying degrees of tricuspid regurgitation and gives evidence of the right-to-left shunt at the atrial level.
8. M-mode assessment reveals a paradoxical interventricular septal motion and confirms the above-described ventricular anomalies.
9. Other associated anomalies.

In neonates, the GOSE score can be applied in order to identify those with higher mortality risk. A value above 1.5 (grade 4) is associated with 100% of early mortality. A ratio

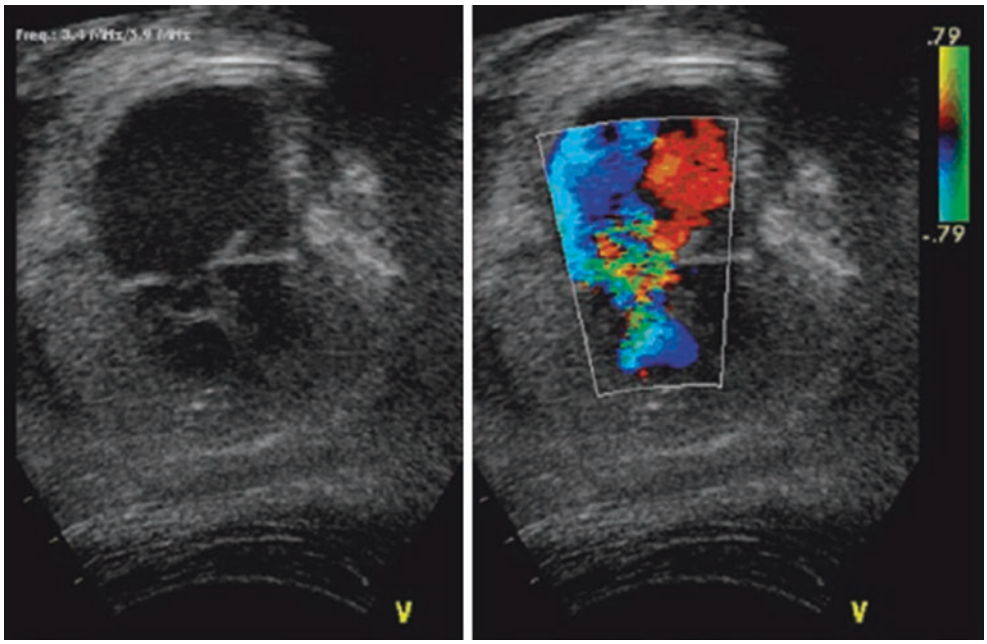

Fig. 36.4 Prenatal echocardiography showing a severe Ebstein's anomaly with significant tricuspid regurgitation

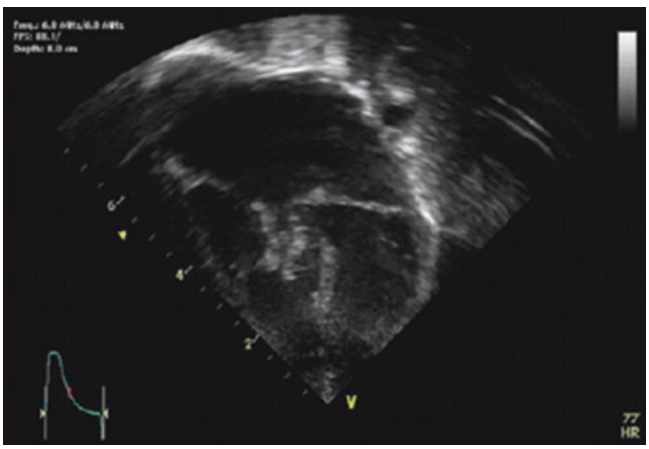

Fig. 36.5 Trans-thoracic echocardiography showing a type A Ebstein's anomaly

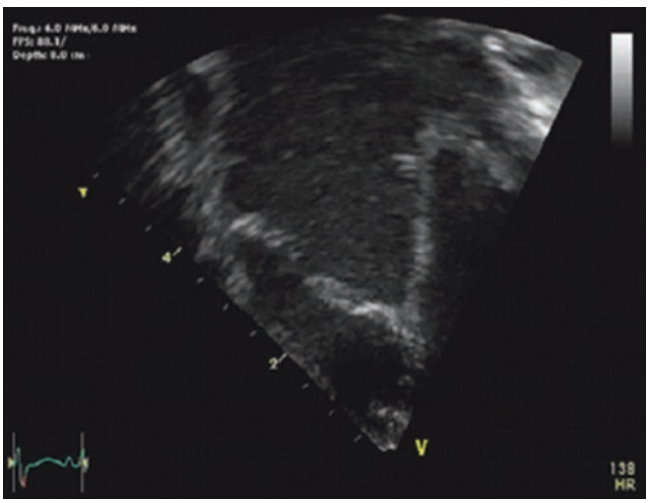

Fig. 36.6 Trans-thoracic echocardiography showing a type D Ebstein's anomaly

between 1.1 and 1.4 (grade 3) is associated with an early mortality of 10% and a late mortality of 45%.

Other echocardiographic signs correlated with mortality below 3 months of age include right ventricular dysplasia, the presence of a compressed left ventricle by the right cavities, and insertion of the anterior leaflet on the right ventricular free wall.

36.4.6 Cardiac Catheterization

Cardiac catheterization is seldom performed in patients with Ebstein's anomaly, because echocardiographic techniques are very reliable.

Moreover, the incidence of arrhythmias during the procedure can reach 25% with a 14% mortality associated with such events.

Yet, cardiac catheterization may be useful when the anomaly is associated with other complex malformations or else to perform electrophysiologic studies that can identify anomalous accessory pathways and guide ablative therapy. In cases of late presentation or in the presence of left ventricular dysfunction, hemodynamic catheterization can help with the measurement of intracardiac pressures. This is especially useful if a bidirectional cavopulmonary shunt is being considered or in the case of a single ventricle pathway before the modified Fontan procedure is performed.

In cases of anatomic right outflow tract obstruction, pulmonary valvuloplasty may be performed in the cardiac catheterization laboratory. In the setting of significant tricuspid regurgitation and pulmonary regurgitation, attention must be paid to the potential development of a circular shunt complicating pulmonary valvuloplasty.

36.4.7 Magnetic Resonance Imaging

Magnetic resonance imaging may provide accurate assessment of the size and function of the right and left ventricles. It can further distinguish and accurately determine and size and functions of both the functional and atrialized right ventricles. It is particularly interesting in grown-up patients in whom the echographic window is limited.

36.5 Preoperative Medical Management

Medical treatment of Ebstein's anomaly may be complex and difficult. Age and symptoms at presentation are variable and determine a broad therapeutic spectrum.

36.5.1 Neonatal Period

In the neonatal period, while PVR are labile and decreasing over time, the two main problems faced by clinicians are cyanosis with hypoxemia and congestive cardiac failure. Clinical presentation depends on the anatomic and functional aspects. Arrhythmias are seldom observed in this period of life. *One important ingredient for success is patience*. Indeed, neonates with Ebstein's disease should be allowed time to transition toward a steady physiological state, particularly with regard to the stabilization of PVR [7, 16–18].

Patients with Ebstein's disease and cyanosis may require the use of PGE_1 to maintain ductal patency and induce pulmonary vasodilation to promote antegrade pulmonary blood flow.

In case of persistent and significant circular shunt, caregivers might need to stop PGE_1 infusions in order to reduce the size or abolish the flow through the ductus arteriosus. This might be problematic when there is an anatomic pulmonic stenosis, justifying a cardiac catheterization to relieve the obstruction.

Caregivers may need to employ further medical strategies to decrease pulmonary vascular resistances. These strategies include:

1. Mechanical ventilation
2. The use of $NaHCO_3^-$ for blood pH alkalinization
3. The use of inhaled nitric oxide (iNO) or other pulmonary vasodilators

Patients in cardiac failure may benefit from the use of low-dose dopamine and milrinone. Milrinone also plays a role in reducing pulmonary resistances. Dobutamine is utilized in some centers, although it may be pathophysiologically inadequate to choose this drug in such a context.

Induction of diuresis with loop-diuretics is often necessary, particularly in the presence of neonatal anasarca.

Early and aggressive nutrition is a benefit for these patients.

36.5.2 Infants, Children, and Grown-Up Patients

Infants, children, teenagers, and young adults may require treatment for three major problems that are often inter-related:

1. Progressive cyanosis
2. Progressive cardiac failure
3. Cardiac arrhythmias and conductive disorders

Medical therapy usually relies upon the use of systemic vasodilators (mostly angiotensin-converting enzyme inhibitors), diuretics, and digoxin. Antibiotic prophylaxis for bacterial endocarditis may be considered. Patients with persistent or recurrent arrhythmias may need the use of anti-arrhythmic drugs and may require electrophysiological studies and radiofrequency ablation of accessory pathways.

36.5.3 Surgical Management

Surgical treatment may be corrective or palliative. Correction means repairing the underlying tricuspid valve displacement and regurgitation, trying to rehabilitate the functional right ventricle and repairing any associated anomalies. However, in the very young patient, palliation may be the best, compromising as a bridge to later definitive repair. The general trend, although no consensus exists, is to perform surgery sooner than later once signs of heart failure begin to appear.

In *neonates*, surgical treatment is reserved to those severely symptomatic and refractory to medical treatment, or else with obstructive anatomic forms. Neonates who are refractory to the above-described medical measures have a higher mortality and should be considered for a surgical approach.

The choice of the surgical technique depends on the anatomic form and has been controversial [1, 2, 6, 8, 9, 19–30]. At the beginning, the surgical procedures for Ebstein's anomaly treatment included systemic-pulmonary anastomosis (Blalock-Taussig and Potts-Smith), ASD closure, and

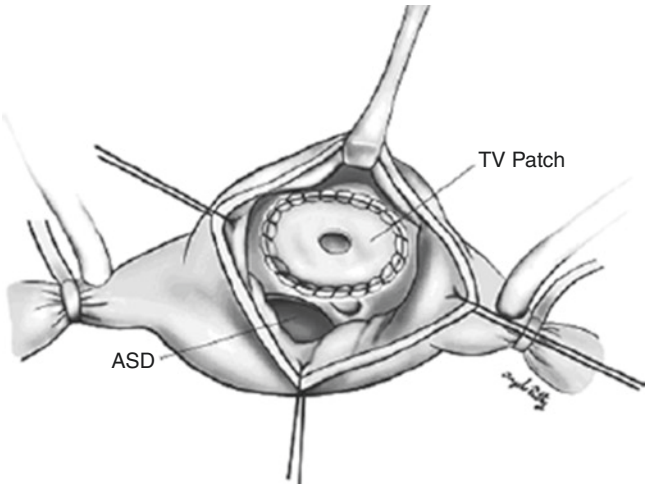

Fig. 36.7 The Starnes technique. With cardiopulmonary bypass support and under cardioplegic arrest, the right atrium is opened. The interatrial communication (ASD) is enlarged and the tricuspid valve is closed with a fenestrated patch (TV patch). Also, a reduction atrioplasty is performed

anastomosis of the superior vena cava to the right pulmonary artery (Glenn operation) [28, 31–34].

Patients with persistent cardiac failure due to severe tricuspid regurgitation, massive right atrial dilatation and right-to-left shunt at the atrial level may need a Starnes procedure [27], which excludes the right ventricle by partially closing the tricuspid valve, plicating the right atrial wall and enlarging the atrial septal defect (Fig. 36.7).

The different degrees of anatomic severity determine technical aspects of the surgical management, including tricuspid valve repair and replacement. As previously described, Ebstein's anomaly is characterized by an apical displacement of the septal and posterior leaflets of the tricuspid valve, resulting in a division of the right ventricle to a proximal atrialized chamber and a distal functional cavity. The degree of displacement of the septal and posterior leaflets determines the different types of functional anomalies described by Carpentier [6].

Conservative surgery to restore competent tricuspid function and preserve right ventricular contractility is preferable to valve replacement whenever repair is feasible, particularly in type A and B and the vast majority of type C cases. Although tricuspid valve replacement was the first successful surgical procedure for biventricular correction of Ebstein's anomaly, its subsequent use did not consistently produce good results and was fraught by high mortality rate [1, 9, 22]. Tricuspid valve repair avoids the risks of prosthetic valve dysfunction, thromboembolism, endocarditis, and patient-prosthesis mismatch resulting from the child's somatic growth. Durability of bioprostheses in patients with Ebstein's anomaly compares favorably with that in other cardiac valve positions and also with that in patients suffering from other tricuspid valve diagnoses [35]. However, the follow-up of children under 12 years of age, after tricuspid valve repair, has shown freedom from reoperation for tricuspid regurgitation was only 91.0% ± 4.3%, 79.6% ± 6.5%, and 68.0% ± 8.3%, at 5, 10, and 15 years [36]. Additionally, there was an increased attrition rate in replacements after 10 years, which does not reduce the importance of attempting efficient and durable tricuspid valvuloplasty, especially in children.

Aims of the conservative approach are:

1. To reduce the paradoxical motion of the atrialized portion by plication
2. To close the interatrial septal defect
3. To map and section the accessory pathways (Maze procedure)

The wide variety of anatomical and pathophysiological presentations of Ebstein's anomaly makes it difficult to achieve uniform results with surgical repair. The feasibility of conservative surgery, using the Danielson technique, depends on the size and mobility of the anterior leaflet, the tethering of its free edge, and the number of its fenestrations. The wide variety of anatomical and pathophysiological presentations of Ebstein's anomaly makes it difficult to achieve uniform results with surgical repair. Successful repair of the tricuspid valve has been reported by Danielson and collaborators in around 58% of cases, whereas a valvular replacement has been required in 36% [8]. This procedure comprises transverse plication of the atrialized portion of the right ventricle, with the placement of four or five mattress sutures on the anomalous attachment line of the anterior and posterior tricuspid leaflets, which are subsequently passed through to the true tricuspid valve annulus. Sequential tying of these sutures leads to approximation of the displaced leaflets and the true tricuspid annulus, obliterating the atrialized right ventricle (transverse plicature). Next, the posterior part of the tricuspid annulus is plicated to further reduce the tricuspid annulus circumference. This technique became one of the most commonly used surgical repair techniques for the treatment of Ebstein's anomaly (Fig. 36.8) [8, 37, 38]. Another new surgical technique was described by Carpentier in 1998. In contrast to the transverse plicature of the atrialized right ventricular chamber described by Danielson et al., Carpentier's procedure involved vertical plication of the atrialized right ventricle [6, 37, 39]. Furthermore, the tricuspid valve was brought to the anatomically correct level, thus achieving good right ventricular morphology. The tricuspid valve annulus was remodeled and reinforced with a prosthetic ring. Carpentier's group applied this procedure to the vast majority of anatomical presentations of the disease, but their initial series showed a high hospital mortality rate of 14%, as well as frequent long-term com-

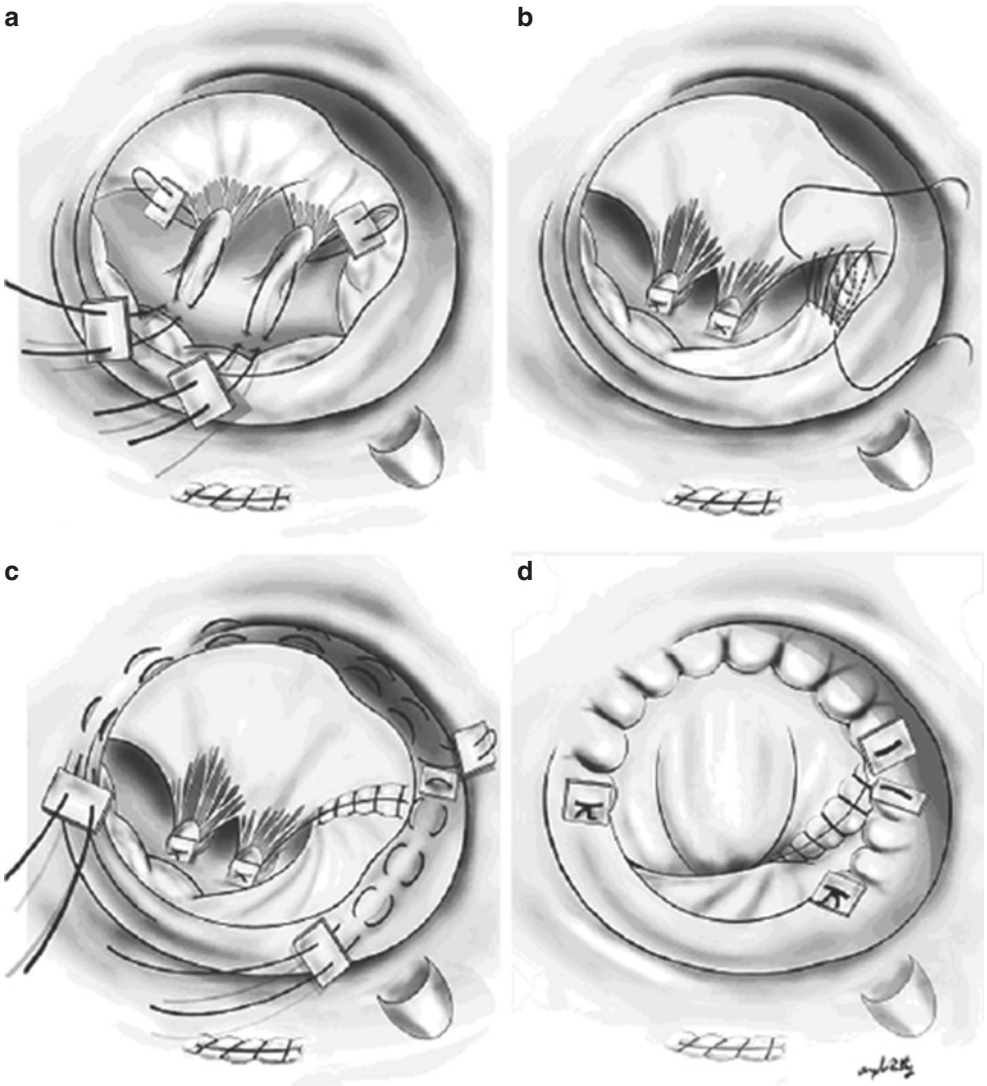

Fig. 36.8 The Mayo Clinic (Danielson's) technique. (**a**) The papillary muscles supporting the anterior leaflet are moved toward the ventricular septum with pledgeted sutures, and the atrial septal defect is closed. (**b**) The right edge of the anterior and septal leaflets is approximated, plicating the posterior leaflet in the process. (**c**) Anterior and posterior annuloplasty sutures are placed. (**d**) Once repaired, the tricuspid valve function depends on the ability of the anterior leaflet working as a monocusp valve

plications. The experience of the Carpentier group, representing the second largest published series, included an overall mortality rate of 9% [6, 39].

The cone procedure was described by da Silva in 1989 [40]. Initially called conical reconstruction of the tricuspid valve, surgical goals of this method included undoing most of the tricuspid valve anatomical defects that occurred during embryological development and creating a cone-like structure from all available leaflet tissue (Fig. 36.9) [40]. It aimed to cover 360° of the right AV junction with leaflet tissue, allowing leaflet-to-leaflet coaptation through a complete clockwise rotation of the lateral margin of the tricuspid valve megaleaflet while preserving its right ventricular apex attachments. Furthermore, the entire circumference of this cone base (which might or might not include a contribution from the septal leaflet, depending on its state of development) is sutured to the normal level of the tricuspid annulus. AV block is also avoided by the use of very superficial sutures near the AV node area. The final result is intended to mimic the normal tricuspid valve anatomy, in contrast to previously applied procedures in which a monocusp valve coapts with the ventricular septum [6, 20, 24, 37]. The cone technique can also be used to treat patients presenting with Ebstein's anomaly with Carpentier's type D anatomy. There have been low mortality rates and good long-term outcome with rare surgical re-intervention. Neonatal repair using the cone procedure has shown excellent results as well [41–45].

In *older and adult patients*, surgery has been reserved for those with:

1. Significant functional limitation:
   (a) NYHA class I or II with worsening symptoms or with a cardiothoracic ratio greater than 0.65
   (b) NYHA class III or IV
   (c) Background of paradoxical embolism

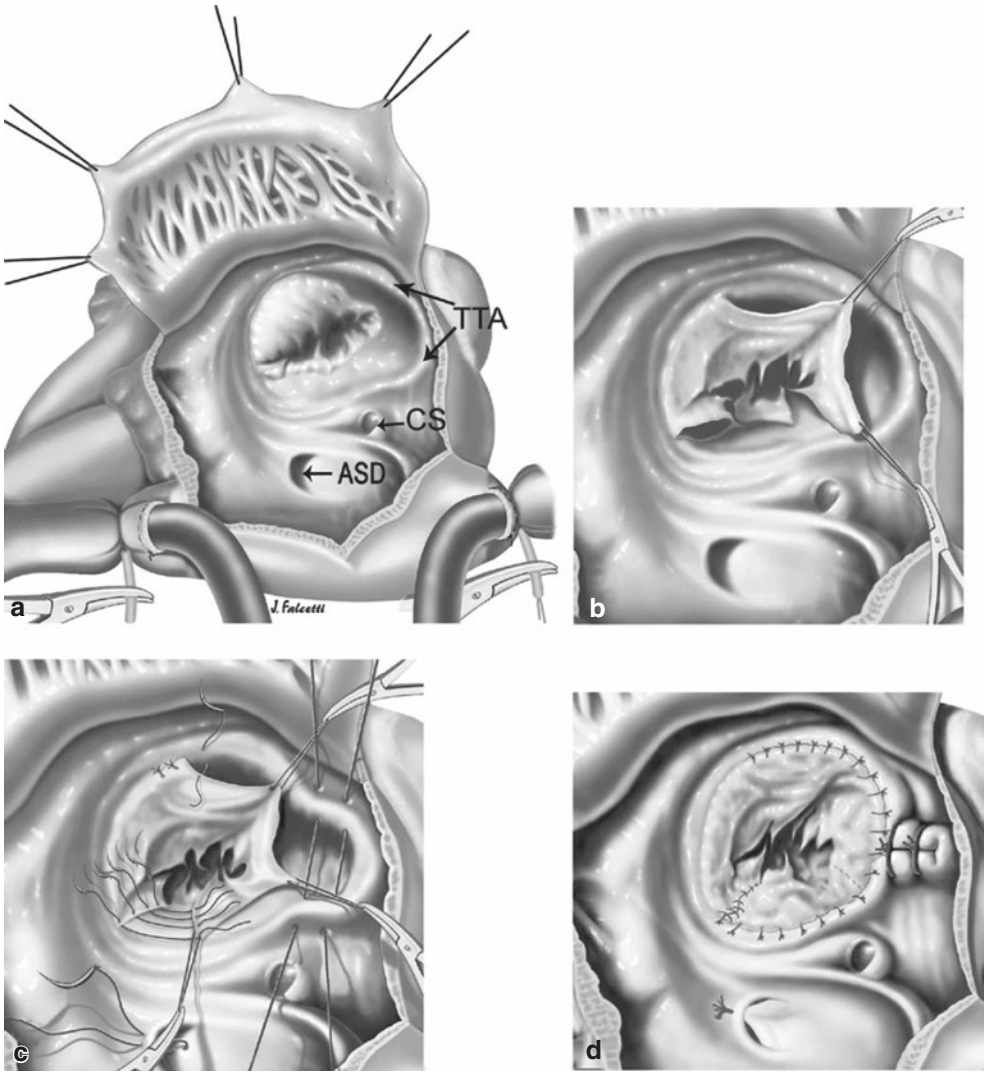

Fig. 36.9 Operative steps for Ebstein's anomaly repair using the cone (da Silva's) technique. (**a**) Opened right atrium showing displacement of the tricuspid valve. *TTA*, True tricuspid annulus; *ASD*, atrial septal defect; *CS*, coronary sinus. (**b**) Detached part of the anterior and posterior leaflet forming a single piece. (**c**) Clockwise rotation of the posterior leaflet edge to be sutured to the anterior leaflet septal edge and plication of the true tricuspid annulus. (**d**) Complete valve attachment to the true tricuspid annulus and valved closure of the atrial septal defects. (From da Silva et al. [40], 2007 with permission)

2. Progressive cyanosis (saturations lower than 80% and/or significant polycythemia)
3. De novo, recurrent, or refractory arrhythmias

Concomitant bidirectional cavopulmonary shunt, translating into a one-and-a-half-type ventricular repair, significantly reduces the operative mortality for Ebstein's anomaly in high-risk patients with massive tricuspid insufficiency (associated hepatomegaly and/or ascites), a voluminous atrialized chamber, poor right ventricular contractility (as assessed by echocardiography and/or visually during surgery), or long-standing atrial fibrillation [33, 46]. Bidirectional cavopulmonary shunt results in lower preload, reducing strain on the compromised right ventricle, hence preventing postoperative ventricular dilatation.

Patients with accessory conduction pathways should undergo electrophysiological mapping for identification and ablation. A concomitant right-sided Maze procedure should be performed in patients with a history of intermittent or chronic atrial flutter or fibrillation [11, 47–49].

Orthotopic cardiac transplantation may be a pertinent indication in selected patients, particularly in neonates with severe forms of Ebstein's anomaly.

36.6 Postoperative Management

Univentricular, one-and-a-half or biventricular repair of patients with Ebstein's anomaly, mostly in the neonate population, anticipates right ventricular dysfunction. General principles of management focus on the reduction of right ventricular afterload by decreasing the pulmonary resistances, and on judicious volume administration. This protects right ventricular strain and reduces the risks of hemodynamically significant tricuspid regurgitation. General principles concerning management of univentricular repair are specifically discussed in the chapter related to single ventricle.

36.6.1 Respiratory Management

Cardiopulmonary interactions are essential and PVR must be kept in the lower range. For this, it is important to provide an adequate oxygenation and to maintain pH levels around 7.45 with controlled hyperventilation. This may also be achieved with the concomitant administration of alkalinizing drugs. Inhaled nitric oxide is essential to optimize PVR.

Early extubation may be achieved in stable patients. However, particularly in the neonatal group, sternal closure may be voluntarily delayed for an average of 48 h and extubation is planned following sternal closure.

36.6.2 Cardiovascular Management

As previously described, inotropic support and afterload reduction are crucial for these patients. Low dopamine and milrinone are the most commonly utilized and effective vasoactive medications. Drug-induced sinus tachycardia should be avoided since it may decrease the filling of an abnormally compliant right ventricle, hence reducing the stroke volume. Postoperative arrhythmias are a frequent occurrence. These anomalies have been reported in 42% of postsurgical patients in the neonatal period and significantly account for morbidity and mortality. The most common disorders are supraventricular tachycardia, transient atrioventricular heart block, ventricular arrhythmias, and junctional ectopic tachycardia. All arrhythmias in the postoperative course of Ebstein's surgery ought to be aggressively managed with anti-arrhythmic drugs, optimization of electrolytic balance, and identification and rectification of arrhythmogenic factors. Current PALS recommendations are to be followed, including the cardioversion if poor tolerance is present.

36.6.3 Sedation and Analgesia

Pain control and sedation are crucial after palliative or corrective surgery. The common therapeutic association combines benzodiazepines with opioids and dexmedetomidine. Early administration of non-opioid analgesia reduces the need for and the risks for undesirable side effects of opioid drugs. Neonatal patients who tend to develop pulmonary hypertension or maintain high PVR may need the use of muscle relaxants in combination with the above, until stable. These authors do not recommend the systematic use of these agents.

36.6.4 Fluid Management

Fluid management of patients with Ebstein's anomaly who have undergone a cardiopulmonary bypass procedure, should follow the general guidelines, with a restriction of 30–50% on day 1, followed by 50–75% on day 2 and 100% from day 3. Closed heart palliative surgery does not require a restricted fluid administration. These principles must be individualized and adapted to the patients' characteristics, aiming for a negative fluid balance whenever possible. Caregivers ought to keep a very close follow-up of volume administration as patients with this physiology and right ventricular dysfunction may be exquisitely sensitive to volume.

36.7 Prognosis

Natural progression of Ebstein's disease varies with the degree of tricuspid and right ventricular compromising. Symptomatic neonatal forms are worrisome and yield a more unfavorable prognosis. Nevertheless, most of the patients present with symptoms in their middle teenage years, and around 5% of them survive beyond the age of 50 years. Previous collaborative studies from the years 70 describe the follow-up of more than 500 patients between 1 and 25 years of age, documenting the following data:

1. Seventy-two percent of infants below 1 year of age develop cardiac failure.
2. Seventy-one percent of children and adolescents, as well as 60% of adults, are in NYHA class I and II.
3. The high mortality at a young age declines significantly later in life.

Prognosis depends greatly on the severity of the disease, the available treatment options, and the surgical results. The main residual lesion of concern that influences mortality is the right ventricular obstruction. Other prognostic factors have been described in literature:

1. Male gender
2. Early age at presentation as described above
3. Cardiothoracic ratio greater than 0.65
4. Septal leaflet attachment ratio of more than 0.45
5. Increasing ratio of the combined area of right atrium and atrialized right ventricle to that of the functional right ventricle (see echocardiography section) from grade 1 (less than 0.5) to grade 4 (more than 1.5).
6. Higher NYHA class

Based on several clinical studies, Ebstein's anomaly in children can be repaired with low mortality and satisfactory long-term durability, with approximately 90% of late survivors in NYHA functional class I or II.

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Chapter 37
Anomalies of the Coronary Arteries

Brian Fonseca, Eduardo M. da Cruz, and James Jaggers

Abstract Coronary anomalies are the second leading cause of cardiac death in young athletes and have an overall prevalence reported as high as 2–3%. Isolated abnormalities of the coronary arteries are rare in children with an incidence of less than 0.3 to 1%. Some coronary anomalies are innocuous, while others can be very serious defects with risk of catastrophic cardiac adverse events. Coronary anomalies may be classified by anomalies of origin, course, and termination. Clinical presentation may be sudden cardiac events such as sudden cardiac death, ventricular arrhythmia, syncope, or insidious, as with chronic ischemia, heart failure, valvar insufficiency, and atrial arrhythmia. In this chapter, we will concentrate on those anomalies that often have pathologic significance, namely, the anomalous aortic origin of the coronary artery (AAOCA), the anomalous left coronary artery arising from the pulmonary artery (ALCAPA), and the coronary artery fistula.

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37.1 Introduction

Coronary anomalies are the second leading cause of cardiac death in young athletes. Coronary artery anomalies are not uncommon with an overall prevalence reported as high as 2–3%. Some are innocuous, while others can be very serious defects with risk of catastrophic cardiac adverse events. While several classification systems have been described, it is convenient to think of coronary anomalies in morphologic categories: anomalies of origin, course, and termination. Some coronary anomalies represent variations of normal, while others have pathologic significance. Clinical presentation may be sudden cardiac events such as sudden cardiac death, ventricular arrhythmia, syncope, or insidious, as with chronic ischemia, heart failure, valvar insufficiency, and atrial arrhythmia.

Anomalous aortic origin of the coronary artery (AAOCA) may have significant pathologic significance. In this anomaly, the coronary artery arises from the wrong or inappropriate sinus. Also, coronary arteries can have abnormal position within the sinus, multiple ostia, and intramural origin of the coronary artery.

Anomalous coronary arteries may have an abnormal course (retro-aortic, inter-arterial, pre-pulmonic or intraconal). AAOCA usually has an anomalous origin with intramural and inter-arterial course. Some have little significance such as the anomalous left coronary artery that travels in a pre-pulmonic course or a circumflex coronary that originates in the right sinus and travels posterior to the aorta.

Then there are anomalies of abnormal termination. Examples of these anomalies include coronary artery fistula, myocardial bridging and extra-cardiac termination.

In this chapter, we will concentrate on those anomalies that often have pathologic significance, namely, AAOCA, ALCAPA, and coronary artery fistula. Overall isolated abnormalities of the coronary arteries are rare in children with an incidence of less than 0.3–1%. [1]

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37.2 Pathologic Anatomy

1. *Coronary Artery Fistula (CAF)*: Is an anomalous connection between the coronary artery system and a cardiac chamber or vessel. CAF are thought to be due to failure of regression of primitive connections between cardiac chamber and the coronary arteries [2]. Most commonly they involve the right coronary artery system (55%) followed by the left coronary system (41%) and rarely from both systems (4%). The recipient chamber or vessels in descending order of frequency are right ventricle (44%), right atrium (22%), pulmonary artery (17%), coronary sinus (8%), left atrium (4%), left ventricle (2%) superior vena cava (2%), and pulmonary vein (1%) [2]. Non-congenital causes such as iatrogenic (percutaneous intervention and surgical), infection, and trauma are being more frequently identified [3].
2. *Anomalous Left Coronary Artery Arising from the Pulmonary Artery (ALCAPA)*: In this lesion, the left coronary artery originates from the pulmonary artery instead of the aorta. In rare cases, isolated left coronary arteries (LAD, or circumflex) or the right coronary artery can originate anomalously from the pulmonary artery. The site of origination of the coronary from the pulmonary artery can also vary from near the aortic root to remote from the aortic root. This can play into the technical difficulty of making the diagnosis and dictate the type of surgical repair.
3. *Anomalous Aortic Origin of the Coronary Artery (AAOCA)*: Anomalous origin of the left coronary artery from the right sinus of Valsalva (ALCA) occurs when the left coronary courses rightward, bypassing its normal origin and originates from the right sinus of Valsalva. Typically, this origin is just to the right of the right-left commissure and at a level just cephalad to the sinotubular junction. The anomalous course of the left coronary can be either inter-arterial or intramural where the coronary artery travels within the wall of the aorta, or both. The coronary artery origin is also tangential to the aorta and the coronary artery ostia is oval or slit like. There is a mirror image anomaly where the right coronary artery originates from the left sinus of Valsalva (ARCA).

37.3 Physiology

1. *The physiology of the CAF* depends on of the size of the connection between the anomalous vessel and the recipient chamber, the pressure and resistance differential between the coronary artery and the recipient chamber [2] and the volume of the resulting shunt, which can vary from trivial to profound. This shunt can result in pulmonary overcirculation, diastolic runoff which mimics aortic insufficiency and distal coronary steal with relative myocardial ischemia.

The physiology of anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) depends on the age of the patient, the degree of pulmonary hypertension, and coronary collateralization. Shortly after birth, when pulmonary artery pressure is high, the supply of the anomalous coronary can be antegrade from the pulmonary artery. The principal difference from normal physiology being that deoxygenated systemic venous blood is being delivered to the left coronary artery and the myocardium it serves. As the pulmonary artery pressure decreases over the first 6–10 weeks of life, there will be a concomitant decrease in coronary perfusion pressure. If this is progressive, insufficient left coronary artery perfusion will result in left ventricular dysfunction, followed by watershed infarctions which can result in papillary muscle dysfunction and mitral valve regurgitation and finally irreversible ischemia and transmural myocardial infarction. If this transition occurs slowly or pulmonary hypertension develops, there may be enough time for sufficient collateral flow from the right coronary system to develop to avoid myocardial ischemia. At this point, the coronary blood flow is entirely retrograde from the right coronary artery to the left coronary artery. The principal risk for left ventricular ischemia would then be runoff of retrograde left coronary artery flow into the pulmonary artery. If there is robust collateral flow and there is not excessive runoff into the pulmonary artery, diagnosis can be delayed for years or in some cases decades with a historical series showing 10–15% of patients reaching adulthood before any intervention [4]. The diagnosis of ALCAPA may be challenging, particularly in patients with associated left-to-right shunts and PAH. These patients are often treated for respiratory problems as the clinical findings mimic bronchiolitis.

The physiology of AAOCA is likely normal at rest, and any aberration is the result of alteration in coronary artery blood flow during or shortly after exercise. There is some debate regarding the proximate cause of the abnormal coronary artery flow including a slit like origin, twisting or kinking on the coronary artery and compression of the coronary artery as it passes between the two great vessels [5]. No definitive anatomic feature has been identified that predisposes to sudden death [6, 7]. The likely final pathway is a combination of myocardial ischemia and fatal arrhythmia [5].

37.4 Diagnosis

37.4.1 Clinical Presentation

The clinical presentation of CAF depends on the size of the fistulous connection. Small connections can be asymptomatic and are typically diagnosed incidentally on echocardiography indicated upon the finding of a continuous murmur. Even large fistulae are most often asymptomatic at presentation and signs are typically absent in patients less than 20 years of age [8]. As the size of the shunt increases, clinical presentation can include a continuous murmur, respiratory symptoms from overcirculation or chest pain.

The clinical presentation of ALCAPA is variable and often subtle. The classic presentation is an infant who is 6–10 weeks old with intermittent irritability during feeds representing angina [9]. These patients will have resting tachycardia and the murmur of mitral regurgitation and a gallop rhythm. They may also show evidence of pulmonary edema with rales and resting tachypnea. In the severest cases they can present with left heart failure and shock. The older child or adult make come to medical attention due to exercise intolerance, chest pain, murmur, chest film or ECG findings [4].

The presenting symptoms for AAOCA are often vague but include chest pain, syncope, and dyspnea. Symptoms occur most often but not exclusively during exercise. Unfortunately for those patients with AAOCA who go on to have sudden cardiac death 50% of them have had no antecedent symptoms [10, 11]. From observational studies the risk of sudden death seems to start once a child can participate in vigorous exercise in the early teens and seem to diminish after the age of 40. With improvement in the quality and access to echocardiography, the diagnosis is often made incidentally without symptoms during the evaluation for murmurs or noncardiac chest pain.

37.4.2 Chest X-Ray

The chest film findings will vary by the size of the CAF and the recipient chamber. Volume load to the heart can result in cardiomegaly, and pulmonary overcirculation can result in increased pulmonary vascular markings, pulmonary artery dilation, and pulmonary edema [8].

In infancy the chest radiograph will show cardiomegaly and pulmonary edema, but a normal chest film can be seen in patients with small CAF who present latter in life [4].

CXR for AAOCA will be normal.

37.4.3 ECG

There is no typical ECG presentation of CAF, and the majority of patients present with a normal ECG. There are no specific findings such as ventricular hypertrophy, atrial enlargement, atrial arrhythmia due to long-standing atrial enlargement, and rarely ischemia [8].

The classic presentation is an ECG that shows evidence of an anterolateral infarct with abnormal Q waves in I and AVL and the precordial leads V4-V6.

ECG is not useful in diagnosing AAOCA as symptoms and sudden death occur with exercise. Unfortunately exercise testing, while helpful if positive, have insufficient negative predictive value to adequately exclude patients who will go on to have sudden cardiac death [10].

37.4.4 Echocardiography

CAFs are generally diagnosed on echocardiography. Imaging the entire course of the fistula can often be quite challenging by echocardiography but can be accomplished with careful color Doppler examination. Although the exact origin of the fistula can be challenging to visualize, dilation of the coronary system that feeds the fistula is often quite striking. The insertion the fistula can usually be documented as a continuous Doppler into the recipient chamber/vessel and can guide thinking about the expected physiology. Ancillary findings such as cardiac chamber dilation, ventricular function, diastolic runoff in the aorta without aortic regurgitation and wall motion abnormalities can be helpful in risk stratifying and managing these patients.

Careful examination of the coronary arteries by echocardiography at an experienced center is required to make this diagnosis. The anomalous left coronary can course quite close to its normal insertion into the aortic root before making a turn to the pulmonary artery. Therefore, it is important to show color flow Doppler exiting the aorta and flowing antegrade into the coronary to exclude this diagnosis (Fig. 37.1). Depending on the pulmonary artery pressure and the presence of collaterals, you may see diastolic reversal in the anomalous coronary with flow from the coronary into the pulmonary artery. It is important to that the Nyquist limit be appropriately lowered to capture this low velocity flow [12]. ALCAPA with extensive collateralizing from the right coronary artery system will show significant dilation of the right coronary artery which is an important ancillary sign. Other ancillary signs include left ventricular dysfunction, brightness of the papillary muscles (Fig. 37.2), and mitral valve regurgitation. Given the difficulty of making this diagnosis,

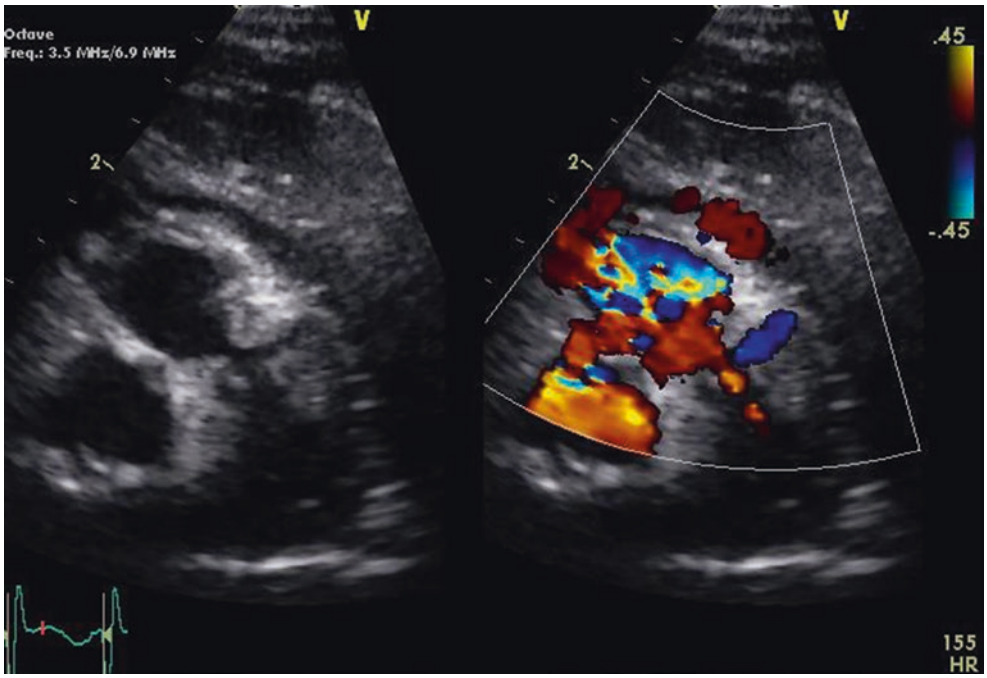

Fig. 37.1 Off-axis, short-axis color flow Doppler echocardiogram image showing what at first glance appears to be normal origin of the left coronary system from the aortic root. Color flow Doppler, however, shows flow from the pulmonary artery towards the aortic root (blue) instead of the normal pattern of flow from the aorta anterior towards the transduced which would be red. Another tell-tale finding not shown her is dilation of the right coronary artery from collaterals from the right coronary supplying flow to the left system

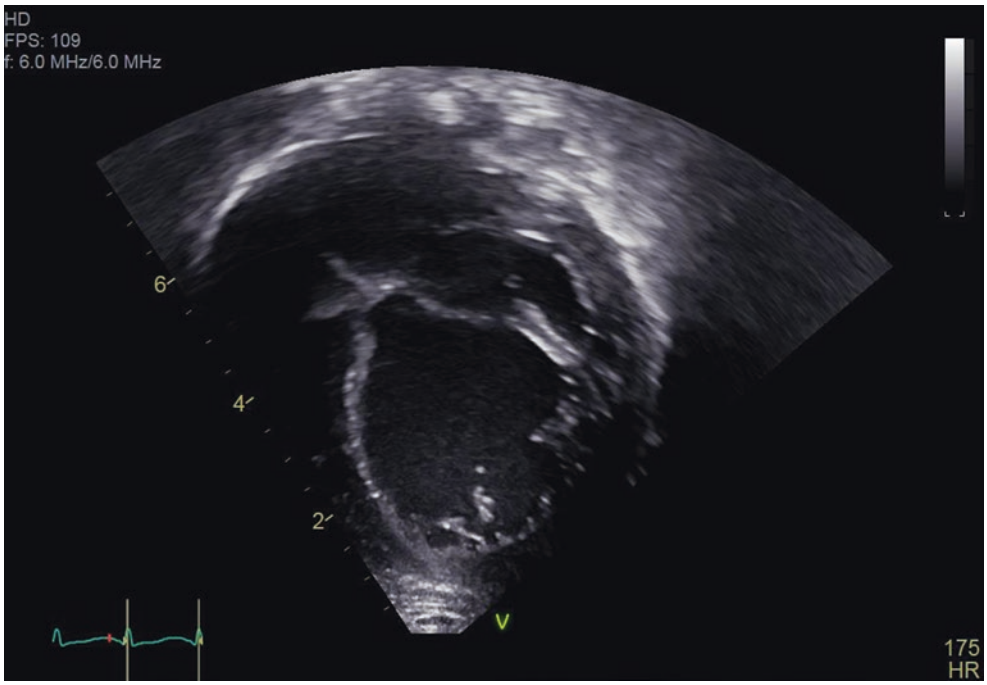

Fig. 37.2 Horizontal long-axis echocardiogram image showing a dilated left ventricle with characteristic brightness of the papillary muscles indicating watershed infarction of the papillary muscles which may result in variable degree of mitral valve regurgitation

in our center, we would not exclude this entity in a patient with suggestive echo or clinical findings by echocardiography alone and would refer to further imaging.

Similar to the echocardiographic diagnosis of ALCAPA, careful 2D and color flow Doppler examination of the coronary arteries is required to make the diagnosis of AAOCA. Our institutional experiences in addition to published reports show that the sensitivity of echocardiography for this diagnosis can be increased by following a structured protocol which includes a color flow Doppler sweep through the ascending aorta between the right and left sinus of Valsalva to capture any intramural segment [13] (Fig. 37.3). If this diagnosis is suspected by history and/or echocardiography, we routinely refer to CT for the final diagnosis, and expert consensus recommends screen with echocardiography followed by confirmation with CTA or MRA [14].

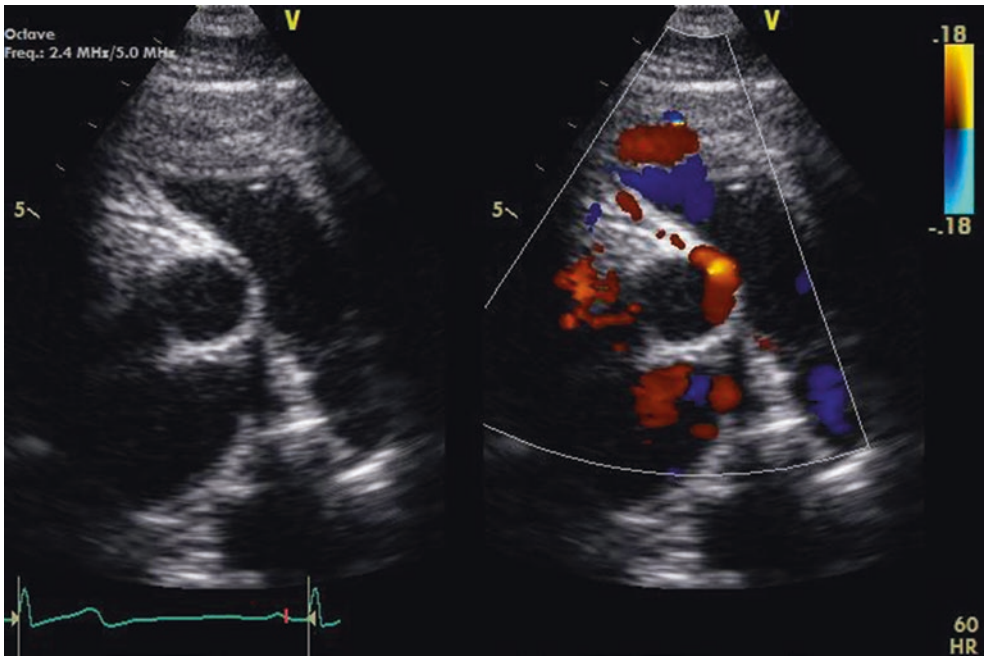

Fig. 37.3 Short-axis echocardiogram image showing anomalous origin of the right coronary artery from the left sinus of Valsalva. The echocardiogram shows the origin to be leftward of normal and tangential. It is often difficult to show the relationship of the coronary origin to the commissures with this modality prompting referral to CTA or MRA for more definitive diagnosis. We have found color flow Doppler is very sensitive screen when focused in between the right and left sinus of Valsalva. In this case mildly accelerated diastolic flow can be seen in this region lending support to the diagnosis

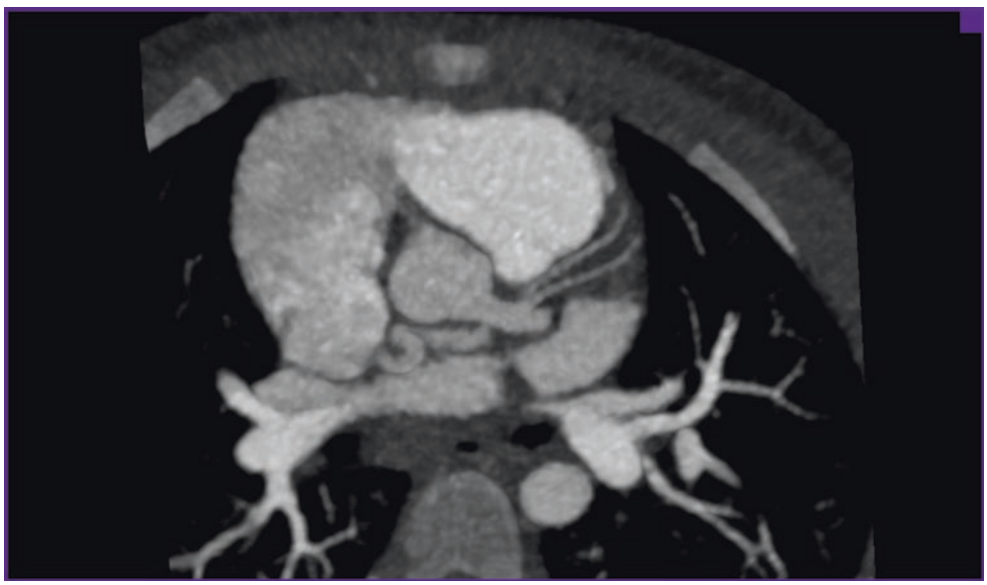

Fig. 37.4 A multiplanar reformat of a CT scan obtained in a 4 year old with a coronary artery aneurism from the left main coronary artery to the right atrium and separately to the left atrium. Note that the severely dilated left main coronary artery transitions to a normal sized left anterior descending coronary distal to the drainage to the low pressure chamber (left atrium)

37.4.5 CTA/MRA

Our institutional practice is to obtain a CTA or MRA to document the entire course of the CAF, which can often be difficult by echocardiography alone. This can be reliably done with either CTA or MRA regardless of patient age in an experienced center. Ancillary findings include dilation of the coronary system feeding the CAF and chamber dilation (Fig. 37.4). The difficulty in these cases is determining where occlusion of the fistula will be successful without impairing coronary perfusion to distal coronaries and myocardium. This is where three-dimensional images produced by these modalities are crucial. The added benefit of MRA is lack of ionizing radiation and the ability to quantify the shunt, chamber dilation and myocardial infarction. Modern CT scanners, however, produce, very high-resolution images that are superior to those obtained by MRI at low radiation doses.

The diagnosis of ALCAPA can be made readily with a high-quality gated CT scan (Fig. 37.5). With modern CT scanners, adjustments can be made to compensate for high heart rates in infants and children and to limit the radiation

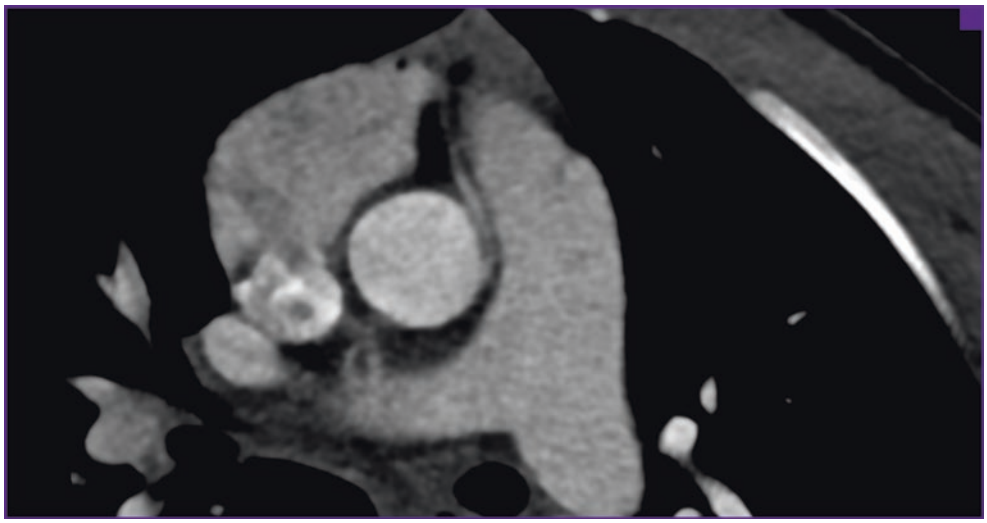

Fig. 37.5 Axial multiplanar reformat of a gated CTA showing a relatively cephalad, leftward and tangential origin of the right coronary artery from the left sinus of Valsalva. The right coronary artery can be seen taking an inter-arterial course between the ascending aorta and main pulmonary artery where it is significantly narrowed

dose. MRI is not typically used in the primary diagnosis but may be used to document myocardial viability and to visualize myocardial perfusion after repair [15].

In our institution, we believe the added resolution afforded by CTA gives us more diagnostic confidence in the intramural nature and length of the coronary artery which is useful in surgical planning. With modern techniques, the radiation dose is kept at an acceptable level. Both CTA and MRA are adequate for the diagnosis of AAOCA and the decision to use one or the other rests on patient age, institutional experience and availability. The 3-dimensional nature of the acquisition is very helpful as typically the origin of the anomalous coronary is superior to the sinus of Valsalva. This makes determining the location relative to the commissures impossible to perform in a single plane. The higher resolution of a CT scan allows for visualization of more subtle aspects of the proximal course and the coronary os which give a better anatomic definition of the lesion for surgical planning.

37.4.6 Invasive Angiography (IA)

With the advent of CT and MRI imaging, IA is rarely used in a primarily diagnostic role. If percutaneous closure is attempted, however, selective angiography is crucial for planning and avoiding occlusion of distal coronary arteries.

Invasive angiography is still a reasonable choice for the diagnosis of ALCAPA. It can nicely document the anomalous origin of the left coronary artery and runoff into the pulmonary artery. It can also document the extent of collateralization from the right coronary artery system.

Invasive angiography has been considered the gold standard for diagnosing AAOCA, but this is changing with increased access to high-quality echocardiography, MR coronary angiography, and coronary CT [16]. Although careful XRA can demonstrate the anomalous origin, it is often impossible to correctly identify an intraarterial course [16]. The addition of IVUS to the XRA may help increase the sensitivity of this test but carries additional risk [17]. MRCA and CTA have been shown to be more sensitive tests for this diagnosis [18, 19]. This is due to the fundamental differences between planimetry, which is limited to the AP (coronal) and lateral (sagittal) planes, and tomographic 3D techniques (MRCA/CTA) which allow visualization of the coronary arteries in the optimal axial plane.

37.5 Preoperative Management

Preoperative management must be individualized. Once the anomaly has been identified, management prioritizes on therapy of cardiac failure and of any multisystemic compromising in case of shock. In this latter scenario, unless the circulatory failure is refractory to medical therapy or if the patient is deemed to rapidly progress toward further deterioration, any surgical indication should be delayed until multiorgan stability is attained.

Symptomatic patients should be comprehensively monitored with an arterial catheter and an indwelling central catheter. A Swan-Ganz catheter is a useful tool for a comprehensive hemodynamic assessment and may be a good indication in patients who progress inadequately or whenever a differential diagnosis of the type of shock is required. However, in many pediatric centers, this is an uncommon practice and fraught with potential complications in small patients.

Near-infrared spectroscopy (NIRS), mixed venous saturation, and modern technology by thermodilution (including arterial wave form analysis) are important paraphernalia in the management of patients in critical conditions.

37.5.1 General Measures

- Administration of oxygen keeping in perspective the risks of reperfusion injuries
- Initiate inotropic drugs if necessary. These drugs must be administered very cautiously since they may trigger malignant arrhythmias by reperfusion. Phosfodiesterase inhibitors are particularly useful in this context because of their effect in reducing ventricular afterload. Other alternatives are dopamine, and the nitric derivates (IV nitroglycerin and isosorbide dinitrate). In case of severe and refractory ventricular dysfunction, levosimendan is a potentially interesting drug although reported pediatric experience is still limited in this patient population. Epinephrine (adrenaline) and norepinephrine (noradrenaline) are frequently utilized in association with dopamine, milrinone, and vasodilators.
- Administration of loop diuretics (furosemide, bumetanide) as boluses or incontinuous IV infusions
- Compensation pf all metabolic, electrolytic or acid-basic disorders
- Optimization of hematocrit levels (>35%)
- Attempt to minimize oxygen consumption and respiratory work; in case of low cardiac output in patients with limited reserves, it is reasonable to electively mechanically ventilate patients. Positive pressure ventilation by CPAP, BiPAP, or invasive ventilation is essential for patients in established or eminent cardiogenic shock. During the intubation process, rapid sequence drugs should be used (i.e., etomidate and rocuronium). Intubation may lead to cardiac arrest and cardiovascular collapse, and it is therefore advisable to alert the surgical team to the potential need for ECMO. Some patients with ventricular hyperexcitability may benefit of a dose of lidocaine on induction, to reduce the risks for ventricular arrhythmias during the intubation. In patients with ALCAPA, it is important to avoid hyperventilating and hyper-oxygenating the patients since these maneuvers may aggravate coronary ischemia by decreasing pulmonary vascular resistances.
- In the setting of refractory shock, proactively consider mechanical circulatory support.
- Aggressively treat all multiorgan dysfunction (peritoneal dialysis or Continuous Veno-Venous Hemofiltration or Hemodiafiltration in case of renal failure, compensation of coagulation disorders and administration of vitamin K in case of hepatic dysfunction, cerebral and splanchnic protective measures, to mention some)
- Symptomatic treatment of all intercurrent infections is key; prevention also plays an important role with regard to respiratory syncytial virus (polivizumab) and influenza virus (anti-flu vaccination)
- Optimization of enteral and/or parenteral caloric intake is also paramount

37.5.2 Specific Measures

37.5.2.1 ALCAPA

- Start a continuous intravenous heparin infusion
- Administer antiarrhythmic drugs as required; in case of ventricular hyperexcitability, lidocaine or amiodarone may be indicated and very cautiously administered.
- Initiate mechanical ventilation if the patient is in shock or has unstable hemodynamics.
- Initiate ECLS as required, sooner than later when medical therapy is not effective.
- Consider an urgent cardiac catheterization for diagnostic and eventual interventional purposes if diagnosis is unclear.
- Urgent surgical repair: this applies to the anatomical reimplantation of the anomalous coronary artery or to an intrapulmonary tunnelization of the anomalous artery towards the aorta (Takeuchi procedure). Ligation of the ALCAPA is very seldom the technique of choice. Ostial stenosis or atresia represent a surgical challenge with inconsistent results; tolerance to this condition relies on the degree of collateral circulation patients may develop from the right coronary artery.
- Some deemed inoperable cases may become candidates for an orthotopic cardiac transplant, eventually bridged with a ventricular assistance device.

37.5.2.2 Coronary Fistula

- Same indications as described for the ALCAPA. in case of ischemia or complications.
- Schedule an elective or urgent cardiac catheterization – depending on the clinical scenario – for diagnostic and eventual interventional purposes. Many coronary fistulas are occluded by percutaneous interventions.
- Surgical ligation of the fistula if not possible by cardiac catheterization

37.5.2.3 Anomalies of the Origin, Course, or the Termination of Coronary Arteries in the Context of Congenital Cardiac Defects

- There are no specific measures, except for the importance of the iconographic documentation of the anomaly to provide surgeons with a maximum of anatomical information. This may be achieved by echocardiography, CTA, cMRI or cardiac catheterization [20, 21]

37.6 Indications for Surgical Repair

37.6.1 Coronary Artery Fistula

Most patients who experience symptoms related to a coronary artery fistula present during the fourth through sixth decades of life. It is thought that some fistulas spontaneously close in childhood, but some persist into adulthood, and the coronary artery can become quite dilated, and the left to right shunt can result in significant CHF. Ischemia may result from a steal of blood into the low-pressure fistula. Endarteritis of the fistula has been reported. The dilation of the coronary can be quite significant and alarming, but rupture is exceedingly uncommon. They are most likely to have congestive heart failure from the left to right shunt.

Therapy is indicated in all symptomatic patients. Percutaneous device closure has become the first-line therapy whenever possible.

37.6.2 Anomalous Coronary Artery from the PA

Indication for repair of this defect is usually upon diagnosis as long as there is not significant cardiac dysfunction or complicating factors like suprasystemic pulmonary hypertension. In most cases, associated cardiac defects like mitral valve disease, pulmonary stenosis, and the presence of pulmonary hypertension make perioperative care very complex. Patients with ALCAPA whose coronary collateral system is well developed in infancy may survive into adulthood without developing symptoms. However, the blood flow in the left coronary becomes retrograde and preferentially flows into the pulmonary artery (coronary steal), resulting in significant myocardial ischemia unless there is significant pulmonary hypertension to prevent a steal situation. Anomalous right coronary artery from the pulmonary artery (ARCAPA) is more likely to be associated with other congenital heart defects and less likely to present in infancy. In fact, 50% of the patients with this lesion are asymptomatic at presentation. Thus, the defect may have a higher prevalence than thought. Like ALCAPA, if symptoms are present they are likely to be of CHF. AV valve insufficiency is unusual. Repair of ALCAPA or ARCAPA is to establish a two coronary artery system by translocating the anomalous coronary to the aorta, and is indicated at the time of diagnosis.

37.6.3 AAOCA

Because of the risk of sudden death and other adverse cardiac events, most cardiologists and surgeons recommend surgical repair of AAOCA ALMCA especially with symptoms, or evidence of ischemia on provocative testing. Controversy exists regarding management of the AAOCA ARCA. Most, but not all, cardiologists recommend surgical repair for the symptomatic ARCA patient, but there has been increasing reluctance to recommend surgery for the asymptomatic patient with ARCA because of the relatively low risk of sudden death in this patient population especially in the young (<10 years) and the older (>30 years). Also, morphologic characteristics of the AAOCA do not seem to predict risk of adverse outcome, making decision for decision for surgical intervention even more difficult. The small risk of sudden death or cardiac ischemia must be weighed against the risk of the operation. Unfortunately, even though the mortality and morbidity is minimal with current surgical therapy, the long-term outcome of the manipulated coronary artery is yet to be determined. If surgical repair is declined or deferred, avoidance of strenuous physical activity and competitive athletics is often prescribed, but is not necessarily protective because in athletes who had sudden cardiac death, more than half had a negative stress test [10].

Still, some cardiologists believe that the risk of sudden death with the asymptomatic ARCA is so small, that exercise limitation is not necessary. Until there is some rational consensus or data-driven treatment algorithm regarding the nonoperative management, there will continue to be controversy and consternation by patients and practitioners alike.

37.7 Surgical Repair

37.7.1 Coronary Fistula

The management of coronary fistulae must be individualized on the basis of the presence or absence of cardiovascular symptoms, the magnitude of the volume load on the heart, and the presence or absence of myocardial ischemia or ventricular dysfunction. Individual cases and small case series (nonrandomized, observational cohorts of both percutaneous and surgical correction have shown similar rates of residual fistula flow (20%–30%) during follow-up. Surgery consists of ligation of from the outside of the heart or patch or suture closure from the inside of the heart at the fistula termination point. It is unusual to compromise the coronary artery flow with ligation but CPB standby may be prudent in these cases. It is important to have very accurate preoperative imaging and to close all entrance points. There is a risk of recurrence with either transcatheter or surgical closure. High-risk features for subsequent residual fistula were found to be more likely in patients with a fistula draining into the CS, regardless of whether they had undergone surgical or percutaneous intervention. Even under open surgical inspection, this abnormal coronary connection can be particularly difficult to

close completely, consequent to the multiplicity of distal coronary artery-to-CS connections and the location of the connection on the posterior base of the heart. Percutaneous closure is often feasible when the fistulous communication departs from the coronary artery proximally. Percutaneous closure of the fistula must close the fistulous connection distal to the most distal coronary arterial branches that supply myocardium. Retrograde closure at the site of connection to the vein or cardiac chamber is also a viable approach. Surgical repair is often preferred when the fistula is large and tortuous, with distal connections to the low-pressure chamber. In the most recent American College of Cardiology/American Heart Association Guidelines for the Management of Adults with Congenital Heart Disease, percutaneous or surgical closure is a Class I recommendation for large fistulae regardless of symptoms and for small- to moderate-size fistulae with evidence of myocardial ischemia, arrhythmia, ventricular dysfunction, ventricular enlargement, or endarteritis [22].

37.7.2 Anomalous Coronary from the PA

The earliest reports suggested that simply ligating the left or right coronary artery before it entered the RPA would relieve the steal physiology and resolve the problem [23].

However, improved outcomes result from the reestablishment of a two coronary systems which is the recommended approach. This is accomplished through a standard median sternotomy with cardiopulmonary bypass and usually with the aid of intraoperative transesophageal echocardiography. Most patients who survive to adulthood with this defect will have some degree of pulmonary hypertension and may have decreased left ventricular function and mitral valve insufficiency. Intra- and postoperative management may be aided with the utilization of a PA catheter monitoring. An important component of proper CPB management involves careful delivery of cardioplegia. Simple antegrade deliver may not protect the ventricular endocardium because the epicardial coronary arteries vessels may empty into the pulmonary circulation with passing through the myocardial capillary bed. It is important to occlude the branch or main pulmonary artery during cardioplegia deliver thereby preventing runoff. One may also consider retrograde cardioplegia deliver of even direct cannulation of the anomalous coronary after incision in the PA to better accomplish myocardial protection. One must also be prepared for significant dilated collateral vessels on the main PA and epicardium around the base of the PA and aorta. These vessels can be a source of significant postoperative bleeding. Once the heart is cold and at standstill, the pulmonary artery is incised anteriorly, just above the pulmonary valve. The origin of the anomalous coronary is determined and is usually easily harvested with a cuff of surrounding PA sinus. The left main coronary is mobilized and excised from the PA with to allow a transfer to the aorta without tension and with the proper orientation. A site on the left sinus of the aorta is chosen for transfer of the left coronary. In the older patient, it is usually not necessary to divide the aorta, but the surgeon should not hesitate to do this if necessary to accomplish a proper transfer. The harvest site of the left coronary is usually repaired with some patch material in effort to prevent any distortion of the pulmonary artery or valve, as well as to prevent compression of the left coronary with a pulmonary artery reconstruction under tension.

In some situations where the anomalous left coronary seems to be too remote from the aorta and an anastomosis directly on the aorta would be on substantial tension, the transected main pulmonary artery is used as a conduit tube in a variation of coronary angioplasty. A conduit tube of native pulmonary artery is anastomosed side to side to the aorta. Another alternative is to use enlarged autologous aortic and pulmonary arterial flaps to create an extended left main stem coronary artery during anastomosis of the anomalous left coronary artery from the pulmonary artery to the aorta. The Takeuchi repair that involves creation of an intraluminal tunnel from orifice of the anomalous coronary artery along the posterior wall of the PA and creation of a side-to-side anastomosis of the PA and aorta. This procedure has resulted in significant PA stenosis and coronary stenosis and is not favored.

37.7.3 AAOCA

The surgical correction for AAOCA is performed as an open cardiac procedure, usually via median sternotomy or partial sternotomy and cardiopulmonary bypass with cardioplegic arrest. Intraoperative TEE is generally recommended to evaluate efficacy of repair. In most patients with ALMCA and ARCA, correction can be accomplished with either excision and reimplantation or a modified unroofing technique. The unroofing technique is usually possible in patients with typical intramural and inter-arterial course and has excellent short-term results [24, 25].

With the unroofing procedure, the aorta is opened and coronary ostial anatomy is confirmed. It is very important to define the extent of the intramural segment. Excess intimal tissue and ostial flap are incised and resected to a point in which the coronary exits from the aorta in the appropriate sinus. This approach relieves the flap-like intimal covering over the ostium of the coronary and relieves the potential compression between the great vessels and increases the angle by which the coronary exits the aorta. When the intramural segment travels below the level of one of the aortic

commissures, it may be necessary to detach the aortic valve commissure, unroof the intervening intramural segment and reattaching the commissure. Care must be taken to avoid injury to the valve leaflets and to ensure proper orientation of the commissure. Alternatively, a neo-ostium can be created, leaving the commissure intact [23]. This is most commonly applicable to the anomalous left coronary from the right sinus because the intramural course is often at or below the level of the commissure and the intramural segment is often longer. In some patients in whom the intramural segment is so short or even nonexistent, coronary is best excised from the aorta and reimplanted in the appropriate sinus. This is more commonly applicable in the anomalous right coronary artery. If at all possible, the coronary should be harvested as a patch to include a cuff of native aorta to facilitate a safe implantation into the aorta. The harvest site is usually repaired with prosthetic patch material. In patients with the variety of single coronary and inter-arterial course, the coronary can be excised from the single coronary trunk and directly reimplanted into the appropriate sinus. This is obviously more easily accomplished in the older patient with larger coronary arteries. This will effectively relieve compression between great vessels.

Other surgical techniques recently described include main pulmonary artery translocation to the left pulmonary, sometimes in combination with coronary artery patch augmentation [26, 27].

Others have described dividing the right pulmonary artery from the main PA, and anastomosing it back to the PA anterior to the aorta (Hemi-Lecompte maneuver) [28].

This may potentially relieve the compression between great vessels, however does nothing for the intramural component of the defect. This operation may be more applicable for the patient with a single right coronary artery with an inter-arterial left main coronary artery without an intramural segment.

Coronary bypass surgery has been used to treat patients with AAOCA, especially adults. In the absence of concomitant coronary artery atherosclerotic disease, this approach is not recommended because the flow in the native anomalous coronary system may be near normal except in states of exertion. This will predispose any bypass graft to risk of thrombosis or failure because of competitive flow. So, if CABG is used, ligation of the native proximal coronary should be considered. The use of this strategy is discouraged owing to the risk of thrombosis of the graft as a result of competitive flow or the risk of leaving the distal circulation fully dependent on a graft if the proximal coronary is ligated to prevent competitive flow. In a series reported by Krasuski, survival during the entire follow-up period in patients with AAOCA and inter-arterial course appeared better in the surgical cohort versus those managed medically (82% versus 53%at 10 years) [29].

There is no consensus among surgeons as to superiority of one technique over another. However, because one cannot be certain as to the exact pathophysiology of the actual or potential ischemia, the surgery in theory should address all potential mechanisms without creating the potential for future coronary complications.

37.8 Postoperative Management

Surgery for anomalies of coronary arteries is generally well tolerated and results predictable. Postoperative requirements depend to a great extent on the preoperative conditions. Generally, if the patient was well balanced prior to the intervention, no significant complications are anticipated. However, the postoperative course may be fraught by challenges in patients who present with established ischemia or infarct and in cardiogenic shock. Patients must be cautiously monitored for persistent or recurrent acute ischemia, ventricular dysfunction, low cardiac output syndrome and arrhythmias due both to the ischemic event or to reperfusion injuries. A significant echocardiographic improvement may be documented over the first 48 h of postoperative course, although total recovery is not expected before weeks or months of progression, if ever.

Patients with ALCAPA generally are repaired in infancy and this defect is often associated with significant left ventricular dysfunction and mitral valve insufficiency. It is not uncommon for these patients to require inotropic and lusitropic support and careful hemodynamic monitoring for several days following repair. Mitral valve insufficiency may persist for several weeks following repair, but as left ventricular function improves, the mitral valve function generally improves as well. Long-term outcome is generally very good.

AAOCA patients typically have uncomplicated postoperative courses. Continuous telemetry is monitored and may show ECG changes with ST segment changes although true coronary insufficiency is rare. Ventricular dysfunction associated with ECG changes must be investigated promptly, usually with CT Scan or Coronary angiography.

Patients with coronary artery fistula. are usually older, often adult age. Postoperative recovery is generally rapid and uncomplicated.

37.8.1 General Management

In general patients undergoing these procedures have an uneventful recovery with relatively short intensive care unit stays, on average approximately 4–5 days.

Anticipated postoperative complications may be as follows:

- Ischemia: a continuous ECG monitoring will immediately identify any recurrent ischemic event. Serial control of cardiac enzymes (CPK, CPK MB, LDH, troponin) and pro-BNP may be useful. *Any ventricular arrhythmia should be considered as ischemia until otherwise demonstrated.*
- Arrhythmias: any ventricular arrhythmia should motivate further investigations in order to identify sources of residual or recurrent ischemia. In any doubtful situation, a surgical revision should be proposed. Potentially, any arrhythmia and conductive disorders are possible in the context of coronary surgery, particularly in patients with already compromised myocardial function. A strict metabolic control and rectification of documented disorders regarding potassium, sodium, calcium, and magnesium levels is required.
- Persistence of a severe myocardial dysfunction: these patients may require transient mechanical circulatory support until recovery or as a bridge to cardiac transplant

37.8.1.1 Monitoring

Monitoring of these patients should include an arterial catheter, a central venous catheter, and in case of surgery on cardiopulmonary bypass in patients with significant left ventricular dysfunction, possibly a left atrial catheter and eventually a Swan-Ganz catheter. Tools that evaluate and trend issue perfusion markers are fundamental for target-oriented therapy; these include serial lactate and mixed venous saturation (eventually continuously monitored) measurements, NIRS, and in older patients parallel technologies including pulse wave analysis.

37.8.1.2 Sedation and Analgesia

Sedation and pain control is provided by the association of low dose benzodiazepines and opioids. Alternatively, dexmedetomidine or propofol may be used. Propofol may have an hemodynamic impact in these already fragile patients and must be handled by very experienced practitioners, ideally as a continuous infusion and by avoiding boluses. Etomidate is a drug to consider for rapid sequence procedures. Once the hemodynamic status is stable, multiorgan function is deemed adequate, and in the absence of bleeding or residual ischemia, patients are allowed to breath spontaneously in order to progress towards extubation. This is usually accomplished in the operating room or else during the first few hours in the intensive care unit.

37.8.1.3 Fluid Management

With the exception of the ligation of coronary fistula without ventricular compromising, in which case no fluid restriction is necessary, patients should receive a total of 30–50% of physiological requirements on the first day, 50 to 75% on the second day and 75 to 100% on the third day. Like for all other surgeries on cardiopulmonary bypass, caregivers should aim for a negative or neutral fluid balance. Excessive volume load should be optimized with a titration of loop-diuretics.

37.8.1.4 Inotropic and Vasodilator Drugs

These patients benefit from the universal approach to postoperative cardiac patients associating inotropic/lusitropic and vasodilator drugs, with the aim to support the myocardial function and to reduce ventricular afterload. The combination of milrinone with low doses of epinephrine (adrenaline) is very efficient for this purpose. In patients with conserved ventricular function, the alternative may be the association of dopamine instead, albeit many of such patients may not even require cardiovascular drugs. Many other vasodilators can be utilized depending on the institutional protocols: phentolamine, phenoxybenzamine, hydralazine, nitroglycerine or sodium nitroprusside. Nitroglycerine is an interesting drug for this cohort of patients for its effect in reducing the transmural pressure, therefore optimizing myocardial infusion. Intravenous Nitroglycerin is therefore recommended in the first 24 h as any manipulation of the proximal coronary may result in spasm and ischemia. Epinephrine (adrenaline) is a clear indication in patients with ventricular dysfunction, although it should be used with caution considering the increase in oxygen consumption and the potential for induction of arrhythmias. Levosimendan has arose as a drug with a high interest in patients with persistent ventricular dysfunction and may become a rescue drug in the future; however, further clinical studies are required in the pediatric population.

Extracorporeal life support techniques should be indicated in patients who are in cardiogenic shock and refractory to inotropic and vasodilator drugs.

37.8.1.5 Respiratory Management

In the absence of surgical or postoperative complications, patients are frequently extubated in the postoperative room or weaned over the first few postoperative hours.

Positive ventilatory pressures are a favorable cardiopulmonary interaction in patients with left ventricular dysfunction and therefore transition to noninvasive ventilation (CPAP or to BiPAP) is sometimes indicated.

37.8.2 Specific Management

Details about specific management of left ventricular dysfunction, low cardiac output syndrome and arrhythmias are available in other chapters elsewhere in this book.

37.8.2.1 Signs of Ischemia

All ventricular ischemia must be considered as an emergency. Clinical manifestations of ischemia may vary from an acute left ventricular dysfunction with low cardiac output to ventricular arrhythmias. If general patient conditions so allow, a cardiac catheterization should be performed. Otherwise, the patient should be taken back to the operating room for surgical revision. While awaiting the intervention, nitric derivates should be increased and IV Diltiazem ought to be considered for the possibility of a vascular spasm of the graft.

37.8.2.2 Anticoagulation

With the exception of the ligation of a coronary fistula, all patients should be on a continuous infusion of heparin at 10 U/kg/h, from the sixth postoperative hour, in absence of active bleeding. Once feeding has resumed, all patients with coronary artery repairs should be placed on antiplatelet therapy with aspirin, dipiridamol or clopidogrel, allowing to later suspend the heparin drip. There is no uniform agreement as to the duration of this therapy, but 3 months is usually acceptable management.

Some groups recommend the use of low molecular weight heparin (enoxaparin, fraxiparin, calciparin) for a few days, followed with levels of anti-Xa factor.

37.8.2.3 Arrhythmia

Management of arrhythmias and conductive disorders is discussed in detail in a specific chapter. In patients with ventricular hyperexcitability, lidocaine or amiodarone as a continuous infusion may be considered. Use of amiodarone requires great caution for its negative chronotropic effect.

37.9 Long-Term Results and Follow-Up

It is our practice to obtain exercise stress testing whenever possible in patients at approximately 3 months following surgical intervention although this is a highly controversial area and is really only helpful if positive. In most situations either after adequate recovery or after a negative stress test, patients can resume normal activity with no exercise limitation.

In most larger series, some patients have either recurrence or persistence of symptoms following the surgery and these instances need to be investigated further with imaging studies, usually CT angiogram, or he even cardiac catheterization. CT angiogram will give very accurate data on proximal coronary anatomy and if performed correctly can provide data on the distal coronary anatomy as well. Nuclear perfusion studies have been used and have been positive and some patients following this procedure; however, the significance of these findings in the absence of symptoms is questionable. Other studies have demonstrated an altered heart rate response with exercise testing, again with questionable significance.

The survival following surgical intervention for AAOCA is generally very good with little mortality reported. However, it is important to carefully follow patients that have evidence of aortic valve abnormality as this can progress to significant valve insufficiency and require further intervention. As with any coronary intervention it is important to monitor the ostia patency. It is unclear how long to continue antiplatelet therapy in these patients although it has been our practice to stop it at 3 months following surgery.

Unrepaired CAF have long-term complications that include persistent angina (7–21%), fatigue (24–25%), congestive heart failure (12–32%), and infective endocarditis (3.5–6%). Symptoms seem to be a late finding and are much more common after 20 years of age than before [30]. In a report of 76 patients with repaired CAF, long-term complications such as coronary thrombosis, myocardial infraction and cardiomyopathy were identified in 15% of patients. In this series, CAF egress into the coronary sinus was associated with 10 out of 11 of these patients and seems to be a major risk factor. Other risk factors were advanced age at repair, and modifiable coronary artery disease risk factors [31]. No guidelines for long-term follow-up are available but cases by case surveillance seems warranted.

Once the diagnosis is made, patients uniformly undergo surgical repair. Unrepaired, the mortality is 65–85% in the first year of life [4]. The surgical repair for ALCAPA has evolved over time, but recent trials show short-term mortality of 0–16% with an advantage to patients who were diagnosed early with reduced ischemic insult [32]. Long-term complications of the diseases and repair are persistent mitral regurgitation, left ventricular dysfunction and coronary artery stenosis. Clinical evaluation with echocardiography and noninvasive stress testing is indicated in adults who have undergone ALCAPA repair [22].

For those patients who do not undergo surgical repair, there are published recommendations for exercise restrictions. They exclude all competitive sports for patients with ALCA and patients with ARCA with symptoms, arrhythmias or signs of ischemia on exercise testing. Patients with ARCA

who are asymptomatic, with a normal stress test and no arrhythmias may consider exercise without restriction. After surgical repair, patients with AAOCA may participate in all sports 3 months after surgery if they are asymptomatic and have normal exercise testing and are arrhythmia free [33]. Long-term follow-up is not standardized, but should include lifelong cardiac care. In a recent study, 40% of patients who underwent surgical repair continued to have symptoms. It is unclear whether this is evidence that their presenting symptoms were unrelated to AAOCA or if there is ongoing ischemia which has been reported [34]. Ostial stenosis and sudden cardiac death have been reported after surgical repair, so it is reasonable to consider periodic testing with MRA/CTA and exercise testing. Families should also be counseled about this possibility so that they report symptoms as soon as they occur. Postoperative aortic insufficiency is reported to occur in 17–20% of patients and is a particular risk if the aortic commissure is taken down during the repair [35]. Therefore, these patients should be evaluated with echocardiographic screening in the postoperative phase and followed long term.

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Chapter 38
Aortic Valve Regurgitation

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Abstract Aortic regurgitation (AR) may be caused by valve disease (most commonly, cusp prolapse) or aortic root anomalies, but it is rare in children without other heart disease. It is more commonly associated with aortic stenosis (AS) but may also be seen in patients with ventricular septal defects, tetralogy of Fallot, D-transposition of the great arteries, coarctation of the aorta, endocardial cushion defects, single ventricle, truncus arteriosus, infective endocarditis (IE), and mitral valve disease. Systemic diseases associated with AR include rheumatic fever, systemic lupus erythematosus, and Takayasu arteritis. AR related to dilation of the ascending aorta is seen in patients with Marfan syndrome, bicuspid aortic valve, osteogenesis imperfecta, and rheumatoid arthritis. When significant, it may worsen preexisting AR and lead to aortic dissection. Finally, iatrogenic AR may result from balloon dilation of AS [1]. Aortic regurgitation (AR) may be caused by valve disease (most commonly, cusp prolapse) or aortic root anomalies, but it is rare in children without other heart disease. It is more commonly associated with aortic stenosis (AS) but may also be seen in patients with ventricular septal defects, tetralogy of Fallot, D-transposition of the great arteries, coarctation of the aorta, endocardial cushion defects, single ventricle, truncus arteriosus, infective endocarditis (IE), and mitral valve disease. Systemic diseases associated with AR include rheumatic fever, systemic lupus erythematosus, and Takayasu arteritis. AR related to dilation of the ascending aorta is seen in patients with Marfan syndrome, bicuspid aortic valve, osteogenesis imperfecta, and rheumatoid arthritis. When significant, it may worsen preexisting AR and lead to aortic dissection. Finally, iatrogenic AR may result from balloon dilation of AS [1].

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38.1 Pathophysiology

Both preload and afterload are increased in AR. The effective forward stroke volume is initially well maintained at the expense of high end-diastolic volume and increased LV mass. However, eventually the LV wall thickening fails to manage the excessive regurgitant stroke volume, and the end-systolic wall stress rises [1, 2]. Thus, over the course of its natural history, AR leads to a spectrum of anatomic and physiological changes, including dilation and hypertrophy of the LV, dilation of the mitral valve apparatus and mitral regurgitation, dilation of the left atrium, pulmonary venous congestion and hypertension, and eventually global ventricular dysfunction and congestive heart failure (CHF). Once significant ventricular dysfunction sets in, the ventricle may not recover even following the repair of the aortic valve.

38.2 Diagnosis

Unless AR develops acutely, most children with it are initially clinically asymptomatic; however, as the regurgitation progresses, they may experience dyspnea, palpitations, chest pain, or syncope. Failure to thrive is commonly seen in the younger patients.

On physical examination, children with AR exhibit wide pulse pressure and bounding pulses with abrupt distension and fast collapse (water-hammer pulses), especially over the carotids. There is a prominent apical cardiac impulse and an early (immediately after A2) blowing, decrescendo diastolic murmur best heard along the left sternal border. Other classic

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physical findings in AR include pistol-shot sounds over the femoral arteries and head-bobbing in time with the pulse [1].

Chest X-ray may show pulmonary venous congestion and suggest dilatation of ascending aorta.

Transthoracic echocardiography typically visualizes aortic valve leaflet structure and function in the apical and parasternal long axis views and is sufficient for diagnosis. In addition to defining the extent of AR, ventricular function should be assessed. Finally, since patients with AR may have IE, endocardial vegetations should be sought and, if present, described in terms of size and mobility. In the context of a negative transthoracic examination despite strong clinical suspicion for IE, transesophageal echocardiogram should be strongly considered.

Indications for surgery vary by program; however, the general philosophy as applied to the pediatric patient with AR seems to favor earlier intervention before significant ventricular dilation occurs. Children who are symptomatic despite medical optimal management, and especially those with echocardiographic evidence of moderate-to-severe AR or those with progressive ventricular dilation and dysfunction, should be considered for urgent surgery [1, 2]. Pediatric patients with AR who develop significant LV dilation ($z > 4$) in the context of AR are less likely to return to normal LV function following aortic valve repair.

38.3 Preoperative Management

Patients with AR rarely require ICU admission preoperatively with the exception of those in whom acute AR develops after balloon dilation of the aortic valve or in the context of IE. Unlike chronic AR, acute AR is poorly tolerated, and the development of CHF is rapid and overwhelming.

In the setting of acute AR and CHF, admission echocardiogram and chest X-ray should be obtained, and central venous pressure as well as invasive arterial pressure should be monitored.

Preoperative stabilization of children with acute AR should focus on improving inotropy, judicious afterload reduction, and diuresis and volume restriction. These children usually have low diastolic and mean blood pressure, so aggressive afterload reduction should be avoided so as to prevent coronary diastolic ischemia. These objectives can be achieved by using milrinone alone or in combination with low-dose epinephrine; alternatively, low-dose epinephrine can be combined with nitroprusside. In either case, it is prudent to introduce afterload reduction very carefully and gently titrate the medications to effect.

If IE is suspected, serial blood cultures must be obtained and antibiotics started immediately. A transthoracic or transesophageal echocardiogram should be performed as described above. These patients are at high risk of thromboembolic events, so prophylactic anticoagulation should be considered in these cases.

In those patients who have developed AR in the context of dilated aortic root, β-blockade should be considered in order to decrease the chances of developing aortic dissection.

38.4 Surgical Management

These are two approaches to the management of patients with AR: (1) repair (used increasingly more frequently and with moderate success [3–5]) or (2) replacement of the aortic valve. The general philosophy in the pediatric patient (especially one with tricuspid aortic valve morphology) [6] is to repair the diseased valve and to postpone its replacement as much as possible

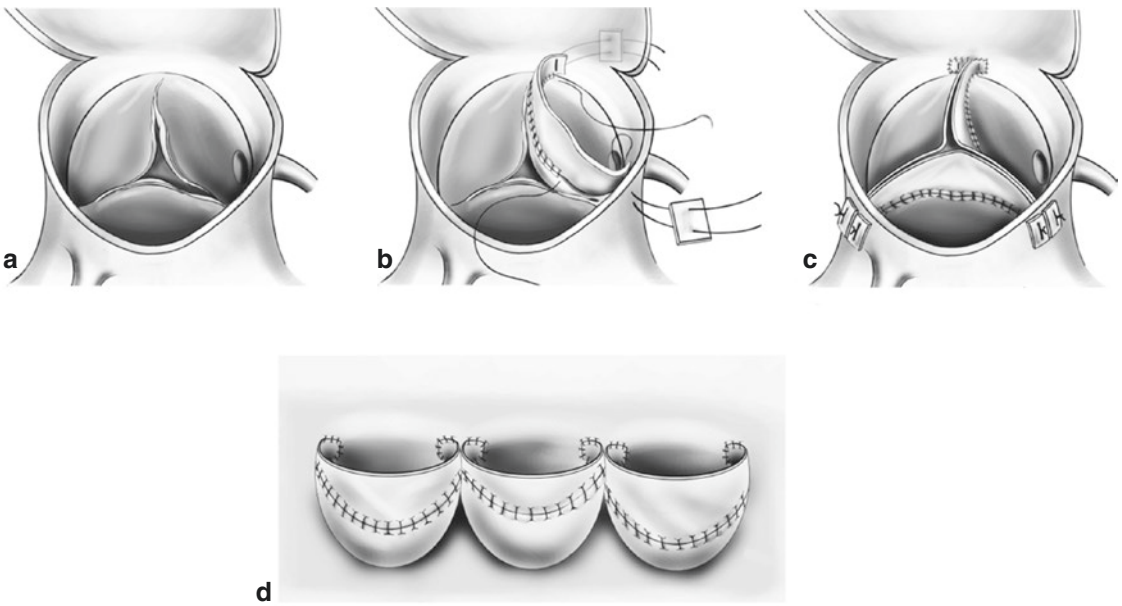

Fig. 38.1 *Pericardial leaflet extension technique.* (**a**) Abnormal trileaflet aortic valve with poor coaptation. (**b**) The pericardial extension is sutured to the left aortic cusp. (**c**) All three aortic cusps have been augmented with pericardial patches creating a competent valve. (**d**) Note that the size of the pericardial patch extension varies for each cusp

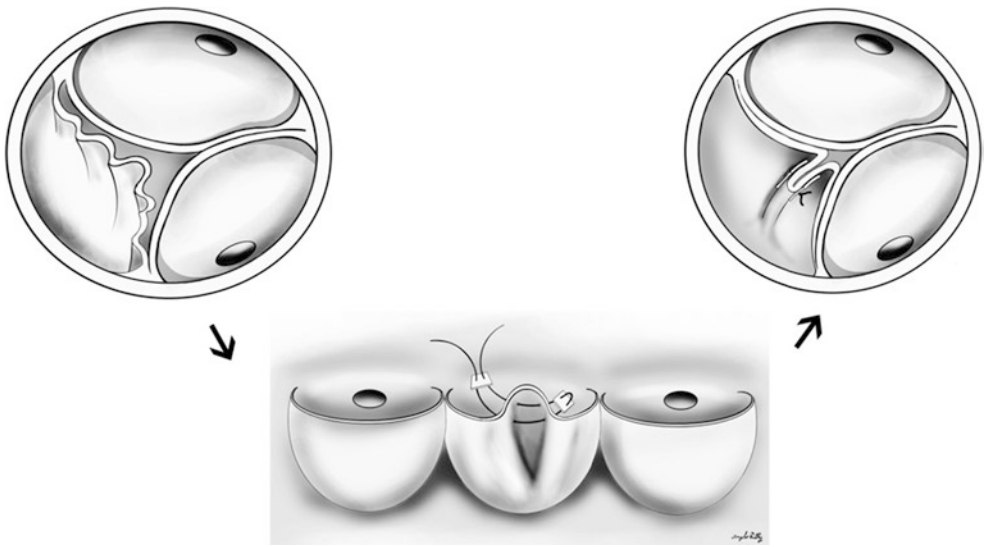

Fig. 38.2 *Aortic leaflet plication.* In the presence of a redundant and prolapsing aortic cusp, a centrally placed plicating suture improves valve coaptation reducing the amount of valve insufficiency

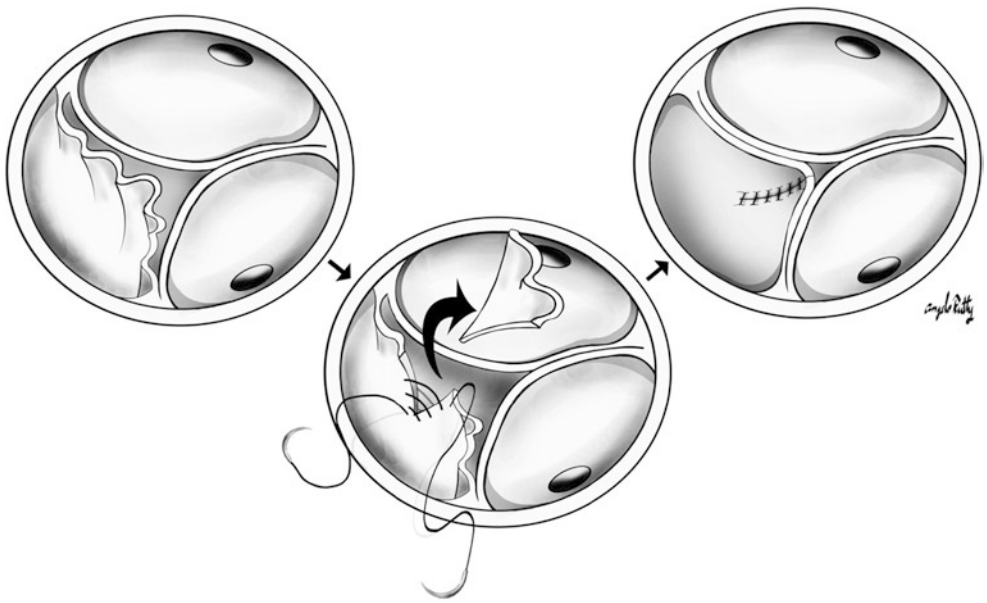

Fig. 38.3 *Partial aortic leaflet resection.* The redundant central section of the prolapsing cusp is resected in order to improve valve coaptation

[1]; however, some surgeons would favor replacing those valves with a nontricuspid morphology [6]. Either approach requires cardiopulmonary bypass (typically under mild-moderate hypothermia) and cardioplegic arrest. The three commonly used repair techniques are shown below (Figs. 38.1, 38.2, and 38.3), while replacement of the aortic valve is discussed elsewhere.

38.5 Postoperative Care after Repair of Aortic Regurgitation

The care of patients after surgery for AR is relatively simple. Unless these patients had significant pulmonary edema preoperatively, they are usually extubated in the operating room or on admission to the intensive care unit. Arterial and central lines are typically left in place for at least the first postoperative day. Chest X-ray and ECG are obtained on the postoperative intensive care admission, and it is important to compare them with the preoperative studies. The majority of patients continue to require afterload reduction and diuresis even after AR repair. Electrolytes should be closely monitored and corrected to avoid arrhythmias. Dexmedetomidine infusion, supplemented as needed with low-dose narcotics and benzodiazepines, provides excellent sedation in these patients. For patients who have undergone aortic valve repair no anticoagulation is typically needed; however, some centers would use aspirin or even coumadin (short term) for complex valve repairs. If a prosthetic valve has been placed, anticoagulation with heparin should start once the bleeding is controlled, typically on postoperative day 2. When oral intake is stable, these patients are transitioned to warfarin (please see the chapter on prosthetic valves for further details).

38.6 Outcomes

Intermediate- and long-term outcomes of aortic valvuloplasty are good [7–9], especially in those patients who had less than moderate AS preoperatively, with about 70% and 50% of patients free of aortic valve replacement at 5 and 7.5 years, respectively [7].

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Chapter 39
Vascular Rings and Pulmonary Sling

Monique M. Gardner, Yuliya A. Domnina, and Victor O. Morell

Abstract Aortic arch anomalies are not uncommon and are the result of embryologic derangements during development of the aortic arches and their branches [1]. Early in gestation, there are both right and left aortic arches. In a majority of people, the right normally atrophies and disappears, leading to a left aortic arch. Vascular rings occur when certain structures persist rather than involute, or involute rather than persist, resulting in encirclement and compression of the trachea and esophagus [2]. This can lead to respiratory symptoms, with an estimated 3–5% of cases of stridor in infancy being due to vascular rings. In addition to airway obstruction, gastrointestinal symptoms such as dysphagia or choking with feedings can occur, but usually less frequently and present later in life (toddler or older children), and are frequently accompanied by respiratory symptoms [3].

Long-term results of the patients operated for vascular ring spectrum are generally favorable. Most infants experience significant improvement in respiratory status immediately after relief of compression caused by vascular ring. However, complete resolution of the symptoms may take a few weeks to months with gradual resolution of tracheobronchomalacia. Nonetheless, 92–95% of infants are expected to be free of their respiratory symptoms by the end of first postoperative year [4].

39.1 Anatomy

The differential diagnosis for patients with respiratory or esophageal symptoms can include the following anatomic anomalies:

1. *Double aortic arch* (Fig. 39.1) is the most common vascular ring, and results when the right arch fails to involute. There are several variations of double aortic arch. In some cases, both arches may be patent; the right arch is dominant in 70% of cases and the left in 20%, and the arches are almost equal in size in 10% of cases. In other cases, there is a more dominant arch (typically the right), with the left arch present but atretic [3].
2. *A right aortic arch with an aberrant left subclavian artery and left ligamentum arteriosum* (Fig. 39.2) is a rather common anomaly. Frequently, the ring is "loose" without

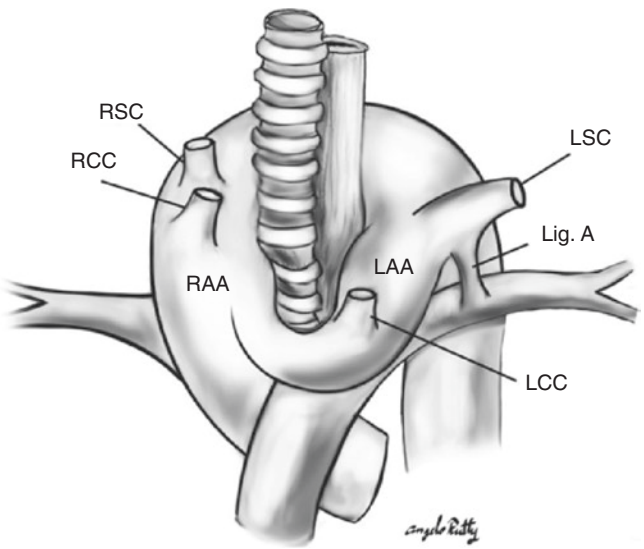

Fig. 39.1 Double aortic arch. (*RAA* right aortic arch; *LAA* left aortic arch; *RCC* right common carotid artery; *LCC* left common carotid artery; *RSC* right subclavian artery; *LSC* left subclavian artery; *Lig.A* ligamentum arteriosum)

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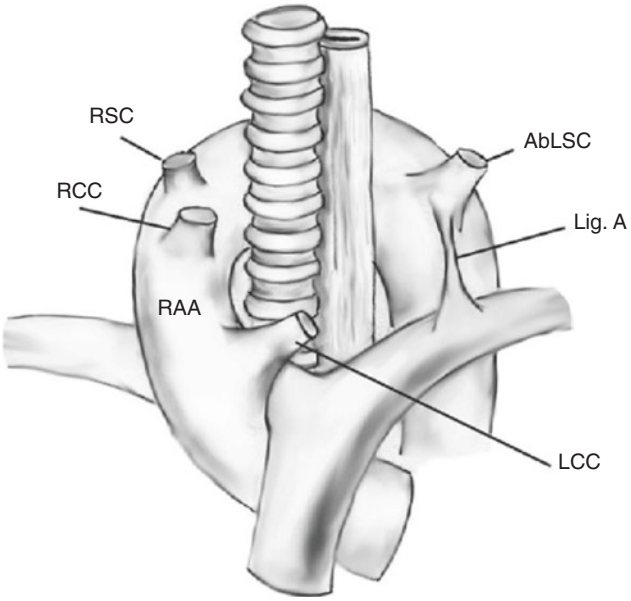

Fig. 39.2 Right aortic arch (*RAA*) with an aberrant left subclavian artery (*AbLSC*) and a left ligamentum (*Lig.A*). (*RCC* right common carotid artery; *LCC* left common carotid artery; *RSC* right subclavian artery)

causing compression of structures, and thus causes no symptoms. If the left subclavian artery arises from a diverticulum of Kommerell, a remnant of the left descending aorta, the ring may be "tighter" and cause symptoms .

3. *A left aortic arch with an aberrant right subclavian artery* (Fig. 39.3) is also common and usually asymptomatic. Rarely, there is an associated right-sided descending aorta and then the ring tends to be tighter and more symptomatic [5].
4. *A pulmonary artery sling* (Fig. 39.4), also known as distal origin of the left pulmonary artery, occurs when the left pulmonary artery originates abnormally from the right pulmonary artery and courses between the trachea and esophagus, resulting in encroachment on the distal trachea and the right mainstem bronchus. Associated intracardiac abnormalities are present in 10–15% of cases [6].
5. *An anomalous innominate artery* (Fig. 39.5) occurs when the innominate artery arises unusually distally from the aortic arch, then courses tangentially anterior to the trachea. The degree of tracheal compression is variable but occasionally is severe.

39.2 Pathophysiology and Clinical Presentation

Despite variability in anatomy of these anomalies, they are all influenced by a common pathophysiologic mechanism; symptoms are due to compression of large airways and/or the esophagus. Patients with severe compression tend to present

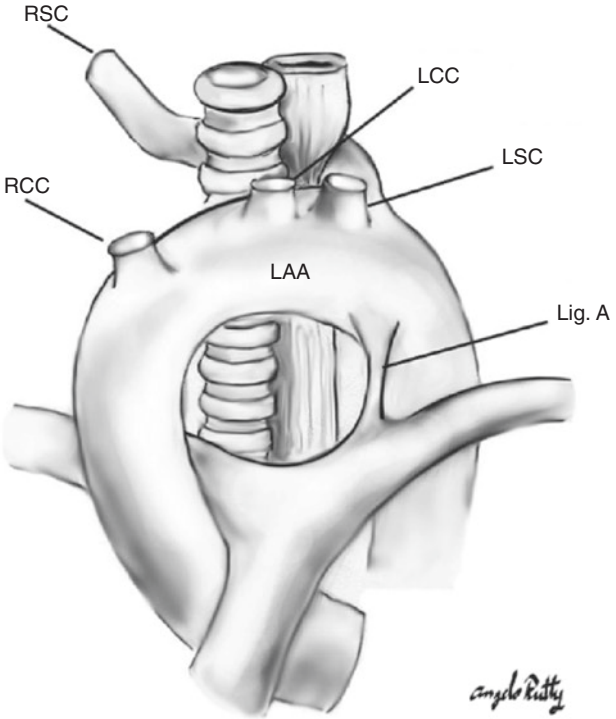

Fig. 39.3 Left aortic arch (*LAA*) with an aberrant right subclavian artery (*RSC*). (RCC right common carotid artery; *LCC* left common carotid artery; *LSC* left subclavian artery; *Lig.A* ligamentum arteriosum)

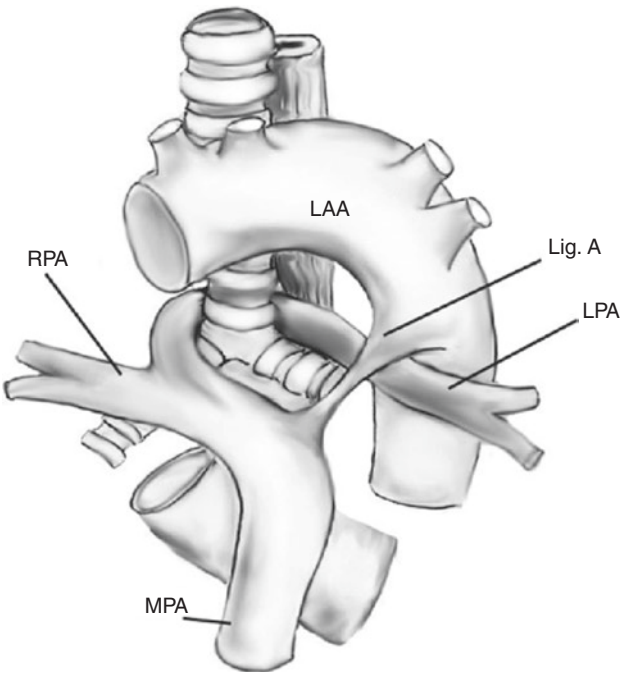

Fig. 39.4 Pulmonary artery sling. (*MPA* = main pulmonary artery, *RPA* = right pulmonary artery, *LPA* = left pulmonary artery, *LAA* = left aortic arch, *Lig.A* = ligamentum arteriosum)

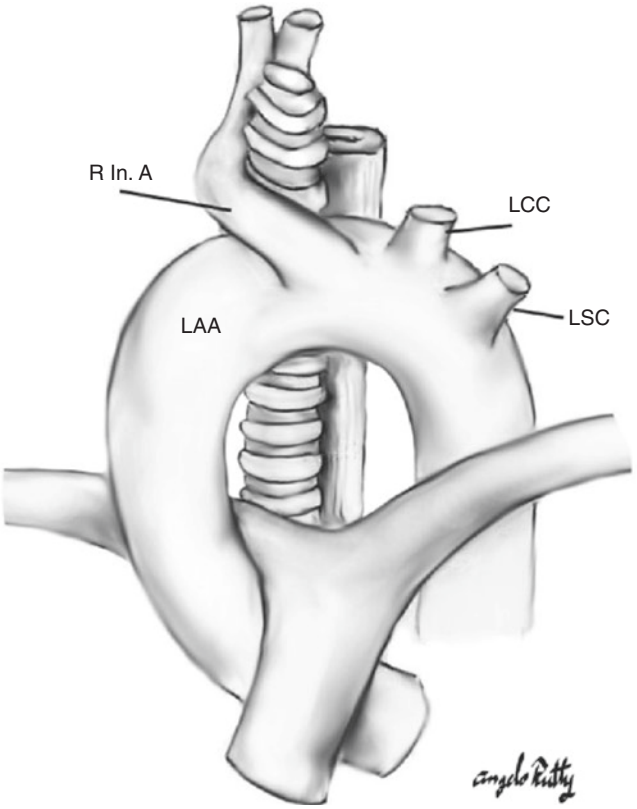

Fig. 39.5 Innominate artery tracheal compression caused by an anomalous origin of the innominate artery (*RIn.A*) form the aortic arch. (*LAA* left aortic arch; *LCC* left common carotid artery; *LSC* left subclavian artery)

early in life. In others, symptoms appear later in life or not at all. Long-standing compression of the trachea and mainstem bronchus by the high-pressure arterial system causes tracheobronchomalacia, with airway collapse on exhalation and consequent air trapping. A barking cough and expiratory stridor are common clinical signs. In infants and children with severe obstruction from innominate artery compression, symptoms commonly worsen during respiratory infections [7]. Similarly, infants with double aortic arch typically present in the newborn period and often have severe symptoms with the classic "barky" cough and nearly constant stridor. Children with a right aortic arch and left ligamentum frequently present somewhat later in life (3–9 months of age) because the ring is "looser," being formed partially by the low-pressure pulmonary artery and the ligamentum arteriosum [8].

Compression of the esophagus may cause dysphagia, but rarely in infancy when diet is largely liquid. However, severely affected infants may show slow feeding, regurgitation, aspiration, and failure to thrive.

Other congenital anomalies, including intracardiac defects, should always be evaluated in patients with aortic arch anomalies. A right aortic arch is common in patients with conotruncal defects, such as tetralogy of Fallot and truncus arteriosus, but a vascular ring is rarely seen in this group. Tracheal anomalies including tracheal rings, absence of the membranous trachea, and tracheal stenosis have been reported in infants with pulmonary sling (so called, ring-sling complex) [9].

39.3 Diagnosis

There are a few diagnostic modalities available for evaluation of the child suspected of having a vascular ring.

Barium esophagography was previously the single most important tool for diagnosing a vascular ring [10]. The retroesophageal indentation by the abnormal vessel is persistent in all views, differentiating it from a peristaltic wave. Pulmonary sling is the only vascular abnormality that causes an anterior (rather than posterior) esophageal indentation. Barium esophagography is normal in patients with an anomalous innominate artery.

Echocardiography is useful in making the diagnosis of most of vascular rings and pulmonary artery sling but is limited because a vascular segment without a lumen and the trachea cannot be visualized. Nonetheless, the sidedness of the aortic arch and direction and origins of the brachiocephalic arteries provide useful information. A recent study showed that barium esophagram when concordant with echocardiographic imaging is 100% accurate [11]. Echocardiography is also important in evaluating other structural cardiac disease, which can be associated with arch abnormalities.

Computed tomography (CT) and magnetic resonance imaging (MRI) are useful in that they identify both the vascular structures and the tracheobronchial anatomy. It is a vital part of preoperative assessment and planning for repair of congenital tracheal stenosis [12]. These studies are employed if the diagnosis is not clear from the other procedures listed above.

Angiography is rarely needed for the diagnosis of a vascular ring, but in unusual cases, it can offer information not available from any other modalities.

Bronchoscopy is an important diagnostic tool for infants and young children with stridor and, in the presence of a vascular ring, shows an extrinsic, often pulsatile, compression of the trachea. Bronchoscopy is also the diagnostic procedure of choice for infants with complete tracheal rings and innominate artery compression syndrome, where there is a pulsatile oblique anterior compression of the trachea. When the bronchoscope is pressed onto the pulsatile area, the right brachial pulse may diminish or disappear.

39.4 Preoperative Management

There is no definitive medical therapy for vascular rings or pulmonary sling, and symptomatic patients should undergo surgical correction as soon as feasible, especially if symp-

toms are severe. Preoperatively, the patient should be given adequate nutritional needs. Supportive respiratory and appropriate treatment of any respiratory tract infection is also paramount. Usually, surgery should not be unduly delayed because of a respiratory tract infection, because surgical correction of the ring allows more adequate and complete clearing of respiratory secretions.

39.5 Surgical Management

For surgical repair, cardiopulmonary bypass is not required for these diverse anomalies except for the repair of pulmonary sling. The surgical approach to a double aortic arch (Fig. 39.6) is through a lateral thoracotomy. The operative goal is to divide the smaller of the two arches at a site that does not compromise the blood flow to the head and arm vessels, usually distal to the subclavian artery. A rare patient was reported to have a coarctation in both arches [13]. Arch division should always be done between vascular clamps with oversewing of the divided stumps, because simple ligation and division has been associated with ligature slippage and subsequent catastrophic hemorrhage.

The surgical approach to the right aortic arch lesions (Fig. 39.6) is also through a left lateral thoracotomy. When the vascular ring is caused by the ligamentum arteriosum, repair is done by division and oversewing of the stumps of the ligamentum. If there is an associated diverticulum of Kommerell, it is either resected and oversewn or pexed to the fascia of the vertebral column. This prevents compression of the trachea or esophagus from the diverticulum itself.

Left aortic arch with right descending aorta lesions must be approached via a right thoracotomy. Division of the ring in these cases is accomplished by dividing the right-sided ligamentum arteriosum [14].

Treatment of anomalous innominate artery is through a small right parasternal incision. The innominate artery is affixed to the posterior periosteal layer of the sternum [4]. Some surgeons opt to do a division and re-implantation of the innominate artery through a midsternal approach instead of above-mentioned suspension technique.

Pulmonary artery sling is repaired via a median sternotomy approach and the use of cardiopulmonary bypass. The left pulmonary artery is transected at its origin from the right pulmonary artery and is passed through the mediastinum posterior to the trachea. The left pulmonary artery is then anastomosed to the main pulmonary artery anterior to the trachea [15].

39.6 Postoperative Management

The postoperative course is usually benign and in the absence of severe tracheomalacia, most of the patients usually do not require prolonged admission to the pediatric critical care unit. The majority of patients are able to be extubated in the operating room, monitored in the hospital for 24–48 h postoperatively, and then discharged home. Invasive monitors in the form of arterial catheter and central venous catheter are usually used intraoperatively and typically discontinued upon transfer to the postoperative care area.

Pain from the thoracotomy incision could interfere with breathing efforts and lead to atelectasis and pneumonia. Injuries to the phrenic and recurrent laryngeal nerve are uncommon. Excessive bleeding is also rare postoperative complication. Disruption of the thoracic duct rarely occurs but when it does can cause postoperative chylothorax [16].

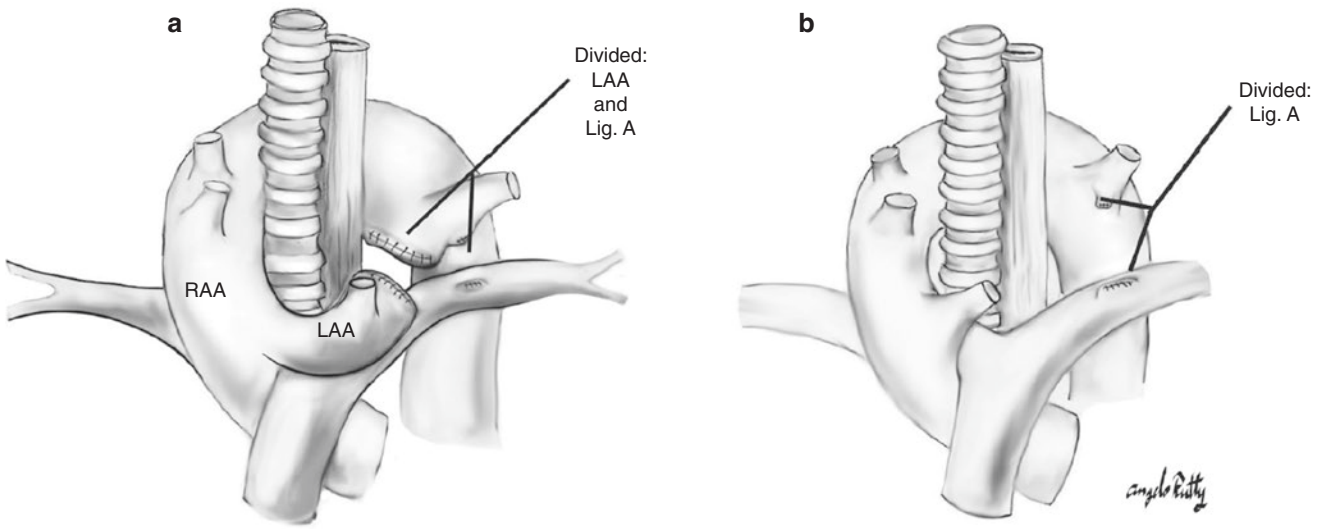

Fig. 39.6 (**a**) Repaired Double Aortic Arch; the smaller left aortic arch (LAA) and the ligamentum arteriosum (Lig.A) have been divided. (**b**) Repaired right aortic arch with aberrant LSCA; the ligamentum arteriosum has been divided

39.7 Long-Term Outlook

Long-term results of the patients operated for vascular ring spectrum are generally favorable. Most infants experience significant improvement in respiratory status immediately after relief of compression caused by vascular ring. However, complete resolution of the symptoms may take a few weeks to months with gradual resolution of tracheobronchomalacia. Nonetheless, 92–95% of infants are expected to be free of their respiratory symptoms by the end of first postoperative year [17].

Patients with pulmonary sling, including associated complete tracheal rings, as well as patients with associated congenital heart disease have poorer outcomes. In patients with a severely deformed trachea or tracheomalacia, additional reconstruction procedures such as a tracheal graft with autologous rib may be required to alleviate life-threatening respiratory problems [18]. A number of patients continue to show evidence of some pulmonary function abnormalities years after surgery [14]. In Backer's series of patients with pulmonary sling, the patency of the left pulmonary artery reanastomosed through median sternotomy and while using cardiopulmonary bypass was 100% with the mean blood flow to the left lung, as measured by nuclear medicine scan, of 42% [17]. The majority of institutions performing surgeries for vascular anomalies on infants with no intracardiac or extracardiac defects report virtually no operative mortality.

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Chapter 40
Takayasu Arteritis

Yuliya A. Domnina, Monique M. Gardner, and Ricardo A. Munoz

Abstract Takayasu arteritis is a rare disease affecting especially young females of Asian and Indian descent. The disease is a great "mimicker," and nonspecific symptoms make the diagnosis difficult. A high index of suspicion and familiarity with the disease is necessary for prompt diagnosis and effective treatment planning. However, recent progress in imaging modalities including magnetic resonance angiography, computed tomography angiography, and positron emission tomography have allowed making specific diagnoses in the early stage (Mavrogeni et al., Semin Arthritis Rheum 42:401–12, 2013). Although the cause of Takayasu arteritis is unknown, the condition is characterized by segmental and patchy granulomatous inflammation of the aorta and its major derivative branches. This inflammation leads to arterial stenosis, thrombosis, and aneurysms (Hall and Buchbinder, Rheum Dis Clin North Am 16:411–422, 1990). Advances in immunosuppressive treatment including new biological anti-TNF agents may lessen the burden of the disease and morbidities associated with it. Because of these changes in diagnosis and treatment, the prognosis of Takayasu arteritis has been improving.

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40.1 Anatomy

Takayasu arteritis (TA), first described by Mikito Takayasu in 1908, is a chronic, medium, and large vessel vasculitis that primarily affects the aorta and its branches, as well as pulmonary arteries. The alternative name for this illness is "pulseless disease." While the etiology is unknown, the disease is characterized by progressive and sustained inflammation of involved vessels that eventually leads to stenotic lesions and aneurysm formation. TA is a rare disorder, with an incidence of 1.2–2.6 cases/million per year, occurring most frequently in the Asia and Africa [1]. A strong association with *Mycobacterium tuberculosis* was found in patients afflicted with TA in those parts of the world. Female-to-male ratio is 9:1 with the peak incidence occurring in the third decade of life, although the disease has been previously been identified in a toddler-aged child [2]. Lower rates of the disease are observed among white European and North American descendants [3].

40.2 Pathophysiology

The cause of Takayasu arteritis is unknown, but immunogenetic factors appear to play a major role in pathogenesis. TA has been reported in identical twins, leading to hypotheses of a hereditary basis for disease. In Japan and Korea, TA is associated with human leukocyte antigens HLA-A10, B5, Bw52, DR2, and DR4. These associations have not been confirmed in Western studies. In the United States, TA is associated with HLA-B22, which is also implicated in other autoimmune diseases such as inflammatory bowel disease and spondyloarthropathies [4].

The initial acute phase of vasculitis is characterized by the thickening of the aortic wall with or without alterations in the arterial lumen – the "pre-pulseless phase." In this phase, however, the absence of luminal alterations does not exclude the diagnosis of TA [5]. Microscopic studies reveal pan-arteritis

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involving all layers of the artery, but particularly the media. Intimal thickening is due to endothelium proliferation and tissue edema. Also seen on microscopy is destruction of elastic membrane and infiltration of all layers by lymphoid and plasma cells. Progressive inflammation in the subacute phase manifests by formation of granulomas made of macrophages, epithelioid, and giant cells. In the "pulseless" end-stage sclerotic phase, alterations in the arterial lumen lead to stenosis, vessel occlusion and thrombosis, atypical coarctation, dilation, and/or aneurysms. Vascular stenosis and obstruction predominate in 90–100% of patients, but dilation and aneurysms are not rare (27%) [4].

40.3 Clinical Presentation

Symptoms during the acute phase are nonspecific and can vary to include, dizziness, fever, fatigue, weight loss, myalgia, arthralgia, abdominal pain, nausea, cough, lymphadenopathy, anemia, and transient skin rashes. This variable presentation can make diagnosis difficult and can delay diagnosis for months to even years. Serum measurement of erythrocyte sedimentation rate (ESR) has been used as a marker of disease activity. Other acute phase reactants have been used as good activity markers: alpha-1 acid-glycoprotein, C-reactive protein (CRP), electrophoretic alpha-2-globulin, and haptoglobin level. However normal acute phase reactants do not assure complete disease remission. Sequential imaging evaluations have revealed disease progression (as determined by the presence of new vascular lesions) in over 60% of patients with clinically stable inflammatory profiles and normal ESRs [6].

Progression of the disease into late sclerotic phase can add symptoms related to ischemia, transient ischemic attack or ischemic stroke, seizures, visual disturbances, abdominal angina, extremity claudication, enlarged blood vessels, bruits, absent pulses, and renovascular hypertension. The symptoms of cardiac involvement are related to aortic dilation and may present as aortic insufficiency, congestive heart failure, and arrhythmia. Aortic aneurysms and rupture, as well as thrombus formation, are common causes of death in TA.

40.4 Diagnosis

Criteria for the classification of Takayasu arteritis was developed by comparing patients who had this disease with control patients with other forms of vasculitis. Six criteria were selected for the traditional format classification, with the presence of three or more of these criteria demonstrated a sensitivity of 90.5% and a specificity of 97.8%:

1. Onset at age less than or equal to 40 years
2. Claudication of an extremity
3. Decreased brachial artery pulse
4. Greater than 10 mmHg difference in systolic blood pressure between arms
5. A bruit over the subclavian arteries or the aorta
6. Arteriographic evidence of narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities [7]

Arteriography is the gold standard of radiologic diagnosis of TA as well as an intermittent test to monitor the progression of the disease and pre-intervention. Arteriography often demonstrates long, smooth, tapered vessel narrowing or occlusions. However contrast dye-related renal and radiation exposure are negative aspects of angiography and could be avoided by other imaging modalities, such as magnetic resonance angiography (MRA). Echocardiography can aid in evaluation of the ascending aorta and transverse arch. Duplex color-flow Doppler may reveal thickening of the intima, stenosis, and thrombi in the carotid, subclavian arteries, abdominal aorta, and its branches including renal arteries. However, echocardiography alone is not sufficient for diagnosis of disease and monitoring of disease progression.

40.5 Treatment

The treatment of Takayasu arteritis in the active phase consists of the control of inflammation with the use of steroids, alone or in combination with other immunosuppressive agents. Rheumatologist must be involved from the very early stages of diagnosis and treatment. High-dose corticosteroid administration (1–2 mg/kg/day) for 4–6 weeks is typical first-line therapy with remission attained in 50% of patients. Corticosteroids are subsequently weaned over 4–6 weeks while monitoring for signs of relapse, as 40% of patients will relapse during taper. In patients with steroid-resistance disease, treatment can include weekly intravenous methotrexate (adult dose 15–25 mg/week; pediatric 5–15 mg/m^2/week) or oral cyclophosphamide (1–2 mg/kg/day) to achieve and maintain remission [6]. Cyclosporine is used as an alternative therapy to cyclophosphamide, offering an improved toxicity profile. Biologic agents, specifically anti-tumor necrosis factor (TNF) medications (e.g., etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira)), have shown promising results for otherwise resistant or relapsing cases of TA [8]. Mycophenolate mofetil (well tolerated at 2 g/day) has been shown to reduce clinical disease activity and improve laboratory parameters in patients already having failed treated with other immunosuppressive agents [9].

The other important medical issues relate to the management of hypertension and the prevention and treatment of thrombosis. Some experts advise routine use of low-dose aspirin. The thought is that it will help prevent blood clots from forming in damaged arteries. Hypertension is particularly troublesome in patients with Takayasu arteritis; it could

be worsened by steroids use. Choice of anti-hypertensive agents must be approached thoughtfully and carefully due to frequency of renal artery stenosis.

In the pulseless phase, aneurysmal dilatation and stenotic lesions could lead to severe physiologic consequences due to ischemia to cerebral, coronary, renal, and peripheral arterial beds, thus requiring surgical or endovascular intervention.

40.6 Surgical Management

In the chronic phase of TA, medical management can be insufficient and surgical and percutaneous interventions are required. These can include bypass procedures, percutaneous transluminal angioplasty and stent placement, aortic valve replacement, and aortic root repair.

Aortic valvar regurgitation and resultant congestive heart failure can occur due to progressive aortic root dilation. Aortic regurgitation associated with TA can be managed with prosthetic valve placement. As with other cases, this operation can be complicated by prosthetic valve detachment or pseudoaneurysm formation at the suture line, however, specific to patients with TA, active inflammation on intraoperative specimens was found to be a risk factor for valve or graft detachment [10]. Because dilation of the aortic root progresses with TA, aortic root replacement with a composite graft for aortic is indicated due to concern for development of prosthetic valve detachment [11].

Diffuse, multifocal, and ostial vessel involvement in TA makes surgical revascularization with bypass grafting difficult, with a high rate of re-stenosis [12]. Percutaneous correction of vessel obstruction at multiple sites has emerged as a viable therapeutic alternative with no contraindication, even in the presence of active arterial inflammation. However, as re-stenosis is a known complication and repeated interventions are frequently necessary, a lower re-stenosis rate is observed when the interventions are performed in the stable stage and when postinterventional immunosuppressive treatment is implemented. Short segment stenosis was found less likely to re-stenose than long segment aortic stenosis. Percutaneous balloon angioplasty of the aorta and stent implantation in children with TA has been reported by Tyagi et al. to normalize blood pressure and improve exercise tolerance and symptoms of congestive heart failure with virtually no complications; improvement has been sustained for 3 years [13–15]. Percutaneous balloon angioplasty of renal artery stenosis in children with TA has been found to be a safe procedure with reduction in arterial blood pressure and decreased requirement for antihypertensives [16]. There was a 25% rate of re-stenosis in the follow-up period. The re-stenosis rates have been improved by stent implantation. Immunosuppressant-eluting stents (sirolimus, paclitaxel), which inhibit endothelial proliferation and endovascular inflammation, may decrease the rates of re-stenosis, but this therapy needs to be evaluation in larger population studies.

40.7 Long-Term Outlook

Because of the large vascular territories involved in TA and the progression of the disease, disease morbidity is extensive and can include Takayasu's retinopathy, hypertension, aortic regurgitation, myocardial infarction, aortic root dilation, aneurysm, carotid artery stenosis, seizures, and stroke. Chronic endothelial dysfunction puts patients with TA at risk for premature atherosclerosis. In addition, there are morbidities associated with the therapies used to treat TA, such as steroid-related diabetes, osteoporosis, hypertension, cataracts, and systemic infections. Despite these potential life-threatening complications, 5–10 year survival rates have been reported to be 70–90% [16]. Current immunosuppressive agents in addition to corticosteroids can bring TA to remission. Additionally, novel drugs that target intimal hyperplasia, as well as drug-eluting stents, deserve to be studied for possible utility, as adjuncts to present treatments [17, 18].

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Chapter 41
Aortic Dissection

Yuliya A. Domnina, Monique M. Gardner, and Victor O. Morell

Abstract Spontaneous aortic dissection (AoD) is a rare, life-threatening disease, yet it is the most common catastrophe of the aorta with a high mortality rate of 22–24% (Januzzi et al., J Am Coll Cardiol 43:665–669, 2004). Nontraumatic rupture of an aortic dissection can occur in patients without risk factors. However, there is a higher prevalence in patient populations with risk factors such as dilation of the aorta, connective tissue disorders, vasculitides, and other systemic conditions affecting the aorta. Patients under 40 years of age have a unique set of risk factors for aortic dissection compared to older patients: Marfan syndrome, bicuspid aortic valve, and larger aortic dimensions (Januzzi et al., J Am Coll Cardiol 43:665–669, 2004). The mortality in the younger group of patients is similar to that of the older group. A dramatic improvement has been observed in survival rates of patients with aortic dissections due to increased awareness, improved diagnostic modalities, and advances in operative repair and postoperative surveillance.

41.1 Anatomy

The most common site of dissection is the first few centimeters of the ascending aorta, with 90% of AoD occurring within 10 cm of the aortic valve. The second most common site is just distal to the left subclavian artery. Dissections of the thoracic aorta were initially classified anatomically according to the De Bakey classification (Fig. 41.1) [2].

- Type I: dissection involves the ascending aorta, aortic arch, and descending aorta.
- Type II: dissection localized to the ascending aorta.
- Type III: dissection involves descending aorta distal to the left subclavian artery, with further subdivision based on the extension of the dissection:
  - Type IIIa: extension of dissection proximally and distally.
  - Type IIIb: extension of dissection only distally.

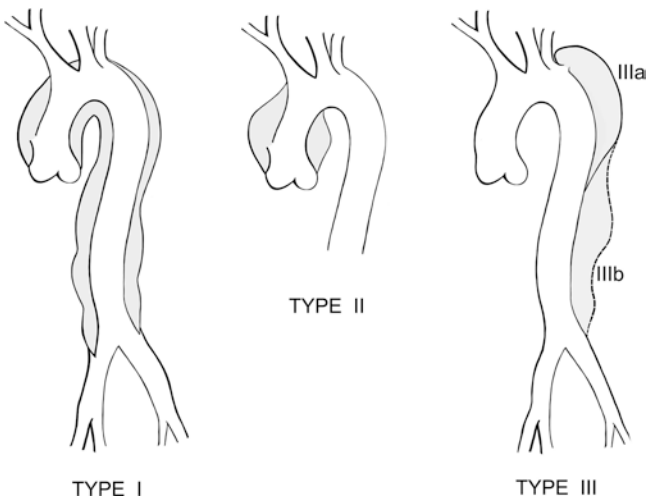

Fig. 41.1 DeBakey classification

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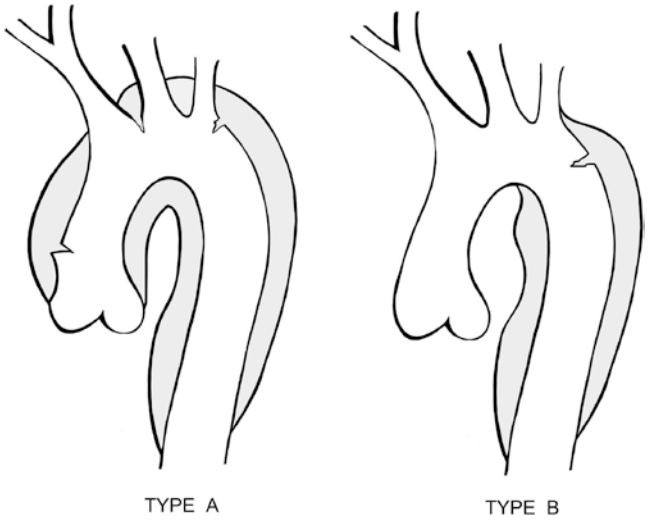

Fig. 41.2 Stanford classification

A simplified classification has been introduced by the Stanford group (Fig. 41.2) and it is based on the presence (Type A) or absence (Type B) of dissection of ascending aorta [3]. Type A involves the ascending aorta, while type B does not.

41.2 Pathophysiology

Disease pathology, both in symptomatology and histology, varies based on the location of the aneurysm.

Ascending aortic aneurysms and dissections typically present in the fourth to sixth decade of life with a hereditary predisposition, but there is a bimodal distribution, with younger patients having syndrome aortopathies. Despite age of presentation, all ascending aortic aneurysms have similar histopathologic changes including fragmentation of elastic fibers (called elastolysis), smooth muscle cell loss and dedifferentiation, and mucoid degeneration and medial degeneration—collectively termed cystic medial degeneration [4].

Degenerative aneurysms of *descending and abdominal aorta* tend to present and dissect in patients over 65 years old and have more typical characteristics of an atherosclerotic process. The initiating event of aortic dissection is a tear in the intimal layer, followed by formation and propagation of a subintimal hematoma. The propagating hematoma creates a false lumen or double-barreled aorta. The intimal tear is more likely to occur in the ascending aorta (65%) or in the descending thoracic aorta (20%), with a fewer cases originating from the transverse arch (10%). In about 13% of aortic dissections, there is no evidence of an intimal tear. In these cases, the inciting event is thought to be an intramural hematoma, with hemorrhage within the media [5].

41.3 Clinical Presentation

Sudden, severe chest pain is the most common presenting symptom in patients with an aortic dissection. Aortic dissection should always be considered in the differential diagnosis of all patients presenting with chest pain and in particular in patients with known conditions or high risk factors for AoD. Location of pain and radiation usually corresponds to the affected area of the aorta and involved in the dissection. Substernal chest pain frequently mimics chest pain of acute myocardial infarction and is associated with ascending aorta or aortic root dissection. Dissection in this area could cause interruption of coronary flow and result in myocardial ischemia. Pain that is described in the neck, jaw, or interscapular area may indicate that the dissection involves the transverse aortic arch, involving the head and neck vessels or the descending thoracic aorta. Additionally, aortic dissection could be painless. Painless dissection is more common in patients with syndromic aorthopaties. Other physical signs may include cardiac findings, such as hypotension or hypertension, wide pulse pressure and new diastolic murmur due to aortic insufficiency, tachycardia, muffled heart sounds, and electrocardiographic (ECG) changes. Respiratory symptoms can include dyspnea and orthopnea which are markers of acute heart failure. In rare cases, impairment of the recurrent laryngeal nerve which lies in proximity to the aortic arch can be involved in an aortic dissection and cause dysphagia and hoarseness [6]. Neurologic symptoms are common at presentation and can include syncope and seizures, altered mental status, and focal motor or sensory neurologic deficits (paresthesia, hemiparesis, and paraplegias).

41.4 Diagnosis

Tests used to diagnose aortic dissection include computerized tomography (CT) and CT-angiogram of the chest with iodinated-contrast material, transthoracic (TEE) and transesophageal echocardiogram (TTE), and magnetic resonance angiogram (MRA) of the aorta and aortogram. Studies from the International Registry of Aortic Dissection (IRAD) have shown that in patients with suspected AoD, echocardiography (both TTE and TEE) was performed in 33% of patients, computed tomography (CT) in 61%, and magnetic resonance imaging (MRI) in 2%, and angiography in 4% [7]. Demonstration of the intimal flap separating two lumens is the basis for diagnosis of aortic dissection. If the false lumen is completely thrombosed, central displacement of the intimal flap, calcification or separation of intimal layers can be regarded as definitive signs of aortic dissection. The other diagnostic goals include:

- Localizing intimal tear.
- Delineating the extent of dissection.
- Assessing side branch involvement.
- Distinguishing between communicating and noncommunicating dissection.
- Detecting and grade aortic regurgitation.
- Detecting extravasation (periaortic or mediastinal hematoma, pleural or pericardial effusion) [8].

41.5 Preoperative Management

While arranging for appropriate diagnostic confirmatory tests, patients should be moved to the intensive care unit for monitoring and treatment. An ECG must be obtained in all patients as a baseline preoperatively and can provide a screening for possible coronary involvement in the dissection. Two large bore IV should be placed for volume resuscitation and medication administration. Arterial line should be placed in the right radial artery as the involvement of the brachiocephalic trunk is rarely seen. Periodic blood pressure monitoring of all four extremities is indicated to rule out pseudo-hypotension due to obstruction of the aortic branch. It is of paramount importance to provide pain relief, as the severe pain experienced in aortic dissection can itself stimulate sympathetic output and could lead to elevation of blood pressure, in turn stimulating propagation of dissection. Morphine sulfate in age- and size-appropriate dosing is a drug of choice in the hemodynamically stable patient. Blood pressure needs to be controlled with systolic blood pressure goal (SBP) between 100 and120 mmHg, and mean blood pressure (MAP) between 60 and 75 mmHg in adults; for children, goals for blood pressure management should be within age-appropriate norms. Beta-blockers (e.g., esmolol, propranolol, and labetalol) are the agents of choice for hypertension associated with AoD due to the prominent effect on the reduction of the force of left ventricular ejection. If beta-blockade alone does not control hypertension, nitroprusside (a potent vasodilator) may be added for combination therapy. Patients on aggressive blood pressure management must be closely monitored for symptomatic hypotension, which may evidence itself as oliguria or altered mental status.

Hemodynamically unstable patients should be intubated and mechanically ventilated, with expedited surgical management. If diagnostic imaging is contraindicated due to patient instablility, TTE or TEE can be performed as the sole diagnostic procedure in the intensive care unit or in the operating room in the interest of time. For the hypotensive patient, careful volume repletion should be performed if blood sequestration in the false lumen, pleural, or pericardial space is suspected [8].

41.6 Surgical Management

Type A dissections require prompt surgical intervention in order to prevent aortic rupture and death. The principles of the surgical repair include (a) the elimination of the proximal extension of the dissection in order to prevent rupture, (b) the re-establishment of intimal continuity, usually requiring resection or exclusion of the intimal tear, and (c) the elimination of aortic insufficiency with aortic valve resuspension or valve replacement.

The repair is performed via a median sternotomy incision and with cardiopulmonary bypass. An important technical aspect during the establishment of the extracorporeal circulation is the cannulation of the true arterial lumen in order to provide adequate end-organ perfusion; femoral artery cannulation is the preferred approach when possible. A period of deep hypothermic circulatory arrest might be required, as repair involves the aortic arch. An interposition tube graft is used to replace the ascending aorta up to the level of the proximal arch (Fig. 41.3). In the presence significant aortic root damage, especially in patients with Marfan's syndrome or with annuloaortic ectasia, the recommended surgical repair includes a root replacement, either with a valve-sparing procedure or with placement of a valve-conduit (Bentall procedure) (Fig. 41.4). The in-hospital mortality rate associated with this type of surgical repair is between 5% and 30% [9, 10].

Type B dissections in general do not require acute surgical intervention, except for patients who present with or develop aortic rupture, persistent pain, or end-organ ischemia (renal, hepatic, intestinal, spinal cord, or lower extremity). The surgical approach is through a left thoracotomy and it requires a period of aortic cross-clamping. The repair involves the replacement of the descending thoracic aorta with an interposition graft. In order to prevent spinal cord ischemia (5–20% incidence), some form of distal perfusion technique (partial femoral artery to femoral vein bypass, left atrial to femoral artery bypass, shunt) is frequently utilized. Also, it is important to re-implant the intercostal arteries. The operative mortality associated with a type B dissection repair is approximately 20% [11].

41.7 Postoperative Management

Postoperative care should be provided in the intensive care unit experienced in care of cardiac patients. Central intravenous line and arterial line are usually placed during preoperative care or in the operating room. Post-repair TEE is frequently obtained in the operating room to ascertain the quality of the repair. Evaluation should include

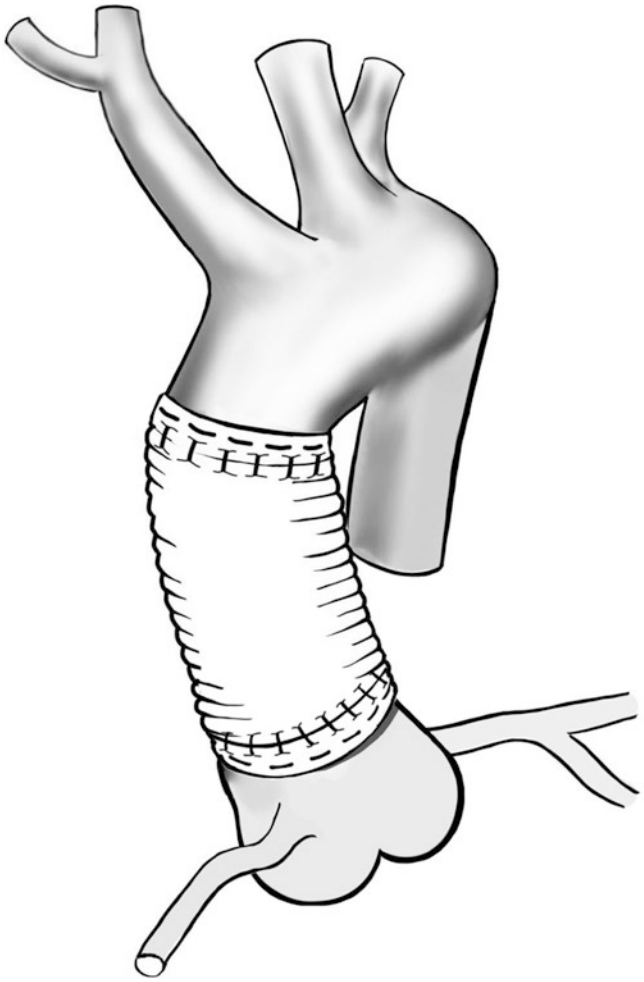

Fig. 41.3 Interposition graft. The ascending aorta is replaced with a prosthetic conduit; the native aortic root is preserved

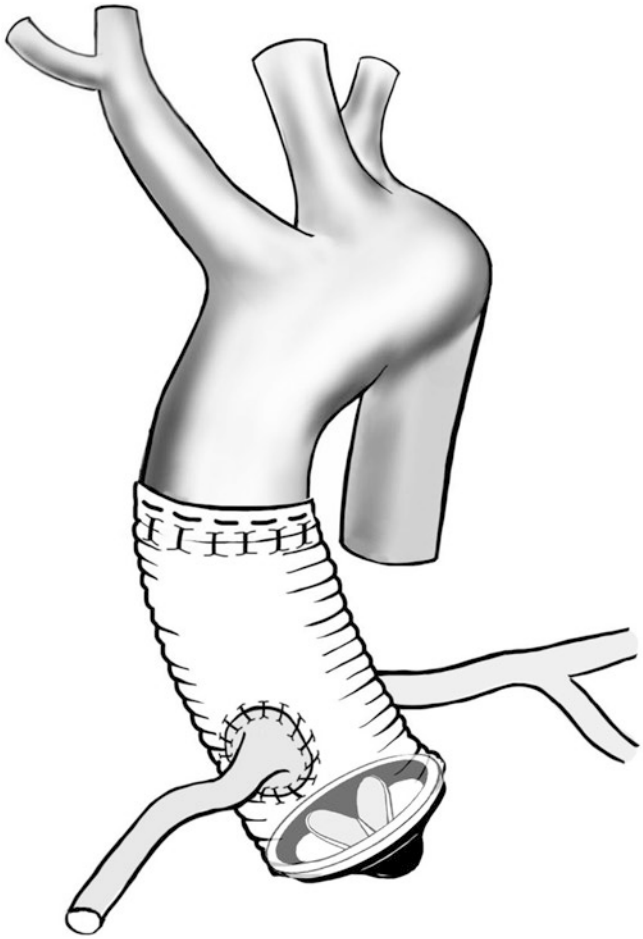

Fig. 41.4 Bentall procedure. The aortic root is replaced with a mechanical valve-conduit; it requires coronary reimplantation

demonstrating any residual aortic valvar insufficiency or stenosis, residual gradient across the aortic anastomosis, coronary flow, and postoperative cardiac function.

If the patient was relatively asymptomatic before the surgery, early extubation could be considered, but it is of a paramount importance that proper analgesia be provided. Hypertension due to sympathetic stimulation in the setting of inadequate pain control can increase the risk of postoperative bleeding along extensive suture lines. An infusion of dexmedetomidine (central sympatholytic; sedative, analgesic, and anxiolytic, IV infusion rate 0.3–1 mcg/kg/h) along with fentanyl infusion (opioid analgesics, 0.5–1 mcg/kg/h) is an excellent and safe alternative to a well-established regimen of morphine (opioid analgesics, IV intermittent dosing 0.05–0.1 mg/kg every 2–4 h) and midazolam (benzodiazepine; sedative and anxiolytic, IV intermittent dosing 0.05–0.1 mg/kg every 1–2 h).

Besides issues with analgesia, hypertension is a common problem after repair, especially if it was present in the preoperative period. In contrast, patients with syndromic aorthopathies frequently manifest with aortic dissection without hypertension. Systolic hypertension usually occurs within first 24–72 h postoperatively. Medical management can be difficult, as hypertension can be resistant to arterial vasodilators such as nitroprusside, where sometimes intravenous (IV) doses of 10 mcg/kg/min are required. When nitroprusside is used in higher doses (6–10 mcg/kg/min), serum concentration of methemoglobin should be monitored at least every 12 h. For further blood pressure management, arterial vasodilators are frequently supplemented with intravenous beta-blockers, with esmolol being the primary drug of choice (100–500 mcg/kg IV loading dose to be administered over 10–20 min; IV maintenance dose 25–250 mcg/kg/min). Especially in cases of previously documented cardiac dysfunction, esmolol should be used carefully with frequent monitoring as it can be a cardiac depressant and can cause heart failure. Additionally, esmolol could cause bronchospasm, nausea, and vomiting. Once enteral intake is resumed,

Angiotensin Converting Enzyme (ACE) inhibitors such as captopril or enalapril could be utilized for long-term blood pressure control.

41.8 Long-Term Outlook

A dramatic improvement has been observed in survival rates of patients with aortic dissections due to increased awareness, improved diagnostic modalities, and advances in operative repair and postoperative surveillance. International Registry of Aortic Dissection (IRAD) has reported a mortality for type A dissections of 27% when surgically managed and 53% for medical management, with a 29% mortality for type B dissection when surgically managed, and 9% when medically managed. [12] The best prognosis is reported for type B dissection limited to the descending aorta, with a 2-year survival rate of 80–86% [8]. Close follow-up is indicated for any patient with aortic dissection, as serial evaluation for aortic expansion, aneurysm formation, signs of leakage at anastomoses, and organ malperfusion are key. Regular imaging with TTE at follow-up visits is indicated, with magnetic resonance imaging (MRI) the well-accepted first choice if more detailed imaging is required. [8] The single most important factor is excellent blood pressure control, with goals in adult patients of under 135/80 mmHg and below or at age-appropriate norms in younger patients.

All patients with dilated aorta and Marfan syndrome, vascular Ehlers-Danlos syndrome, Loeyz-Dietz syndrome, bicuspid aortic valve, or a family history of dissection or thoracic aortic aneurysm need regular aortic surveillance with cross-sectional imaging and echocardiography. Appointments should be biannual after the initial meeting and then at least yearly thereafter. All patients with a thoracic aortic diameter at any level that exceeds an aortic index (measured/predicted diameter indexed to body surface area) of 1.3 or an absolute diameter of 40 mm require vigilant thoracic aortic surveillance. Elective aortic replacement should be considered for Marfan patients with a maximal aortic root diameter over 43 mm and for patients with bicuspid aortic valve or familial aneurysm/dissection with a maximal ascending aortic diameter of 45 mm [4]. Elective repair should also be strongly considered in patients with annual growth of ascending aorta more than 1 cm in diameter.

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Part III

Other Topics

Chapter 42
Acute Pulmonary Hypertension

Eduardo M. da Cruz and Dunbar Ivy

Abstract Pulmonary arterial hypertension is a hemodynamic condition defined as a pulmonary artery systolic pressure higher than 35 mm Hg or a pulmonary artery mean pressure higher than 20 mm Hg. However, this may depend on the level of the systemic pressure, and another potential definition could be pulmonary pressure > 60% systemic with signs of low cardiac output. Pulmonary hypertension in the critically ill pediatric cardiac patient remains a clinical challenge. Clinical practitioners still have to face significant problems particularly in the acute postoperative phase. This chapter provides a summary of the main aspects to be taken into account whenever managing acute pulmonary hypertensive crisis.

42.1 Introduction

Pulmonary arterial hypertension is a hemodynamic condition defined as a pulmonary artery systolic pressure higher than 35 mm Hg or a pulmonary artery mean pressure higher than 25 mm Hg. However, this may depend on the level of the systemic pressure, and another potential definition could be pulmonary pressure > 60% systemic with signs of low cardiac output.

Pulmonary hypertension in the critically ill pediatric cardiac patient remains a clinical challenge [1–6]. Clinical practitioners still have to face significant problems particularly in the acute postoperative phase. An in-depth understanding of this entity is fundamental in order to appropriately manage these patients and – very importantly – to know how to prevent or blunt the severity of the pulmonary hypertensive crisis that may characterize them. It is therefore important to describe the current knowledge regarding the pathophysiology of pre- and postoperative pulmonary hypertension in the cardiac patient.

In the preoperative phase, the increase in pulmonary pressure associated with congenital heart disease is either, in the vast majority, secondary to an increase in pulmonary blood flow (left to right shunts) or to increased postcapillary pressures (left heart obstruction or left ventricular dysfunction either systolic or diastolic). Albeit major advances in the understanding of the regulation of the pulmonary vascular bed and the pulmonary endothelial lesions leading to pulmonary vascular disease have been achieved and despite the advances in surgical repair and the discovery of potential therapies in the pre- and postoperative period, pulmonary hypertension still carries a significant mortality and morbidity in this population. The reported incidence of postoperative pulmonary hypertensive events has decreased from 31% in the 1980–1984 era to 6.8% in the 1990–1994 era, whereas the mortality has decreased, respectively, from 5.7% to 2.4% and continues to improve [7]. This data reflects in part the improved understanding of the pathophysiology and the rapid translation of this knowledge into therapy. However, acute pulmonary hypertension after cardiac surgery remains a major contributor to hospital length-of-stay and need for prolonged mechanical ventilation.

42.2 Pathophysiology

It has been recognized for many years that the endothelium is vital for the maintenance of normal vascular function by regulating flow, by solute exchange, and by inhibiting thrombosis; conversely, endothelial dysfunction plays a major role in several cardiovascular disorders.

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In congenital heart disease with significantly increased pulmonary blood flow or pulmonary venous hypertension, progressive anatomic and functional abnormalities of the pulmonary vascular bed occur. This state is characterized by progressive smooth muscle hypertrophy and hyperplasia, intimal proliferation, and pulmonary vasoconstriction. In addition, there are changes in the extracellular matrix and adventitia with synthesis and deposition of collagen and elastin. The role of hemodynamics in the development of pulmonary vascular disease has been clearly demonstrated. Endothelial dysfunction occurs indeed before the onset of pulmonary hypertension or histological evidence of smooth muscle dysfunction.

Several studies have focused on the endothelial dysfunction induced by increased pulmonary blood flow, such as encountered in many congenital heart diseases cursing with increased pulmonary vascular resistance. Complex interactions between vasoactive substances produced by the vascular endothelium may in part explain the changes in pulmonary vascular tone. The cellular and molecular mechanisms underlying the pulmonary vascular remodeling in response to the mechanical stimulus of increased flow are however not completely understood. Shear stress has been shown to alter the production of vasoactive substances. Endothelial shear stress is directly proportional to blood flow velocity and is inversely proportional to the radius of the vessel. A high blood flow rate alters the mean shear stress and may directly damage the endothelial cell; this in turn may impair the balance between the vasoconstrictor/vasodilator effect and promitotic and antimitotic functions and lead to smooth muscle cell hypertrophy and proliferation. Cooper et al. [8] showed that, in healthy adults, normal basal pulmonary vascular tone is in part related to nitric oxide production. This basal nitric oxide production may be increased in response to receptor-mediated stimulation, leading to further vasodilatation. Nitric oxide dependence of basal pulmonary resistance has also been described in children. Thus, impairment of nitric oxide production, secondary to an injured endothelium, may contribute to the increased pulmonary vascular resistance as observed in infants and children with congenital heart disease. As a matter of fact, Celermajer et al. [9] demonstrated that in children with congenital heart disease and abnormal pulmonary hemodynamics, endothelium-dependent pulmonary artery relaxation is impaired and that this impairment may be one of the early events in the pathogenesis of pulmonary vascular disease.

Animal and human data strongly suggest that alterations in endothelin-1 (ET-1) metabolism, secondary to endothelial injury, also contribute to the development of pulmonary hypertensive disorders and their associated increased vascular reactivity [10, 11]. Lamb models with increased pulmonary blood flow secondary to experimentally created congenital heart disease also show alterations in the endothelin-1 cascade. At 4 weeks of age, these same lambs have increased plasma and lung tissue concentrations of endothelin-1 that is secondary to an upregulation of endothelin converting enzyme. In addition, there is loss of ET_B receptor-mediated pulmonary vasodilatation and augmented ET_A receptor-mediated vasoconstriction. This is associated with increased ET_A receptor gene expression and decreased ET_B receptor expression. Recent data have also demonstrated the emergence of ET_B receptor-mediated pulmonary vasoconstriction in these lambs at 8 weeks of age, suggesting a role for both ET_A and ET_B receptor-mediated effects in the pathophysiology of pulmonary hypertension. Finally, smooth muscle cells from this model suggest a hyperproliferative state and metabolic shift [12].

Several human studies demonstrate increased endothelin-1 concentrations in patients with pulmonary hypertension, including children with congenital heart disease and increased pulmonary blood flow. In addition, patients with advanced pulmonary hypertension have an increase in plasma endothelin-1 concentrations between the right ventricle and pulmonary veins and increased gene expression of endothelin-1 within pulmonary vascular endothelial cells, suggesting increased local production of endothelin-1 within the pulmonary circulation.

Prostacyclin and thromboxanes are also potential actors in the changes of pulmonary vascular tone as their balance may be impaired in patients with congenital heart disease. Thromboxane production is increased in idiopathic and associated forms of PH with decreased prostacyclin synthesis in most forms.

However, not all patients develop fixed pulmonary vascular disease or at least not within the same timing, and this may be related to a particular susceptibility to develop lesions or even the opposite, to be protected from these events. Currently some studies are devoted to assess if there is some genetic susceptibility. The publication of Levy et al. [13] suggested also the role of impaired endothelial cell apoptosis and inflammatory apoptosis in the pathogenesis of pulmonary vascular lesions.

The pulmonary vascular remodeling process is reversible in the early stages of the disease but may progress, with continuous stress, to smooth muscle cell proliferation in small arteries. As described herein, it provokes changes in the extracellular matrix and adventitia with synthesis and deposition of collagen and elastin; this progression renders the vessels relatively unresponsive to vasodilators and may preclude corrective surgery.

The age at which congenital heart lesions cause irreversible pulmonary vascular disease varies. The consequences of increased pulmonary blood flow are more severe in the immature than in the mature animal. Endothelial cell morphology is modified as early as 2 months after birth in children with increased pulmonary blood flow. The development of irreversible lesions is also associated with the type of heart defect, and it seems that a combination of high pressure and high flow causes a more rapid and more severe remodeling. Thus, *surgical correction should be performed early in life* in children with massive increase in pulmonary blood flow: before 2 years of age for ventricular septal defects and even earlier (<1 year or 6 months) for atrioventricular septal defects, transposition of the great arteries with ventricular septal defect, or truncus arteriosus. Currently most centers perform surgical repair in these lesions under 6 months of age.

Beside the age effect, as mentioned above, individual susceptibility based on different genetic polymorphisms plays a major role, and research is currently directed at to understand why two patients with the same malformation and hemodynamic profile will not develop pulmonary vascular disease at the same time.

42.3 Classification

Heath and Edwards describes progressive pulmonary vascular changes induced by pulmonary hypertension. Nevertheless, this classification has very poor clinical and hemodynamic correlations, particularly in the setting of acute pulmonary hypertension.

42.3.1 Heath and Edwards Classification

- Grade I: Hypertrophy of the media of small muscular arteries and arterioles.
- Grade II: Intimal cellular proliferation in addition to medial hypertrophy.
- Grade III: Advanced medial thickening with hypertrophy and hyperplasia including progressive intimal proliferation and concentric fibrosis. This results in obliteration of arterioles and small arteries.
- Grade IV: "Plexiform lesions" of the muscular pulmonary arteries and arterioles with a plexiform network of capillary-like channels within a dilated segment.
- Grade V: Complex plexiform, angiomatous and cavernous lesions, and hyalinization of intimal fibrosis.
- Grade VI: Necrotizing arteritis.

The term of *obstructive pulmonary vascular disease* relates to pathological changes described in grades III to VI.

Currently, there is an anatomo-pathological classification [14, 15], developed in 1998 at the World Symposium of Primary Pulmonary Hypertension in Evian, France, and later modified in Venice (2003) and Nice (2013). This World Health Organization (WHO) classification is based upon a combination of factors: pathological findings, clinical presentation, hemodynamic profile, and therapeutic strategies.

42.3.2 World Health Organization (WHO) Classification

- WHO Group I: Pulmonary arterial hypertension
- WHO Group II: Pulmonary arterial hypertension associated with left heart disease
- WHO Group III: Pulmonary arterial hypertension associated with lung disease and/or hypoxemia
- WHO Group IV: Pulmonary arterial hypertension secondary to chronic thromboembolic disease
- WHO Group V: Multifactorial pulmonary arterial hypertension

42.4 Postoperative Pulmonary Hypertension

42.4.1 Cardiopulmonary Bypass and Ischemia-Reperfusion Injury

Reperfusion of tissues exposed to ischemia can lead to a cascade of events that produce cellular dysfunction and necrosis. This phenomenon has been implicated in the pathogenesis of some complications encountered after cardiopulmonary bypass. Cardiopulmonary bypass is known to induce a generalized inflammatory response with the systemic release of proinflammatory cytokines, the activation of the complement system, and endothelial dysfunction. This phenomenon is thought to be triggered by the exposure of blood to nonphysiologic surfaces and the development of ischemia-reperfusion injury. Endothelial cell dysfunction is common after cardiopulmonary bypass and structural and functional damage to the pulmonary vascular endothelium has been demonstrated. During cardiopulmonary bypass, lungs are hypoxic and ischemic, as the pulmonary circulation is excluded to abolish pulmonary venous return. It was long postulated that the lung was resistant to ischemia because of its dual pulmonary and bronchial blood supply and its direct source of oxygen from the alveolar space. However, bronchial flow is estimated at 0.5% of the bypass flow, and indeed it has been demonstrated that pulmonary vascular endothelial cells undergo ischemia-reperfusion injury. This phenomenon further aggravates the inflammatory response and subsequent lung damage as shown by a decrease in pulmonary endothelium-dependent relaxation after cardiopulmonary bypass. Lung injury following cardiopulmonary bypass is well described. Clinically, it is manifested as reduced oxygenation, reduced lung compliance, and most importantly increased pulmonary vascular resistance and augmented pulmonary vascular reactivity. Injury to the pulmonary vascular endothelium is considered to be a major factor. In fact, patients with preexisting pulmonary vascular endothelial dysfunction are at greatest risk for developing clinically significant bypass-induced lung injury. Both animal and isolated organ models of ischemia-reperfusion confirm pulmonary vasoconstriction and increased pulmonary vascular resistance after reperfusion. Wessel et al**.** [16] in children and Morita et al. [17] in an animal models showed that this might be related to a decrease in nitric oxide production.

A decline in the output of nitric oxide from the vascular endothelium is due either to an enhanced inactivation of nitric oxide by free radicals (superoxide breakdown) produced in

postischemic tissues or a decrease in endogenous nitric oxide production or combination of both. It has also been suggested that nitric oxide is a physiologically relevant scavenger of free radicals and may be considered as an important cytoprotective modulator. Thus, nitric oxide may play an important role in mitigating the extent of ischemia-reperfusion injury. Moreover, its antiplatelet and leukocyte properties may be of major importance to prevent platelet aggregation and leukocyte sequestration during and after cardiopulmonary bypass. Two approaches may be adopted to overcome the decrease in nitric oxide availability: either to increase production through the administration of its precursor L-arginine or citrulline or to substitute with intravenous NO donors, or inhaled NO.

In several animal and human studies, plasma ET-1 concentrations are consistently increased during and following cardiopulmonary bypass. In a study of children with congenital heart disease, the plasma concentration of ET-1 3 hours after CPB correlated with the degree of post-CPB pulmonary hypertension, suggesting a role for ET-1 in the pathophysiology of cardiopulmonary bypass-induced pulmonary hypertension. In addition, several animal studies suggest that blockade of endothelin receptors attenuates post-CPB pulmonary hypertension and its associated altered reactivity. Thus, in lambs with preexisting pulmonary hypertension secondary to increased pulmonary blood flow, the increase in pulmonary vascular resistance following bypass was completely blocked in lambs pretreated with either dual or ET_A receptor antagonists. In addition, the augmented pulmonary vascular reactivity following bypass, which is responsible for the potentially life-threatening acute increases in pulmonary vascular resistance, was also completely blocked in those lambs pretreated with endothelin receptor antagonists. A recent study showed that ETA blockers might have a place in the therapeutic armamentarium**.**

In the particular situation of congenital heart surgery where preoperative endothelial dysfunction exists in many instances, further injury to the pulmonary endothelium due to ischemia-reperfusion may explain the increased pulmonary vascular resistances occurring in some patients postoperatively.

The pathophysiological events described above give a strong rational to support the use of the therapies discussed hereafter.

42.5 Diagnosis

42.5.1 Clinical

Clinical diagnosis is facilitated by the use of indwelling catheters allowing to continuously monitor pulmonary pressures and/or left atrial pressures. As the pulmonary pressures increase, patients may display signs of increased right preload and right cardiac failure, concomitantly with signs of abruptly decreased left preload with low systemic cardiac output. This may be aggravated by compression of the left ventricle by the right ventricle, once the latter develops iso- or supra-systemic pressure levels. At this point, there may also appear signs of ischemia by reduction of right coronary flow, and patients may desaturate due to the appearance of right-to-left intracardiac shunts. Patients may also have arrhythmias, persistent hypoxia, or metabolic acidosis that may be an alert sign particularly in the absence of indwelling catheters, prompting caregivers to closely evaluate hemodynamics and to rule out pulmonary hypertensive spells.

42.5.2 Chest X-Ray

Chest X-rays are unspecific for the diagnosis of acute pulmonary hypertensive spells although there can appear signs of hypovascularization. Yet, this technique remains a useful tool to rule out triggering factors like volume overload and the presence of intrathoracic comorbidities like atelectasis, pneumothorax, or pleural effusions.

42.5.3 ECG

ECG may be useful in patients who develop secondary arrhythmias or ischemic changes throughout a pulmonary hypertensive crisis.

42.5.4 Echocardiography

Echocardiography undoubtedly remains the cornerstone technique to rapidly assess pulmonary hypertension and its impact on cardiac function in the intensive care setting [18], mostly in patients who do not have indwelling catheters. It is imperative though to be able to estimate right pressures by tricuspid regurgitation, although the interventricular septal geometry (Figs. 42.1, 42.2, 42.3, and 42.4) may be suggestive of the degree of right ventricular pressure regime, hence pulmonary hypertension, unless there is a right outflow tract obstruction or peripheral pulmonary branch stenosis. Also, the presence of pulmonary regurgitation may allow a more comprehensive estimation of pulmonary diastolic and mean pressures. In patients with residual interventricular shunts, echocardiography may document the systolic pressure gradient between the ventricles and therefore provide a reasonable estimation of the right systolic pressures and their trends. In patients with pulmonary hypertensive spells, echocardiography is instrumental in assessing right and left ventricular function, the degree of intracardiac shunting if any, and also the presence of residual lesions that might be at the origin of the spells. Last but not least, it allows follow-up of therapeutic efficiency.

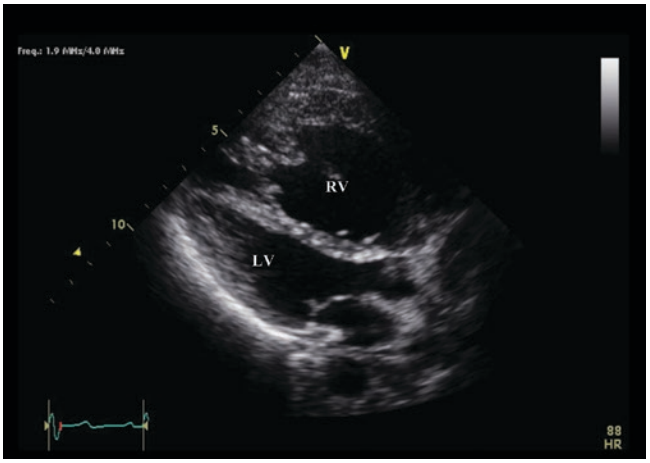

Fig. 42.1 Echocardiography documenting severe PAH with right-to-left shift of the interventricular septum in a long-axis view (LV left ventricle, RV right ventricle)

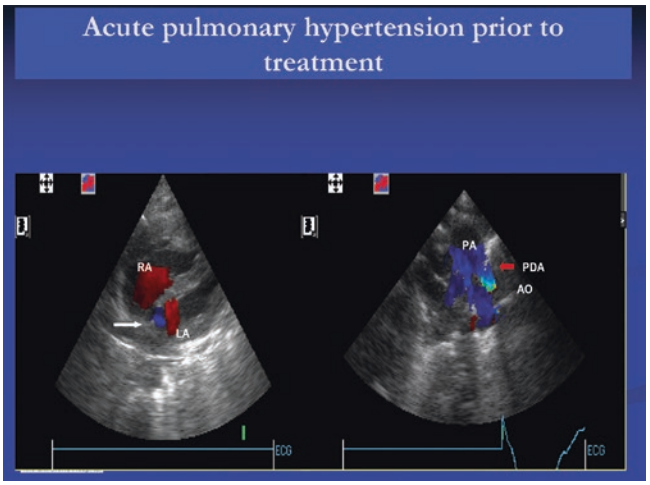

Fig. 42.3 Echocardiography showing severe pulmonary hypertension with a right-to-left shift through the foramen ovale (white arrow) and the ductus arteriosus (red arrow), prior to treatment

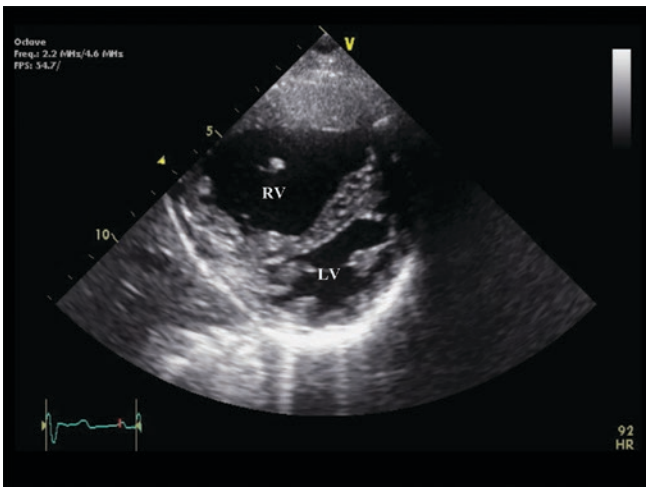

Fig. 42.2 Echocardiography documenting severe PAH with right-to-left shift of the interventricular septum in a short-axis view (LV left ventricle, RV right ventricle)

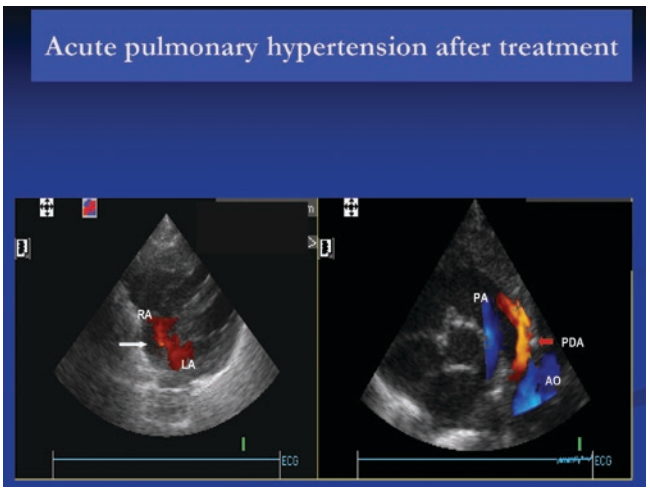

Fig. 42.4 Echocardiography showing significant improvement of pulmonary hypertension after treatment with iNO, with a left-to-right shunt through the foramen ovale (white arrow) and the ductus arteriosus (red arrow)

42.6 Management of Pulmonary Hypertension After Cardiac Surgery

Probably the most important measures with these patients concern the *prevention* of pulmonary hypertensive crisis. Potentially malignant pulmonary hypertension spells are usually iso- or supra-systemic and may induce low cardiac output, hypoxia, acidosis, or cardiac arrhythmias. Sudden pulmonary hypertensive crises may punctuate the postoperative course despite accurate and effective surgery and are associated with significant mortality and morbidity. Even though it has been thought that this may become a relatively unimportant problem because of the recent progresses in cardiac surgery, it seems that increased pulmonary vascular resistance after surgery remains a significant problem [19–22]. Potential therapeutic strategies for the treatment of acute pulmonary hypertension after cardiac surgery are summarized in Table 42.1 and will be discussed hereafter.

Clinical tolerance and progression in patients with pulmonary hypertensive spells depend on a number of factors among which the characteristics of the right ventricle are determinant. More often than not, pulmonary hypertensive spells peak during the postoperative inflammatory phase through the first 48–72 hours in the cardiac intensive care environment. Patients with refractoriness to conventional therapy or with recurrent spells may develop severe right ventricular dysfunction that complicates the therapeutic equation. Right ventricular failure is complex and

Table 42.1 Summary of therapeutic strategies in acute pulmonary

Encourage	Avoid
Anatomic investigations	Residual anatomic defects
Creation of a right-to-left shunt as a "pop-off"	Intact atrial septum in the setting of overt right ventricular failure
Sedation, analgesia, or anesthesia	Agitation and pain
Moderate hyperventilation	Respiratory acidosis
Moderate alkalosis	Metabolic acidosis
Balanced metabolic status	Volume overload
Adequate inspired oxygen	Alveolar hypoxia
Normal lung volumes	Atelectasis or overdistension
Normal hematocrit	Excessive hematocrit
Ino-lusitropic support	Low cardiac output and low coronary perfusion
Vasodilators	Pulmonary vasoconstriction
Nutritional support	Right ventricular increased afterload

Modified from Wessel [55]

multifactorial, and the main aspects to target concern the reduction of right ventricular afterload and judicious management of fluids. In such context, therapy has to ally management of pulmonary vascular resistances with consideration about decompressing the right-sided circulation (i.e., by creating an atrial pop-off) and any other pathophysiological condition that increases strain on the target organs by increase of their afterload due to high right filling pressures. The latter includes proactive relief of intra-abdominal pressure in case of ascites (insertion of a peritoneal catheter) that often causes a "tamponade effect" on the kidneys and insertion of pleural drains to evacuate effusions in the pleural cavities.

The primary therapeutic goal-oriented interventions in the management of acute pulmonary hypertension spells prioritize on the decrease of pulmonary vascular resistances and pressures. Along these lines, it is essential to avoid triggering pulmonary vascular reactiveness and to support the right ventricular function as described above. Maintaining a physiological balance between pulmonary and systemic vascular resistances and warranting an effective cardiac output and tissue perfusion are key objectives. Maintenance of systemic blood pressure is important to promote coronary flow and prevent or diminish interventricular septal shift.

General measures to promote an anabolic status (i.e., early enteral or parenteral nutrition, reducing oxygen consumption, reducing stress response) should be undertaken as soon as possible after surgery.

42.6.1 Preventive Measures

Preventing the pulmonary hypertensive spells is of vital nature as these may be life-threatening in spite of sophisticated interventions. The following is a list of some of the main aspects to consider, pre-, peri-, and postoperatively:

1. Timely surgical indication
2. Minimization of perioperative risks:
   (a) Adequate CPBP conditions
   (b) Surgical technique
   (c) Myocardial protection
   (d) Use of ultrafiltration
   (e) Use of systemic prophylactic steroids?
   (f) Controlled reoxygenation
   (g) Leucocyte depletion?
3. Rectification of all identified "anti-physiological" conditions
4. Ensuring an adequate metabolic and acid-base balance
5. Anticipating, avoiding, and treating the following triggers:
   (a) Fever
   (b) Hypothermia
   (c) Anemia
   (d) Acidosis
   (e) Dehydration
   (f) Volume overload
   (g) Hypoxia
   (h) Hypercapnia
   (i) Sepsis
   (j) Pain, agitation, and delirium

42.6.2 Therapeutic Measures

Therapy should be individualized, but there are standardized aspects to consider regarding analgesia and sedation, ventilation, intravenous and inhaled drugs, and the protection of the right ventricle.

42.6.2.1 Anatomic Considerations

First of all, residual anatomical problems should be systematically excluded as these may be responsible for increased right ventricular pressure as in the case of residual shunts or right ventricular outflow tract obstructions. Thus, anatomic investigations should be exhaustively performed such as transthoracic or transesophageal echocardiography or catheterization, particularly if a potential intervention is anticipated. Anatomic considerations are also important when evaluating the need to support systemic cardiac output through a right-to-left shunt used as a "pop-off" for the right side. Creating or preserving a calibrated atrial septal defect is a common intervention in patients with severe right ventricular failure. Some teams advocate the preemptive use of a valve patch when a ventricular septal defect is closed ("flap" fenestration of the VSD patch). This may be beneficial to maintain cardiac output but to the detriment of cyanosis. Delayed chest closure may be useful to decrease the constrictive effect on a dilated dysfunctional right ventricle.

42.6.2.2 Sedation and Analgesia

Agitation and stress are potential triggers for pulmonary hypertensive crisis and should be avoided. Well-controlled analgesia and sedation should be guaranteed while ensuring spontaneous breathing in stable patients who would be candidates for extubation. However, unstable patients with frequent or poorly tolerated pulmonary hypertensive spells should be kept deeply sedated and eventually on muscle relaxants as required. Adequate sedation and analgesia is usually achieved with a combination of opioids and benzodiazepines administered as continuous infusions and titrated to minimal efficient doses. Fentanyl is a better indication than morphine for this specific group of patients. Other alternatives are available and depend on specific institutional protocols: dexmedetomidine, propofol, clonidine to mention some. Patients who require more prolonged sedation and analgesia may need the implementation of protocols to reduce the risks of withdrawal syndrome and delirium.

42.6.2.3 Ventilation and pH

It is essential to adequately ventilate these patients and to avoid over distention or atelectasis, known to be potential triggers for increased pulmonary vascular resistance. It is important to remember that pulmonary vascular resistance is normal at normal functional residual capacity. Cardiopulmonary interactions are of utmost importance. Positive airway pressures may be detrimental to the preload and also increase the right-sided afterload to which the right ventricle is exquisitely sensitive. In the presence of lung disease requiring positive pressure invasive or noninvasive ventilation, these cardiopulmonary interactions ought to be kept into consideration at all times.

Minimal airway manipulation and suctioning is recommended in labile patients, and if so needed, it should be offered under deep sedation and in the presence of an interdisciplinary team competent to effectively manage abrupt raises in pulmonary resistances.

Alkalosis induces pulmonary vasodilatation whereas acidosis induces vasoconstriction. It is known after the work of Chang et al. [23] that the triggers for pulmonary hypertensive spells are mainly the pH (hydrogen ion concentration) rather than the carbon dioxide levels. The current approach is to maintain a normal or slightly alkalotic pH (as to avoid aggressive ventilation) and only in rare instances to raise pH over 7.5. Morris et al. [24] showed that hyperventilation to increase pH has some deleterious effects such as an increase in systemic vascular resistance that may not be warranted in the postoperative period. Use of sodium bicarbonate or THAM may be considered in some patients in order to induce alkalosis without the potential deleterious effects of hyperventilation. In patients considered as susceptible of developing pulmonary hypertensive spells while being deventilated or with significant pulmonary vascular reactivity, permissive hypercapnia leading to mild respiratory acidosis is a potentially useful test to assess feasibility of safe extubation. Airway extubation should be encouraged as soon as pulmonary reactivity is controlled and stable, even if pulmonary pressures are not strictly normal.

42.6.2.4 Oxygenation

It is well-known that hyperoxia provokes pulmonary vasodilatation and that hypoxia induces pulmonary vasoconstriction. It is therefore important to maintain an adequate oxygenation (PO_2 around 80–100 mm Hg) in the presence of pulmonary hypertensive crisis and with patients at risk. This is obtained with the administration of oxygen and adequate ventilation ensuring a proper lung volume. However, the effect of oxygen seems not so clear in the setting of pulmonary hypertension after cardiac surgery as well as in the so-called fixed lesions. Caregivers must also remember that high levels of inspired oxygen may be deleterious and induce lung damage. Last but not least, tolerance is required with regard to the degree of desaturation in patients with an atrial and/or ventricular pop-off; indeed, such patients can be significantly desaturated but hemodynamically stable and with adequate tissue perfusion markers in which case further attempts to raise saturation levels is futile and may even be deleterious. It is expected in patients with this physiology that as the pulmonary vascular resistances and the right ventricular compliance improve, the degree of right-to-left shunting decreases and even reverts to left-to-right shunting.

42.6.2.5 Pulmonary Vasodilator Drugs

Intravenous and/or inhaled pulmonary vasodilator drugs are the cornerstone of therapy for pulmonary hypertension. Various intravenous vasodilators such as tolazoline, prostacyclin, phenoxybenzamine, phentolamine, and nitrodilators have been used to reduce pulmonary arterial pressure. However, their lack of selectivity and inconsistent efficacy are a limiting factor; these drugs carry a risk of systemic hypotension among others, which may be undesirable after cardiac surgery. In this setting, there is a particular appeal in the therapeutic opportunities offered by agents acting through a selective effect on the pulmonary vascular bed such as inhaled nitric oxide or inhaled prostacyclin.

Inhaled nitric oxide (iNO) improves right ventricular systolic function by decreasing its afterload while increasing left ventricular preload, reducing the "tamponade" effect and restoring systemic stroke volume, pressure and coronary perfusion [25–31]. In patients with poor left ventricular function, iNO should be used very cautiously since the preload increase may be deleterious.

Wessel et al. [28] showed that pulmonary endothelial dysfunction was present after cardiopulmonary bypass; thus, the response to acetylcholine was attenuated, but the response to

inhaled nitric oxide was maintained. These authors hypothesized that a dysfunctional endothelium with reduced endogenous nitric oxide release may contribute to postoperative pulmonary hypertension. Journois and collaborators [29, 30] demonstrated that inhaled nitric oxide was a useful therapy for pulmonary hypertensive crises refractory to conventional treatment. According to Miller et al. [31, 32], even low doses of nitric oxide (2 ppm) appear to be effective in such patients. Beghetti et al. [33, 34] showed that the effect of low-dose nitric oxide was maintained over several days at concentrations carrying little risks of toxicity. Nitric oxide has been used with success in several different congenital heart defects where increased pulmonary vascular resistance may complicate the postoperative course such as mitral valve stenosis, total anomalous pulmonary venous return, bidirectional Glenn anastomosis, and the Fontan circulation. It is also useful and frequently used after cardiac and/or lung transplant. However, a beneficial effect in patients with cavopulmonary anastomosis is not consistently reported and this is despite an increase in cGMP levels [35] which is proof of effective delivery.

Inhaled nitric oxide improves right ventricular function after left ventricular assist device implantation, perhaps through an increase in pulmonary venous return and left atrial pressure, thus facilitating pump flow.

Patients who remain dependent on nitric oxide and have rebound pulmonary hypertension upon weaning are candidates to therapy with sildenafil as a bridging strategy to suspend the NO [36, 37].

Inhaled prostacyclin is increasingly used as delivered by aerosol and may overcome the necessity of a special device to deliver NO. Several series have been published with epoprostenol or iloprost [37–41], but one of the major problems is to define the dose to be delivered as well as the exact dose delivered when the drug is administered in ventilated patients.

Intravenous adenosine has been reported in neonates, particularly with low weight, but the drug has not been studied on a large scale [42].

When the use of combined vasodilators is not effective or is sub-optimal, it is appealing to try to counteract vasoconstriction and endothelin is a logical target. Animal and preliminary human studies are encouraging, and several research protocols are currently under use with selective or nonselective endothelin receptor antagonists, with the most studied being bosentan. These onerous drugs have relatively significant limitations in the setting of acute hypertensive spells as their effect is not immediate, added to a number of adverse effects.

New strategies aiming at protection during cardiopulmonary bypass are being currently studied and may offer new therapeutic approaches in the field of prevention of endothelial lesions. Other potential developments relate to stem-cell therapy, tyrosine kinase inhibitors, myosin activators, Na/K--ATPase inhibitors, adenosine/vasopressin antagonists, micro-RNA modulators, and "gender-customized" therapy.

42.6.2.6 Inotropic and Vasoactive Drugs

After surgical correction of patients with preoperative pulmonary hypertension or at significant risk for postoperative pulmonary hypertensive spells, the classical drug combination includes milrinone [43–48] and a low dose of dopamine, eventually associated with low doses of epinephrine. As previously described, right ventricular function may be compromised for multiple reasons including cardiopulmonary bypass and direct injury by the surgical procedure itself. Increased pulmonary vascular resistances further compromise right ventricular function; as a result, the right ventricle becomes dilated and induces an "intrapericardial tamponade" effect of the left ventricle. This in turn results in secondary diastolic dysfunction of the left ventricle which further reduces cardiac output leading to systemic hypotension and coronary hypoperfusion of the right ventricle. The effect of the usual inotropes such as epinephrine on the right ventricle as well as the potential deleterious effect on the pulmonary vascular resistance is still a matter of debate. It is also known that some therapies may not have the same effects on the systemic or the pulmonary circulation. It is anyway tempting and justified to use catecholamines in this setting trying to find a balance between the potential beneficial and the detrimental effects, namely, with regard to the myocardial oxygen consumption. Epinephrine can improve global cardiac function but is known to be deleterious to the myocardium if used at high doses and for a prolonged period of time. However, it may still have a place at low doses. Norepinephrine through an increase in systemic vascular resistances may improve coronary perfusion and as such improve right ventricular function. The virtues of the drug should be balanced against its side effects. The theoretical perfect drug to treat pulmonary hypertensive spells and right ventricular failure should improve myocardial performance and vasodilate the pulmonary vascular bed without inducing tachycardia and oxygen consumption. Milrinone is a phosphodiesterase inhibitor that has some of these properties, and it is key in postoperative care, but caution against hypotension should be considered. The role of type 5 phosphodiesterase inhibitors in the presence of pulmonary hypertension has a major interest, but type 3 inhibitors such as milrinone have been by far more studied and largely used in pediatric practice.

Some new therapies are under development. Nesiritide or natriuretic hormone shows some synergistic effect with nitric oxide and sildenafil, but so far data remains scarce in this population and further studies are required. The same applies to levosimendan, a calcium sensitizer that enhances contractility and has some vasodilatory properties without increasing myocardial oxygen consumption. It has also been shown to have some pulmonary vasodilator effects in the presence of acute pulmonary hypertension, but thus far data in children is scarce and further studies are also needed.

42.6.2.7 Intracardiac Shunt Creation

Unless the cardiovascular surgeon opts to leave an atrial and/or ventricular level shunt as a potential way to decompress severe right ventricular pressures, some patients with right ventricular failure refractory to medical therapy will benefit from the creation of a calibrated atrial communication in the catheterization laboratory. This pop-off, albeit allowing significant cyanosis by right-to-left shunt, may be lifesaving.

42.6.2.8 Extracorporeal Life Support

Patients with pulmonary hypertension and with acute decompensation or with pulmonary hypertensive spells may have severe right ventricular failure with a dismal prognosis [49, 50]. Three main indications for ECLS ought to be mentioned in patients who fail to respond to conventional therapy:

1. PAH refractory to targeted medical therapy
2. PAH with cardiogenic shock and intolerance to pulmonary vasodilators
3. E-CPR

In this context, the goal is to provide a therapeutic window to optimize pulmonary hypertension medications and right ventricular function as a bridge to recovery or as a bridge to transplant [51]. ECLS may address key mechanisms of the pulmonary hypertension decompensation, reduce the right ventricular pre- and afterload, provide pump function, reduce tricuspid valve regurgitation, and improve left ventricular filling and function. There is a very large variability of practice and no consistent criteria to initiate support are available. The main available support alternatives concern venoarterial ECMO [52, 53] and pumpless para-corporeal membranes that have seldom been utilized in the pediatric population [49, 54].

In patients at high risk of severe pulmonary hypertension spells, it is vital to preemptively discuss limitations of intervention and criteria for discontinuation of cardiovascular assistance prior to proceeding with surgery.

42.7 Conclusion

Management of acute pulmonary hypertension in the cardiac intensive care setting should be multifactorial and multidisciplinary as it remains challenging and still carries, even if decreased compared to the previous decade, a significant mortality and morbidity. An increased knowledge of the mechanisms as well as the introduction of new therapies has led to better prognosis. Appropriate and goal-oriented therapy requires the identification and rectification of the potential causes and a thorough evaluation of the patient's pathophysiology. Beside the pharmacological approach, caregivers should consider the creation of anatomic paths to decompress the right ventricle, as the final cause of death remains right ventricular failure.

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Chapter 43
Chronic Pulmonary Hypertension

Benjamin S. Frank, Asrar Rashid, and Dunbar Ivy

Abstract This chapter discusses the anatomical and physiological basis for chronic pulmonary arterial hypertension and its diagnosis and management. Pulmonary arterial hypertension (PAH) can lead to significant cardiac dysfunction and is associated with an increased risk of perioperative cardiovascular complications. The selection of appropriate therapies is complex, requiring familiarity with the underlying disease process, complicated delivery systems, dosing regimens, and medication complications. Recent therapeutic and surgical advances in the management of PAH have led to an improvement in prognosis.

43.1 Definition and Classification

Prior to 2018, pulmonary hypertension (PH) was defined as a mean pulmonary artery pressure greater than 25 mmHg. Pulmonary arterial hypertension (PAH), a subset of PH, was defined in children the same as in adults: mean pulmonary arterial pressure (PAP) greater than 25 mmHg at rest, with a pulmonary capillary wedge pressure less than 15 mmHg and an increased pulmonary vascular resistance (greater than 3 Woods units × M^2) [3]. At the 6th World Symposium on Pulmonary Hypertension in 2018, the definition was changed to include patients with mean pulmonary artery pressure greater than 20 mmHg at rest for both children and adults [192]. As a reference for more detailed criteria, the Nice classification can be reasonably applied to both adults and children [4]. A pediatric-specific classification and functional class system was developed at the Panama PVRI meeting [5, 6]. In younger children, for whom a normal systemic blood pressure is lower than for older children or adults, the ratio of pulmonary artery mean pressure to systemic artery mean pressure can further describe the severity of PAH, with a significant elevation being greater than 0.5. PH by the World Symposium on Pulmonary Hypertension (WSPH) is grouped into 5 categories: PAH, Left Heart Disease, Lung Diseases and / or Hypoxia, Chronic Thromboembolic Pulmonary Hypertension, and Pulmonary hypertension with unclear or multifactorial mechanisms (Table 43.1) [4].

43.2 Pathology and Pathophysiology

In the normal pulmonary circulation, pressure and resistance are 80–90% lower than in the systemic circulation. Pulmonary arteries larger than 1 mm in internal diameter are elastic and have well-developed internal and external laminae within a less distinct medial layer than systemic arteries. Distal to the respiratory bronchioles and smaller than 1 mm, the arterial smooth muscle layer is reduced, and the arteries are only partially muscularized or nonmuscularized. Vascular tone is normally very low.

PAH is a progressive disease characterized by lumen-obstructing structural remodeling within the small arteries of the pulmonary bed [7], leading to a rise in pulmonary vascular resistance, elevated pulmonary arterial pressure (PAP), and eventually to right ventricular failure [8]. Some

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Table 43.1 WSPH classification of pulmonary hypertension (Venice, 2003)

1. Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2
1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
10 Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
10 0. Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Simonneau et al. [4]

of the cellular changes that have been implicated as causative in the chronic vascular remodeling of PAH are detailed in Fig. 43.1 [2]. It has been suggested that muscularization of the terminal pulmonary arterial vascular tree, caused by vascular smooth muscle cell hyperplasia, is the earliest change [9]. In later stages of PAH, the pulmonary arteries are characterized by intimal fibrosis, medial hypertrophy, adventitial proliferation, and obliteration of small arteries. Early in the disease, plexogenic arteriopathy is seen with lesions expressing markers found on both endothelial cells and smooth muscle cells (Fig. 43.2). Other mechanisms, including activation of endogenous vascular elastase [7], inflammation [10], and altered BMPR2 signaling, are known to frequently play a role as well [11, 12]. The abnormal pulmonary vascular resistance (PVR) in affected patients may be further elevated by sustained pulmonary vascular vasoconstriction [13]. The mechanisms involved include endothelial dysfunction, vascular smooth muscle (VSMC) hyperconstriction, apoptosis resistance, and inflammation [7, 13].

The pathobiological progression of PAH depends significantly on the chronicity of the illness. Acute PAH leads to an immediate increase in right ventricular afterload, which causes elevated end-diastolic volume and decreased RV ejection fraction, leading to acute ventricular failure. Chronic elevation in RV afterload causes progressive right ventricular dilation, remodeling, and fibrosis, putting patient at risk for arrhythmias and progressive ventricular failure (Fig. 43.3).

In chronic PAH, worsening of pulsatile ventricular-vascular coupling can further precipitate disease progression. Changes in pulmonary artery wall structure lead to increased vessel stiffness that can amplify the role of pulsatile coupling on afterload, placing additional stress on the RV. The effects on RV afterload from vascular resistance and vascular stiffness are additive, thereby accelerating ventricular failure in this population. Pulmonary vascular resistance (PVR) is the current standard for evaluating reactivity in children with PAH. However, PVR measures only the mean component of right ventricular afterload and neglects pulsatile effects. Total right ventricular afterload can be measured as pulmonary vascular input impedance and consists of a dynamic component (compliance / stiffness) and a static component (resistance). In the normal pulmonary circulation, resistance contributes 90% of total RV afterload, whereas in significant PAH, 30% of RV afterload may be contributed by compliance and 70% by resistance. Increases in PVR and decreases in compliance of the larger pulmonary arteries will increase right ventricular afterload, and can lead to right ventricular dysfunction [14]. The development of chronic PAH has differing implications (Fig. 43.3) [15].

Patients with PAH are prone to pulmonary hypertensive crisis, a potentially fatal complication. PH crises are characterized by a rapid increase in PVR, often to levels higher than systemic vascular resistance, and acute right ventricular failure. Hypercarbia, hypoxemia, acidosis, and noxious stimuli such as pain and airway instrumentation can trigger a pulmonary hypertensive crisis. The resulting decreased cardiac output from the right heart leads to a decrease in pulmonary blood flow, decreased systemic cardiac output, decreased tissue oxygen delivery, and ultimately to biventricular failure.

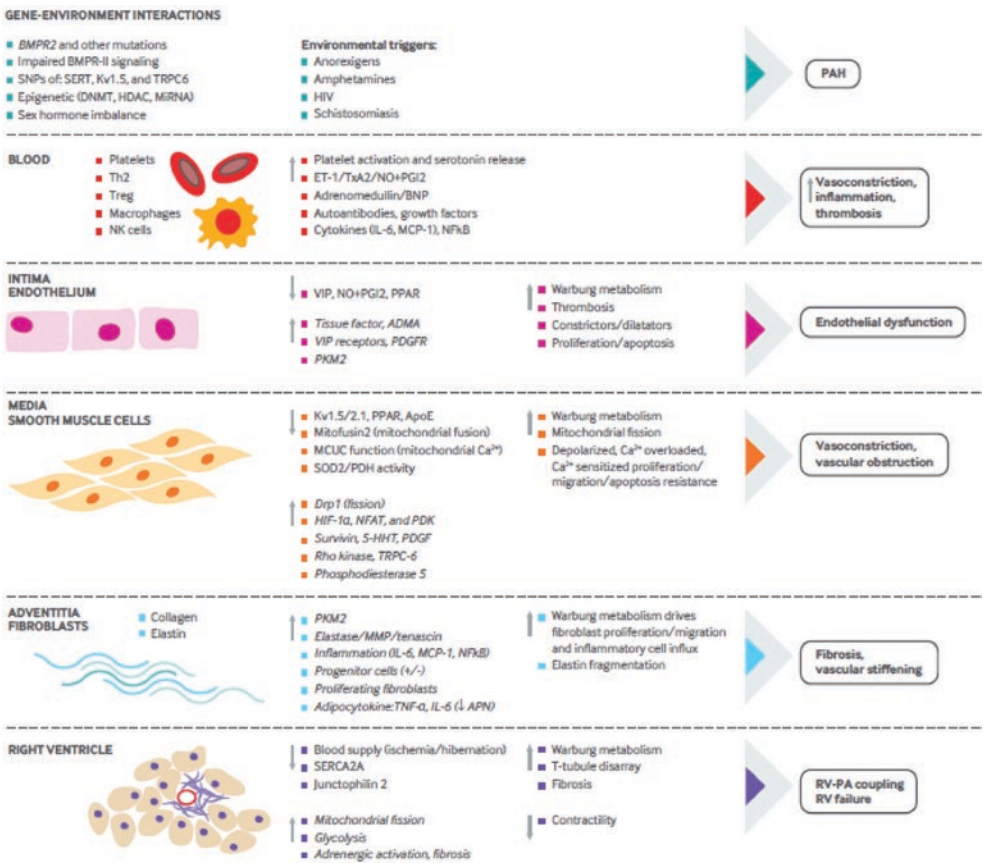
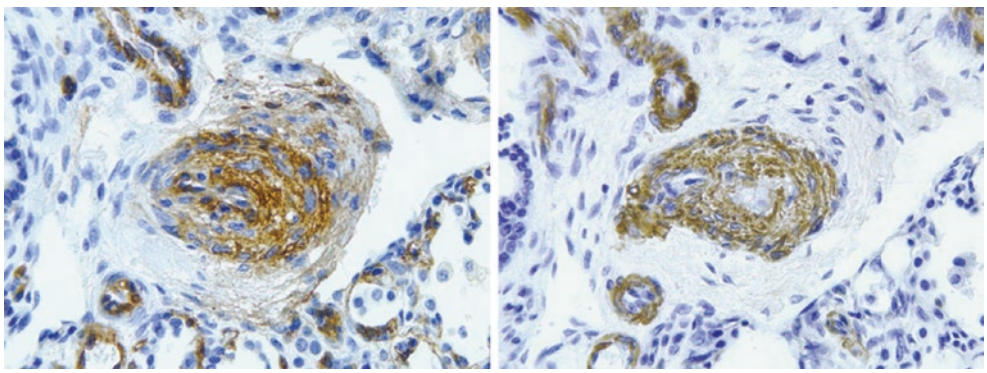


Fig. 43.1 Mechanisms leading to the development of pulmonary arterial hypertension (Thenappan et al. [2])



Factor VIII SMA

Fig. 43.2 Proliferation of PA cells expressing endothelial and smooth muscle markers in PAH

43.3 Clinical Presentation

Diagnosis of chronic PAH is often delayed due to the subtle nature of the symptoms. Symptoms include exertional dyspnea, fatigue, chest pain, and syncope. In infants, symptoms are even less specific and may involve poor appetite, failure to thrive, lethargy, diaphoresis, tachypnea, tachycardia, and irritability [16, 17].

Evaluation See Table 43.2 and Fig. 43.4 for details.

43.4 Chest Radiography

The enlargement of the central pulmonary artery and/or right ventricle on chest radiography suggests the presence of PAH. Prominence of the main pulmonary arteries is apparent in 90% of patients with IPAH, and peripheral pruning of the vessels occurs in approximately 50%. Yet, 6% of patients with confirmed IPAH may also present with normal radiographs [18]. The accuracy of the chest radiography in the detection of PAH is uncertain, and no correlation has

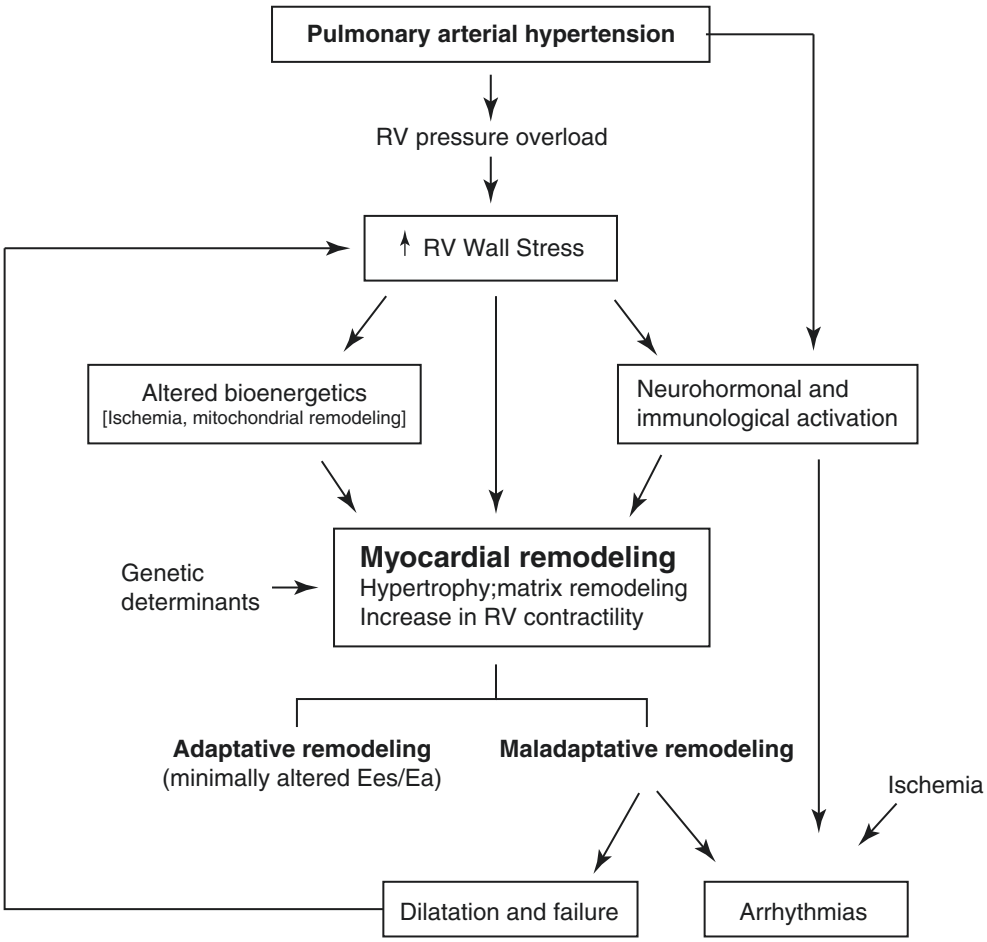


Fig. 43.3 Pathophysiology of chronic PAH. (Vonk-Noordegraaf et al. [15])

Table 43.2 Pulmonary hypertension evaluation

PAH detection	
Chest radiography	Cardiomegaly and enlarged pulmonary arteries
Electrocardiography	Right ventricular hypertrophy
Echocardiography	Right ventricular hypertrophy, quantify right ventricular systolic pressure/function Exclude left heart or congenital heart disease
PAH characterization	
Cardiac catheterization with acute vasodilator testing	Evaluate pulmonary artery pressure, resistance, and degree of pulmonary reactivity
Anemia	Complete blood count with platelet count
Hypothyroid/hyperthyroid	Thyroid function tests
Hypercoagulable evaluation	Disseminated intravascular coagulation screen Antithrombin III Protein C Protein S Lupus anticoagulant Factor V Leiden Prothrombin gene mutation 20,210 Antiphospholipid antibody evaluation
Autoimmune disease evaluation	Antinuclear antibodies (DNA, Smith, ribonucleoprotein, SSA, SSB, anticentromere antibody, anti-SCL70) Rheumatoid factor Complement Erythrocyte sedimentation rate
Human immunodeficiency virus	HIV test
Toxicology screen	Amphetamines, cocaine, meta-amphetamines, fenfluramine, and phenylpropanolamine

Table 43.2 (continued)

Liver evaluation	Abdominal ultrasonography Liver function tests with gamma glutaryl transferase Hepatitis profile
Lung evaluation	Pulmonary function tests (to exclude obstructive/restrictive lung disease) Ventilation-perfusion (V/Q) lung scintigraphy (exclude thromboembolism) Pulmonary wedge angiography High resolution computed tomography (to evaluate for interstitial lung disease) Pulse oximetry/polysomnography (to evaluate hypoxia, diminished ventilatory drive, sleep-related breathing disorders) Lung biopsy
Exercise capacity	6-minute walk test/treadmill exercise test
Genetic testing	Cardiopulmonary exercise testing

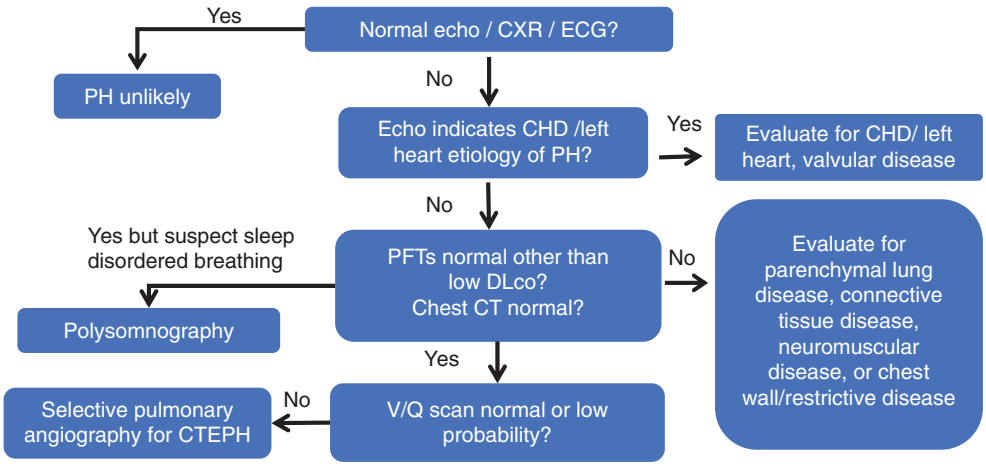


Fig. 43.4 Evaluation of PH. (Adapted from: Ivy et al. [1])

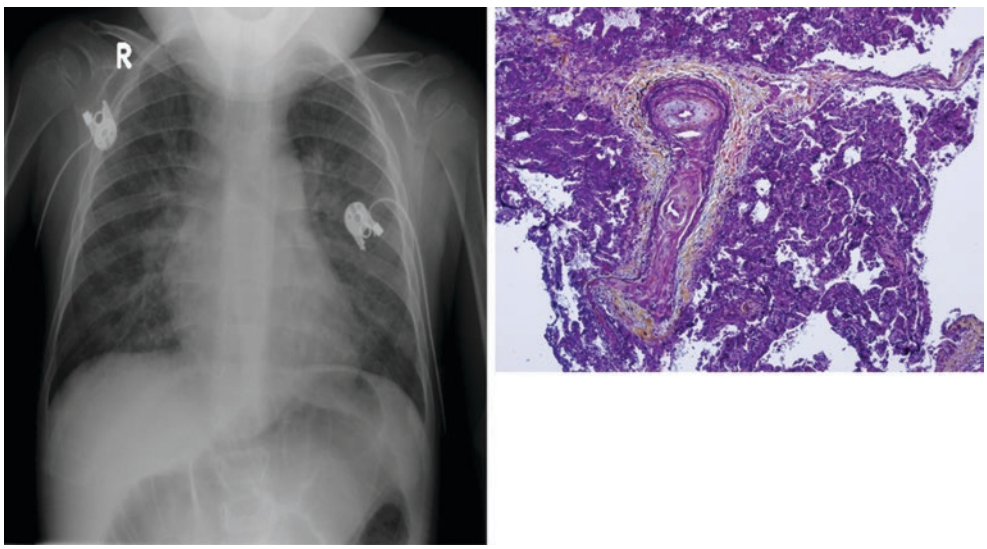


Fig. 43.5 Pulmonary veno-occlusive disease

been established between the extent of the radiograph abnormalities and the severity of PAH.

Chest radiography findings may be useful to uncover secondary causes of pulmonary hypertension. Pulmonary venous congestion may suggest pulmonary veno-occlusive disease (Fig. 43.5) or pulmonary capillary hemangiomatosis; hyperinflation or kyphosis is the sign of restrictive lung disease; asymmetry of the enlarged central pulmonary arteries may warrant investigation of chronic thromboembolic disease or porto-pulmonary hypertension. Asymmetric lung volumes may suggest either pulmonary arterial or pulmonary venous abnormalities. For example, a unilateral small lung may be seen in unilateral "absence" of a pulmonary artery, scimitar syndrome, or congenital diaphragmatic hernia [19].

43.5 Electrocardiography

Electrocardiography (ECG) typically shows right ventricular hypertrophy and right atrial enlargement and, in clinical practice, is often the first test obtained suggesting PAH**.** Evidence of right ventricular hypertrophy on ECG is present in 87% of patients with IPAH and right axis deviation in 79%. ECG parameters reflective of physiologic and anatomic abnormalities in the right atria and right ventricle (a large P-wave amplitude >/ 0.25 mV) in lead II, QR complex in lead V1, or V3R is indicative of right ventricular hypertrophy regardless of voltage. An upright T-wave in V1 is indicative of right ventricular hypertrophy from 7 days to 7 years. However, some studies have suggested that the specificity (69%) and positive predictive value (67%) of ECG is low in children with an echocardiographic diagnosis of PH [20]. However, these authors believe that sensitivity is much higher, especially in combination with a complete physical examination.

43.6 Echocardiography

Echocardiography is the most useful noninvasive screening tool to evaluate patients with a clinical suspicion of PAH. The echocardiogram documents right ventricular size and function, left ventricular systolic and diastolic function, morphology and function of valves, and the presence of pericardial effusion or a patent foramen ovale. An acceleration time to ejection time ratio less than 0.3 suggests the presence, but not the degree, of pulmonary hypertension, especially at higher pressure [21, 22]. Transthoracic Doppler echocardiography can provide an estimate of the systolic pulmonary arterial pressures (sPAP). In the absence of pulmonary outflow obstruction, sPAP is equivalent to the right ventricular systolic pressure (RVSP). The systolic regurgitant tricuspid flow velocity (V) is measured and the right atrial pressure (RAP) is either a standardized value or an estimated value from the flow characteristics of the inferior vena cava or from jugular venous distention [21]. Doppler interrogation of tricuspid valve insufficiency velocity can be used noninvasively to estimate the right ventricular systolic pressure. Pulmonary valve insufficiency is also frequently seen, and characteristics of the pulmonic regurgitant flow velocity can be used to estimate the pulmonary artery diastolic and mean pressures [23].

Although challenging due to the geometry of the right ventricle, a qualitative assessment of RV function is also important. Several measures are available to attempt to quantify the degree of RV dysfunction including the Tei index, (myocardial performance index), RV ejection fraction, RV fractional area change, and the tricuspid annular plane systolic excursion (TAPSE). Normal values for TAPSE in children have recently been published and should serve as a reference for children with PAH [24]. A recent study additionally suggested that 3-dimensional echocardiography may improve assessment of RV function compared to 2-dimensional echocardiography alone [25, 26].

Recent data have additionally identified echocardiographic markers that can be used to track disease severity and, in some cases, predict clinical outcomes [27]. The ratio of right ventricle to left ventricle size at end systole is a strong predictor of outcome (Fig. 43.6) [28]. An increasing RV/LV systolic ratio is associated with an increasing hazard for a clinical event (hazard ratio, 2.49; 95% confidence interval, 1.92–3.24). The presence of a pericardial effusion is rare in children but, when present, suggests a poor prognosis [29, 30].

As PAH progresses and RV function worsens, the systolic portion of the cardiac cycle lengthens leading to an increase in the systolic/diastolic ratio. The S/D ratio is higher in PAH

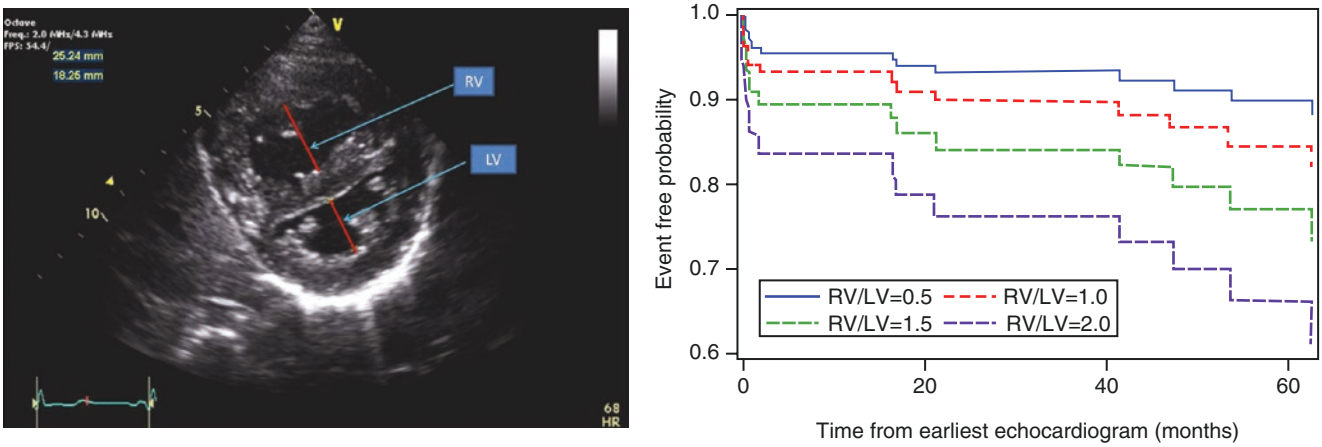


Fig. 43.6 RV/LV ratio predicts outcome in pediatric PAH. (Jone et al. [28])

patients than in controls (1.38 +/− 0.61 vs. 0.72 +/− 0.16, $p < 0.001$) and is associated with worse echocardiographic RV fractional area change, worse catheterization hemodynamics, shorter 6-minute walk distance, and worse clinical outcomes independent of pulmonary resistance or pressures [31, 32]. Tissue Doppler imaging (TDI) directly measures myocardial velocities and has been shown to be an accurate measure of RV and LV systolic and diastolic function. In recent pediatric studies, right ventricular TDI velocity was lower in children with PAH compared to healthy controls [33, 34]. Moreover, tricuspid diastolic velocity (E') had a significant inverse correlation with right ventricular end-diastolic pressure and mean pulmonary arterial pressure. Cumulative event-free survival rate was significantly lower when tricuspid E' velocity was ≤8 cm/s (log-rank test, $p < 0.001$, Fig. 43.7) [34]. As the right ventricle contracts primarily in a longitudinal fashion, RV longitudinal strain is a powerful tool to predict clinical outcome in adults with PAH [35]. Its role in evaluating pediatric patients with PAH remains incompletely understood. Finally, function assessment by 3-dimensional echocardiography correlates well with cardiac MRI in children with congenital heart disease [36] and predicts outcome in children with chronic PAH (Fig. 43.7) [26].

Several ancillary tests are additionally useful to evaluate functional status and trend disease severity in PAH patients. The 6-minute walk (6 MW) test has been used clinically for many years and is a feasible test to quantify submaximal exercise in developmentally able children over 7 years of age. Normal values for 6 MW distance (6MWD) for children have recently been published [37–39]. In general, children with PAH tend to walk further than their adult counterparts with the same WHO functional class. Large registry studies have not shown 6MWD to be predictor of survival [40, 41]. However, a recent single-center observational study suggested that, among children 7–18 years old, 6MWD <352 meters and desaturation during the test (>5% for children with no shunt, >19% for children with a shunt) were associated with worse transplant-free survival [42].

Cardiopulmonary exercise testing in children over 7 years of age is useful to determine peak oxygen consumption, ventilator efficiency slope (VE/VCO2), and anaerobic threshold [43, 44]. Ventilatory efficiency slope is significantly higher in patients with PAH, with an estimated increase of 7.2 for each increase in WHO class, and correlates strongly with invasive measures of disease severity including PAP, PVRI, and outcome [45].

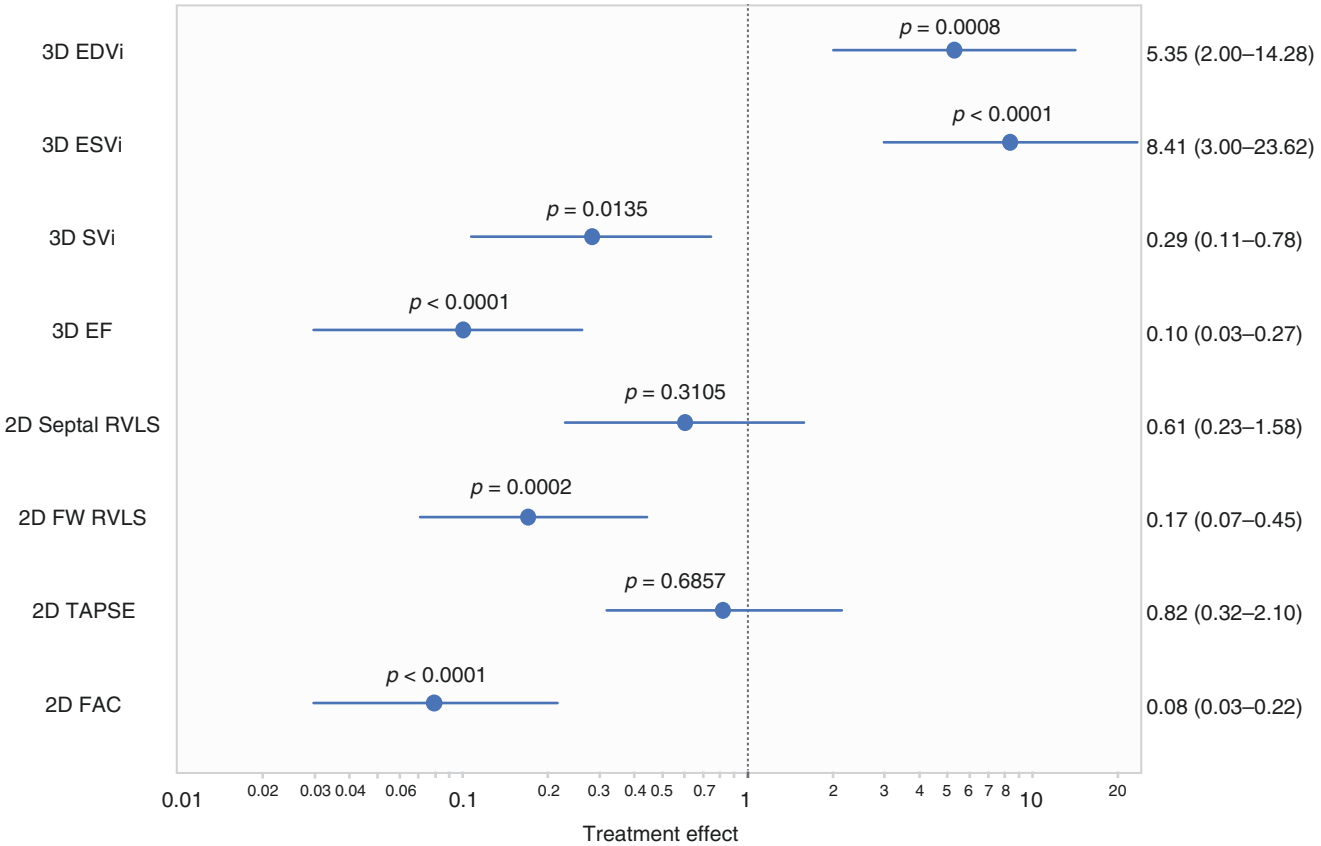


Fig. 43.7 Prognosis of 3D echocardiographic evaluation of right ventricular function and strain. (*Eur Heart J Cardiovasc Imaging*. 2017: Apr 1;18(4))

In adults, brain natriuretic peptide (BNP) is a useful tool to assess mortality risk, progression of the disease, and response to therapy [46]. Recent studies in children have begun to identify usefulness of BNP and N-terminal probrain natriuretic peptide (NT-proBNP) in pediatrics as well [31, 32, 47–50]. Change in BNP measurements over time typically trends with changes in classic hemodynamic and echocardiographic parameters of disease severity for children with PAH. In one study, patients with a BNP value >180 pg/ml had worse survival compared to those with a BNP value <180. An NT-proBNP >1200 ng/L portends a poor prognosis [51].

43.7 Cardiac Catheterization

Right heart catheterization is the gold-standard diagnostic test for pulmonary hypertension. With catheterization, the treating physician can confirm the diagnosis of PAH, assess the severity of the hemodynamic impairment, and target therapy. The pulmonary artery pressures and pulmonary wedge pressures are measured, shunt size and pulmonary blood flow are determined, and pulmonary vascular resistance is calculated by dividing the pressure gradient across the pulmonary vascular bed by the pulmonary blood flow. If right heart catheterization confirms the presence of PAH requiring treatment, a vasodilator study should be performed at the time of catheterization to determine the acute pulmonary vasoreactivity to short-acting vasodilators (discussed later in the chapter). It should be noted that cardiac catheterization is an invasive procedure with associated risks. Sedation, often with general anesthesia, may be necessary to minimize a child's agitation. Care should be taken to avoid rebound effects of inhaled nitric oxide withdrawal acutely and within 12 hours after the procedure.

Acute pulmonary vasoreactivity testing at the time of cardiac catheterization is an important step in the diagnosis, risk stratification, and treatment of IPAH. Children with IPAH who are acute responders may be effectively treated with calcium channel antagonists. A recent consensus statement from the Pulmonary Vascular Research Institute (PVRI) has helped standardize the practice across centers [52]. To perform vasoreactivity testing, a short-acting vasodilator is given, most commonly as a combination of high fractional inspired oxygen with or without 20–40 parts per million of inhaled nitric oxide and hemodynamics are reassessed [53–56]. Barst (1999) and Sitbon (2005) have each suggested potential strategies to classify patients as responders or non-responders, *with the aim to determine which patients are candidates for calcium channel blocker therapy* [53, 54]. The PVRI suggests that patients must achieve PVR < 4.5 Woods units × M^2 and "near-normalization" of pulmonary artery pressures to be labeled as acute responders [52]. There was no difference in the number of responders in children with IPAH comparing the Barst or Sitbon criteria in a Netherlands study [57]. Depending on criteria used and patient population included, the percentage of patients with a new diagnosis of IPAH who are acute responders is between 6 and 20% [57–59]. A recent registry study by Douwes et al. suggested improved survival in those children meeting the Sitbon criteria as acute responders [60].

43.8 Preoperative Management of Patients with Chronic PAH Before Noncardiac Surgery

Children with PAH may require surgical interventions not directly related to their cardiopulmonary disease. At the preoperative stage, a full evaluation of the etiology of PAH is imperative, as well as knowledge of vasoreactivity of the pulmonary bed [22]. PAH carries a significant risk of cardiac dysfunction and thus the increased risk of perioperative cardiovascular complications (Fig. 43.8) [61].

Preoperative management of the child with chronic PAH is based on the following *aims*:

(i) Ascertaining the cause of PAH and its reversibility, which is then related to the patient's suitability for surgical intervention.
(ii) Understanding whether an attempt at preoperative optimization of a patient with PAH should be undertaken. The clinician must understand if a pharmacological intervention should be initiated before surgery or catheterization and, if so, what medication is most appropriate.
(iii) If the child is already on a program of medication for PAH, this should be continued through the perioperative period.

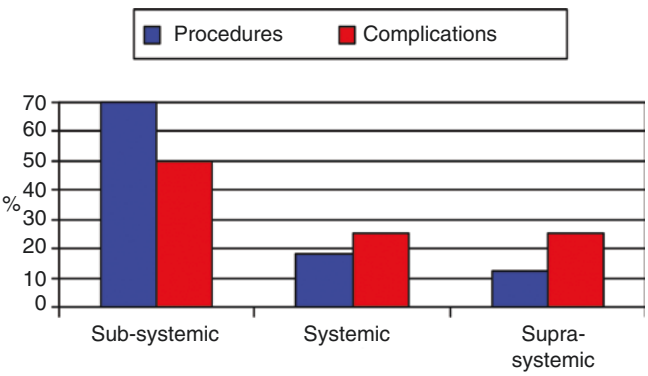


Fig. 43.8 Perioperative complications in children with pulmonary hypertension undergoing noncardiac surgery or cardiac catheterization. (Carmosino et al. [61])

Preoperative assessment in all patients with suspected PAH should include a thorough history, physical examination, a recent electrocardiogram and echocardiogram as a part of an extensive evaluation, and cardiac catheterization, if necessary. Symptoms suggesting increased severity of disease may include exertional dyspnea, reduced exercise tolerance, orthopnea, atypical chest pain, hemoptysis, feeding intolerance, growth failure, or syncope.

Noninvasive testing can be useful for screening and assessing prognosis (Table 43.2). Echocardiography is important in estimating pulmonary pressures and evaluating disease severity. As respiratory disease is an important cause of pulmonary hypertension, radiographic and physiologic evaluation of the lung should be undertaken to exclude parenchymal lung disease. If one has not recently been performed, a preoperative cardiac catheterization can further aid risk stratification and preoperative management through direct measurement of pulmonary artery pressures, calculation of resistance, and acute reactivity testing [22].

43.9 Anesthetic and Surgical Management

Inhaled nitric oxide (iNO) should be readily available for all procedures and anesthesia should be administered by a pediatric anesthesiologist experienced in cardiac anesthesia. As many anesthetics exhibit mixed hemodynamic effects and may be unacceptable when used in full anesthetic dosage, a balanced anesthetic technique in which subanesthetic doses of several drugs can be combined to provide effective general anesthesia while minimizing hemodynamic consequences. Oral or IV midazolam can be administered for preanesthetic sedation. Induction can be cautiously achieved with midazolam, fentanyl, and a small dosage of propofol or low concentration of sevoflurane. Inhaled anesthesia may be maintained with isoflurane or sevoflurane; total intravenous anesthesia (TIVA) can be maintained with infusions of propofol and or intermittent fentanyl. In general, boluses of propofol are avoided as they may cause decreased cardiac output. Our practice is to avoid remifentanil as it may decrease heart rate. Rocuronium or pancuronium may be used for neuromuscular blockade as indicated. Patients may be endotracheally intubated or a laryngeal mask airway may be utilized. Infiltration of surgical sites with local anesthesia may avoid the use of higher doses of general anesthetic drugs. For cardiac catheterization in older or more stable patients, the pediatric cardiologist may administer the sedation using midazolam and fentanyl and the airway is often unaided in these circumstances. Ketamine and propofol have been used together in some centers.

An increased risk of complications has been reported in PAH patients undergoing surgical procedures compared to healthy children [61]. Major complications, most often pulmonary hypertensive crises, are a known risk in patients with severe or suprasystemic PAH (Fig. 43.8) [61]. A pulmonary hypertensive crisis is an emergency and may require specific pharmacological intervention with subsequent mechanical ventilation postoperatively in the Intensive Care Unit [61].

The postanesthesia period is also known to be particularly dangerous. At this point, patients awakening from anesthesia may begin to feel pain and may be agitated, precipitating a PH crisis. Likewise, withdrawal of inhaled nitric oxide used for vasodilator testing may predispose to pulmonary hypertensive events. It has been our practice to continue nasal cannula nitric oxide for 8–12 hours after the procedure in patients with more severe disease.

Total correction of many cardiac lesions in the first months of life may prevent the late development of pulmonary hypertension. The timing of surgery in patients with congenital heart disease depends upon a number of factors. These include age, lesion, vasoreactivity at cardiac catheterization, findings on lung biopsy, and pulmonary wedge angiography.

43.10 Specific Causes of PH

43.10.1 Idiopathic Pulmonary Arterial Hypertension

Idiopathic pulmonary arterial hypertension (IPAH) is a rare disease that occurs most frequently in young adult females [62]. IPAH is characterized by progressive and sustained elevations of pulmonary artery pressure without a defined etiology. While generally developing in the adult population, pediatric IPAH is well reported and carried a dismal prognosis in the NIH cohort, with a median survival of only 10 months in individuals less than 16 years old [63]. Evaluation for possible IPAH in the pediatric age group is similar to that outlined for adults. However, increased scrutiny for the possibility of congenital cardiac disease is appropriate, and positive acute pulmonary vasoreactivity testing may be more common in children [53, 64, 65]. A recent study examined a previously identified cohort of 77 children diagnosed between 1982 and 1995 with idiopathic pulmonary arterial hypertension and followed up through 2002. For acute responders treated with calcium channel blockers (CCB) (n = 31), survival at 1, 5, and 10 years was 97%, 97%, and 81%, respectively; treatment success was 84%, 68%, and 47%, respectively. Survival for all children treated with epoprostenol (n = 35) at 1, 5, and 10 years was 94%, 81%, and 61%, respectively; treatment success was 83%, 57%, and 37%, respectively [64]. The annual incidence and point prevalence of IPAH is 0.7 and 4.4 cases per million children PAH [66].

43.10.2 Heritable Pulmonary Artery Hypertension

Between 6 and 12% of cases of IPAH may be familial in origin [67]. Among adult patients with heritable PAH, *BMPR2* mutations can be identified in approximately 75% [68]. The pattern of inheritance for those with heritable PAH and a *BMPR2* mutation is autosomal-dominant with variable penetrance of the PAH phenotype by gender – 14% for males and 42% for females. The cause in childhood appears heterogeneous in nature, with genetic defects of transforming growth factor-beta receptors playing an important role [69]. *BMPR2* is a type 2 receptor of the transforming growth factor (TGF) -β superfamily of cytokines, members of which are essential for the cellular proliferation, differentiation, and apoptosis. A variety of heterozygous mutations in the gene that encodes for *BMPR2* (chromosome 2q33) have been causally linked to HPAH [70, 71]. These mutations appear to result in uncontrolled proliferation of vascular smooth muscle due to lack of an antiproliferative effect of normal BMPR2 signaling [72, 73]. Although more than 50 disease-causing defects in the *BMPR2* gene have been reported, many have been identified in patients with no family history of pulmonary arterial hypertension, implying either a low disease penetrance or the occurrence of spontaneous mutations [70, 72, 74, 75]. *BMPR2* was found in 6% of a mixed cohort of adults and children with pulmonary arterial hypertension/congenital heart defects [76]. Recently implicated as causative of PAH, *ALK-1* and *TBX4* mutations are increasingly recognized as well [22, 77]. While the gene mutations for both *ALK-1* and *TBX4* can be inherited in an autosomal-dominant fashion, the gene penetrance and potential epigenetic modifying factors are not yet well described. In a Japanese study where children previously thought to have IPAH were retested, subjects were approximately as likely to have a *BMPR2* mutation (17%) as an ALK-1 mutation (12%) [78]. Most recently, Levy et al. found no mutations in any of 23 patients with CHD-PAH but disease-causing mutations in 30% of patients with IPAH (12% BMPR2, 10% ALK-1, 8% TBX4) [77]. Advanced gene-sequencing methods have facilitated the discovery of additional, less common gene mutations implicated among those with PAH (*SMAD-9, CAV1, KCNK3, EIF2AK4*) [22, 68, 74, 77–83]. Other genetic loci may also play important roles. Studies have suggested an important role of the serotonin transporter gene in some adults with PAH [84], and a study in children found that homozygosity for the long variant of the serotonin transporter gene was highly associated with idiopathic pulmonary hypertension in children [85].

43.10.3 Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is the chronic lung disease associated with prematurity. BPD is one of several diseases associated with lung development (Table 43.3, Fig. 43.9). Advances in neonatal care have improved survival of extremely premature infants, but morbidity from BPD is significant, and PAH is diagnosed in up to 20% of preterm babies [86]. Although significant PAH has been associated with mild BPD, increasing PAH severity typically shows a positive correlation with increasing BPD severity. Echocardiographic signs of elevated pulmonary artery pressure are often seen as early as 7 days of life and, when present, are associated with higher risk of late PAH [87]. In this population, PAH is thought to result from a combination of increased vascular tone, hypertensive remodeling, ventilator-induced lung injury, and an underdeveloped pulmonary artery vascular bed. Clinical risk factors for PAH in this population include lower gestational age, small-for-gestational age birth weight, oligohydramnios, preeclampsia, prolonged duration of mechanical ventilation, and prolonged oxygen therapy [87–90]. While PAH can resolve or improve as some premature infants grow, persistence and severity of PAH are associated with significant mortality: one recent study of premature neonates showed only 53% survival 2 years after diagnosis of severe, persistent PAH [88]. Mesenchymal stromal cells are thought to be lung protective in this group, and preclinical animal studies of targeted cell therapy for this population have yielded promising results [91]. Recent guidelines have been published to help standardize provider approach to the diagnosis, monitoring, and management of PH in this particular population [92].

Table 43.3 5th WSPH: Developmental Lung Diseases Associated With Pulmonary Hypertension

Congenital diaphragmatic hernia
Bronchopulmonary dysplasia
Alveolar capillary dysplasia (ACD)
ACD with misalignment of veins
Lung hypoplasia (“primary” or “secondary”)
Surfactant protein abnormalities
SPB deficiency
SPC deficiency
ATP-binding cassette A3 mutation
Thyroid transcription factor 1/Nkx2.1 homeobox mutation
Pulmonary interstitial glycogenosis (PIG)
Pulmonary alveolar proteinosis (PAP)
Pulmonary lymphangiectasia

Ivy et al. [1]

43.10.4 Congenital Heart Disease

A variety of congenital cardiac lesions can cause pulmonary hypertension (Table 43.4) [93]. The age at which these lesions produce irreversible pulmonary vascular disease varies (Fig. 43.10) [94]. In general, patients with a ventricular septal defect or patent ductus arteriosus do not develop irreversible pulmonary vascular changes before

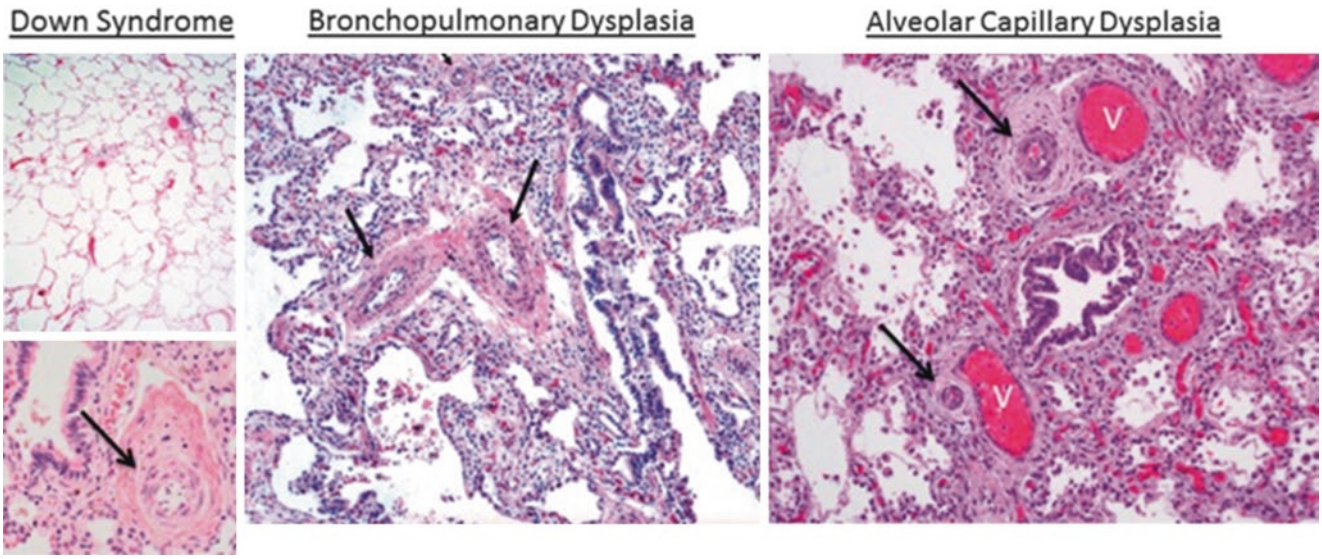


Fig. 43.9 Development of lung diseases associated with pulmonary hypertension. (*Pulm Circ* 2017; 7(1) 7–19)

Table 43.4 Cardiac lesions associated with pulmonary hypertension

Left-to-right shunts	Atrial septal defect Ventricular septal defect Patent ductus arteriosus Atrioventricular septal (canal) defect Aorto-pulmonary window
Increased pulmonary venous pressure	Cardiomyopathy Coarctation of the aorta (left ventricular diastolic dysfunction) Hypoplastic left heart syndrome Shone complex Mitral stenosis Supravalvar mitral ring Cor triatriatum Pulmonary vein stenosis/veno-occlusive disease Total anomalous pulmonary venous return
Cyanotic heart disease	Transposition of the great arteries Truncus arteriosus Tetralogy of Fallot (pulmonary atresia/VSD) Univentricular heart
Anomalies of the pulmonary artery or pulmonary vein	Origin of a pulmonary artery from the aorta Unilateral "absence" of a pulmonary artery Scimitar syndrome
Palliative shunting operations	Waterston anastomosis Potts anastomosis Blalock-Taussig anastomosis

2 years of age. Children with Down syndrome may have an increased risk of pulmonary hypertension if congenital cardiac lesions are present. Similarly, infants with an atrial or ventricular septal defect with concomitant chronic lung disease are at an increased risk for the early development of severe pulmonary vascular disease. In one study of infants with bronchopulmonary dysplasia who underwent cardiac surgery for the repair of congenital heart disease, 25 percent of those who died had pulmonary arterial hypertension [95]. A classification of PAH associated with congenital heart disease has been proposed (Table 43.5) [4].

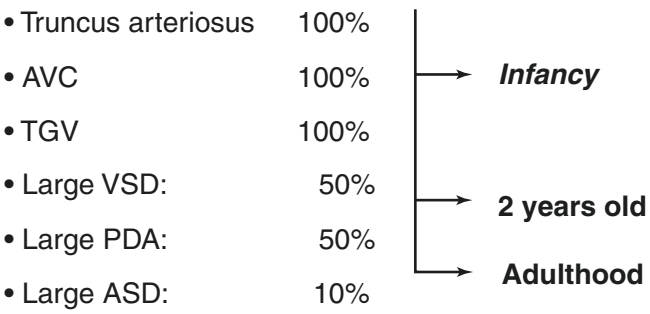


Fig. 43.10 The likelihood of developing pulmonary vascular disease if not repaired within the designated time frame. (Rosenzweig and Barst [94])

Patients with cyanotic congenital cardiac lesions such as transposition of the great arteries, truncus arteriosus, and univentricular heart with high flow also may develop pulmonary hypertension. Palliative shunting operations for certain cardiac anomalies designed to increase pulmonary blood flow also may lead to the subsequent development of pulmonary hypertension. Hypoxia with increased shunting is believed to be a potent stimulus for the rapid development of pulmonary vascular disease.

43.10.5 Eisenmenger Syndrome

Eisenmenger syndrome (ES) describes pulmonary hypertension with bidirectional or right-to-left shunting through a systemic-to-pulmonary connection, such as a ventricular septal defect, patent ductus arteriosus, univentricular

Table 43.5 Clinical classification of pulmonary arterial hypertension associated with congenital heart disease

1. Eisenmenger syndrome	Including large intra- and extracardiac defects which begin as systemic-to-pulmonary shunts and progress to severe elevation of PVRi with reversed (pulmonary-to-systemic) or bidirectional shunting; cyanosis is typically present
2. Left-to-right shunts	Including moderate-to-large defects; PVR is increased, but systemic-to-pulmonary shunting is still prevalent and cyanosis is not present
3. PAH with coincidental congenital heart disease	Marked elevation in PVRi in the presence of small cardiac defects that do not themselves account for the development of elevated PVRi. The clinical picture resembles idiopathic PAH
4. Postoperative PAH	Congenital heart disease has been repaired, but PAH persists or recurs in the absence of significant residual lesions. Typically associated with an aggressive phenotype

heart, or aortopulmonary window [96]. In general, the term "Eisenmenger syndrome" is used mainly for shunts distal to the tricuspid valve, but some studies have included patients with a large atrial septal defect. Patients with ES typically begin life with a net left-to-right shunt, but as pulmonary vascular resistance increases over time, there is a reversal of the shunt to a right-to-left configuration, leading to cyanosis and erythrocytosis. It is not uncommon for patients that are detected late with Eisenmenger syndrome to not have a prior history of congestive heart failure suggesting that PVR may not have fallen to normal levels in the perinatal period. In general, the prognosis of patients with Eisenmenger syndrome is much better than for patients with IPAH, but syncope, right-heart failure, and severe hypoxemia are similarly associated with a poor prognosis. Phlebotomy may be utilized in Eisenmenger syndrome to provide temporary relief of hyperviscosity symptoms or to improve perioperative hemostasis, but should not routinely be performed as this leads to increased stiffness of the red blood cell [97]. Noncardiac operations on Eisenmenger patients are associated with a high mortality rate and should be managed by a multidisciplinary team experienced in the care of patients with this condition. In a recent large study of Eisenmenger syndrome patients, multivariable Cox regression analysis revealed that age (hazard ratio [HR], 1.41/10 years; 95% confidence interval [CI], 1.24–1.59; $P < 0.001$), pretricuspid shunt (HR, 1.56; 95% CI, 1.02–2.39; $P = 0.041$), oxygen saturation at rest (HR, 0.53/10%; 95% CI, 0.43–0.65; $P < 0.001$), presence of sinus rhythm (HR, 0.53; 95% CI, 0.32–0.88; $P = 0.013$), and presence of pericardial effusion (HR, 2.41; 95% CI, 1.59–3.66; $P < 0.001$) were significant predictors of death [98]. Targeted PAH therapy is associated with improved survival in Eisenmenger patients [99].

43.10.6 Single Ventricle Circulation

In the patient with single ventricle physiology who has completed Fontan palliation, flow to the pulmonary circulation occurs via direct vena cava to pulmonary artery connections without an intervening pumping chamber. This circulation strategy relies on several factors for adequate cardiac output: anatomically unobstructed pulmonary arterial blood flow and venous drainage, low pulmonary artery pressure (PAP) and PVR, low ventricular end-diastolic pressure, and adequate systolic single ventricular function.

Pulmonary vascular resistance plays a key role in the outcome of the single ventricle patient [100]. Altered pulmonary perfusion leads to poor pulmonary blood flow and therefore low cardiac output. Retrospective studies have demonstrated that mean PAP >15 mmHg, trans-pulmonary gradient >8 mmHg, and PVRI >2.5 Wood U × m^2 are risk factors for Fontan failure, protein losing enteropathy, and plastic bronchitis [101–103]. For Fontan patients who develop these clinical complications, pulmonary vascular disease due to muscular thickening of the pulmonary arteries has been implicated [104]. Supporting the theory that Fontan patients can have pulmonary arterial disease despite mean PAP below 20 mmHg, treatment with the pulmonary vasodilator sildenafil has, in small series, been shown to improve oxygen saturation, exercise capacity, protein-losing enteropathy, and plastic bronchitis [104–107]. Additionally, blood concentration of the vasoconstrictor peptide endothelin-1 is increased in Fontan patients [108]. Several studies have suggested improvement in exercise tolerance with endothelin receptor antagonists [109–111].

43.10.7 Hemoglobinopathies

Interest is growing in the area of pulmonary arterial hypertension associated with hemoglobinopathies, such as sickle cell disease (SCD). Studies by Gladwin and others have shown that a right ventricular systolic pressure greater than 25 mmHg is predictive of increased mortality in adults with SCD [112]. This form of pulmonary artery hypertension is associated with higher systolic rather than diastolic pressure and is thought to be associated with a combination of pulmonary vascular disease, high cardiac output, and left ventricular diastolic dysfunction. It is likely that the increased mortality in patients with SCD and PAH is multifactorial and includes diminished nitric oxide availability and the presence of diastolic dysfunction. Release of hemoglobin and arginase from lyzed red cells causes scavenging of nitric oxide (NO) and catabolism of L-arginine, the obligate substrate for NO synthase. The resulting impairment in NO bioavailability is associated with pul-

monary vasoconstriction, endothelial dysfunction, thrombosis, and eventual development of plexogenic arterial lesions, the histological hallmark of all forms of PAH [22]. Furthermore, in addition to pulmonary hypertension, diastolic dysfunction is an independent risk factor for mortality in sickle cell disease [113]. In one study, a trial of sildenafil led to an increased number of patients with sickle cell crisis [114].

43.10.8 Thromboembolic Disease

Chronic thromboembolic disease as a cause of pulmonary hypertension in children is uncommon. However, the condition can occur rarely, and an accurate diagnosis is essential for treatment [115, 116]. Predisposing factors include antiphospholipid antibody syndrome, collagen vascular diseases, thrombophilia, bacterial endocarditis, and ventricular-atrial shunt for the treatment of hydrocephalus. Likewise, the use of oral contraceptive agents may cause hypercoagulability, leading to pulmonary thromboembolic phenomena.

The diagnosis of chronic thromboembolic pulmonary hypertension in children requires a high index of suspicion, as well as evaluation by ventilation perfusion, CT scanning, or angiography. In adults with chronic thromboembolic pulmonary hypertension with surgically accessible disease and no severe comorbidities, pulmonary thromboendarterectomy has been demonstrated to improve survival and quality of life in patients [117]. A similar approach should be considered for children who develop this condition despite the relative paucity of data on this procedure in the pediatric age group.

43.10.9 Pharmacological Therapy of PAH

Based on known mechanisms of action, three classes of drugs have been extensively studied for the treatment of PAH: prostanoids, endothelin-receptor antagonists, and phosphodiesterase inhibitors – soluble guanylate cyclase stimulators (Figs. 43.11 and 43.12).

Without therapy, and sometimes despite appropriate surgical correction of congenital cardiac lesions, pulmonary arterial hypertension progresses at a variable rate. As vasoconstriction is an important component in the development of medial hypertrophy, vasodilators are frequently used to decrease pulmonary artery pressure, improve cardiac output, and potentially reverse some of the pulmonary vascular changes noted in the lung. A long-term strategy for the treatment of pulmonary hypertension in children is shown (Figs. 43.13 and 43.14).

43.10.10 Nitric Oxide

The use of newer vasodilator agents, particularly inhaled nitric oxide, has been an important advance in safely determining vasoreactivity. Inhaled nitric oxide therapy improves gas exchange and selectively lowers pulmonary vascular resistance in several clinical diseases, including idiopathic pulmonary hypertension and congenital heart disease [22, 118, 119]. Inhaled nitric oxide diffuses to the adjacent smooth muscle cell, where it activates soluble guanylate cyclase, resulting in an increase in cGMP and vasodilation. Currently, inhaled nitric oxide with oxygen is recommended by many centers as the agent of choice for evaluating pulmonary vasoreactivity. Usually nitric oxide is given with high concentrations of oxygen.

The role of chronic inhaled nitric oxide (iNO) in the treatment of pulmonary hypertensive disorders has been studied [120, 121]. Although iNO therapy causes sustained decreases in pulmonary vascular resistance, adverse hemodynamic effects may complicate iNO therapy after abrupt withdrawal [122, 123]. Inhibition of phosphodiesterase type 5 (see below), which degrades cGMP within vascular smooth muscle, causes vasodilation and may attenuate this rebound effect. Currently few patients are treated with inhaled NO at home, but advancements in the use of NO in the nonintubated patient have led to greater use in the pre- and postoperative setting.

Fig. 43.11 FDA-approved medications for adults with PAH

Oral therapy				Inhaled therapy	Continuous parenteral therapy
ERAs	**PDE5 inhibitors**	**sGC Stimulator**	**Prostacyclin**	**Prostacyclins**	
Ambrisentan	Sildenafil	Riociguat	Treprostinil	Iloprost	Epoprostenol
Bosentan	Tadalafil		Selexipag	Treprostinil	RTS Epoprostenol
Macitentan					Treprostinil (SC or IV)

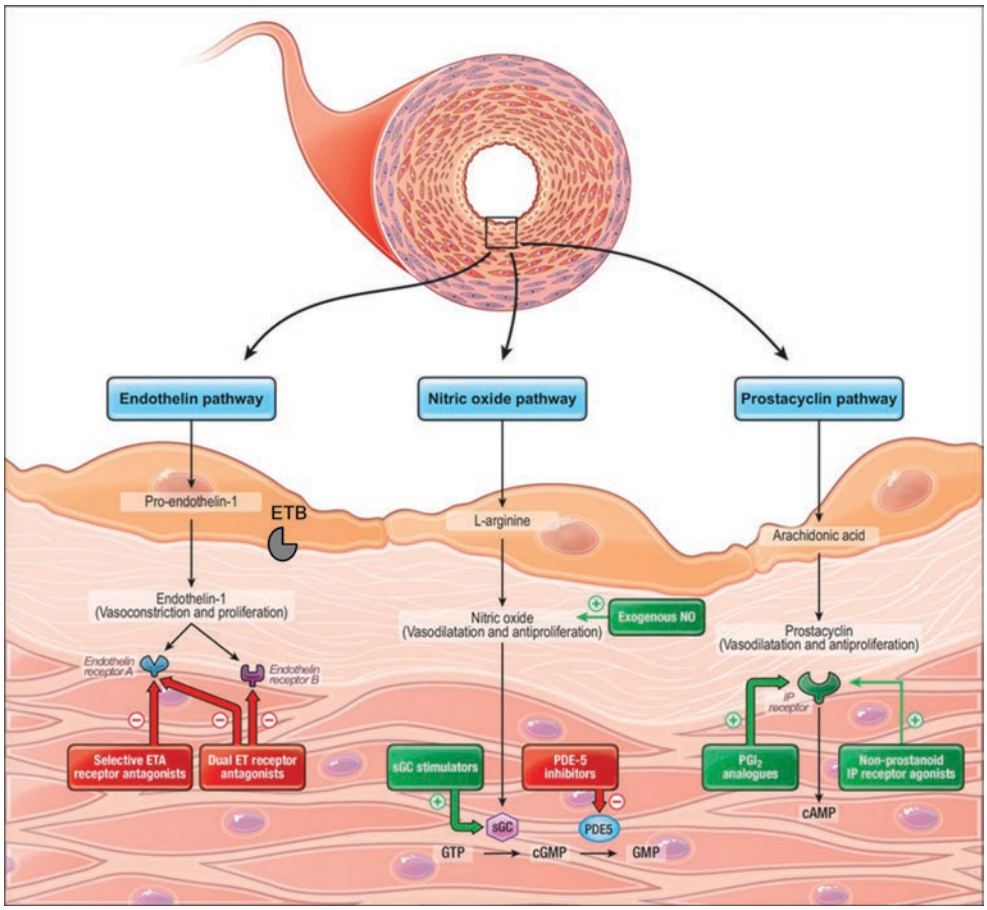


Fig. 43.12 PH pathways for targeted therapy. (*Circulation*. 2014;130:2189–2208)

LOWER RISK	DETERMINANTS OF RISK	HIGHER RISK
No	Clinical evidence of RV failure	Yes
No	Progression of Symptoms	Yes
No	Syncope	Yes
	Growth	Failure to thrive
I,II	WHO Functional Class	III,IV
Minimally elevated	BNP / NTproBNP	Significantly elevated Rising level
	Echocardiography	Severe RV enlargement/dysfunction Pericardial Effusion
Systemic CI > 3.0 L/min/m^2 mPAP/mSAP < 0.75 Acute Vasoreactivity	Hemodynamics	Systemic CI < 2.5 L/min/m^2 mPAP/mSAP > 0.75 RAP > 10mmHg PVRI > 20 WU*m^2

Fig. 43.13 Table of risk in pediatric PAH. (Rosenzweig et al. [192])

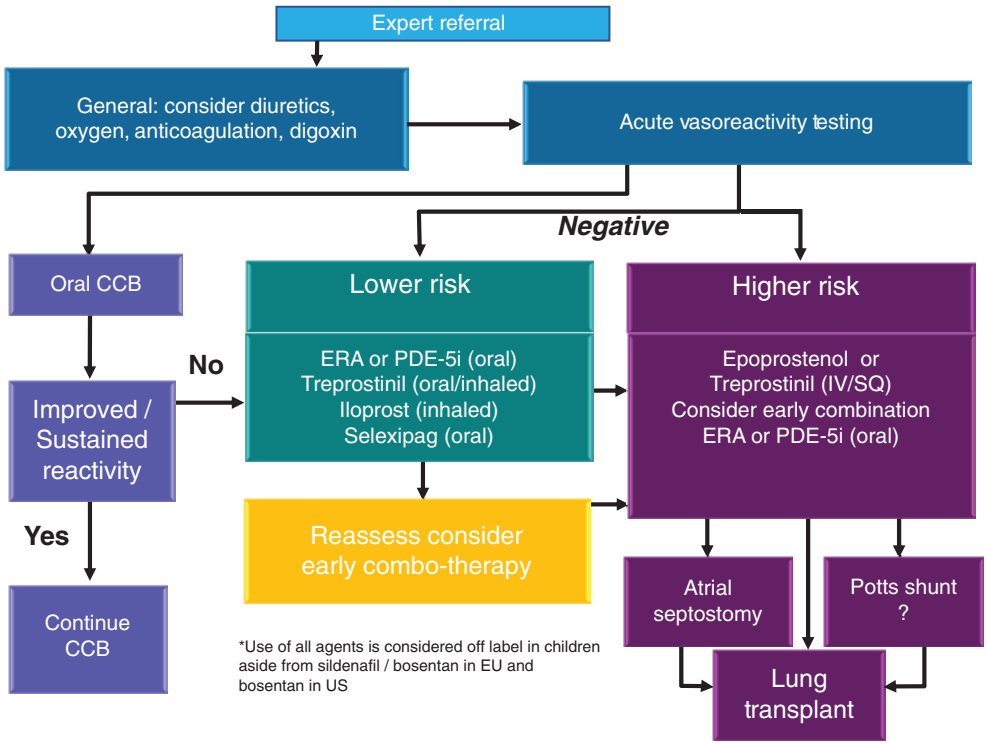


Fig. 43.14 Treatment of chronic PAH in children. (Ivy et al. [1])

Clinically unpredictable or nonsustained responses have been noted with inhaled NO therapy, and its acute withdrawal can result in rapid rises in PVR [120, 124]. Alterations in endogenous endothelial activity during NO inhaled therapy may mediate these clinical findings. ET-1 signaling pathways have been implicated in the rebound phenomena. Reactive oxygen species (ROS) may mediate these alterations and superoxide scavenging to stop the tissue increases in superoxide and peroxynitrite, preserves NOS activity, decreasing eNOS nitration, and prevents the rebound phenomena [22].

43.10.11 Calcium Channel Blockers

The use of calcium channel antagonists to evaluate vasoreactivity is dangerous, as these drugs can cause a decrease in cardiac output or a marked drop in systemic blood pressure [53]. Such deleterious effects may be prolonged due to the relatively long half-life of calcium channel blockers. Consequently, elevated right atrial pressure and low cardiac output are contraindications to acute or chronic calcium channel blockade. The number of patients treated with calcium channel blockers is steadily decreasing.

Our preference is to perform an acute trial of calcium channel blocker therapy only in those patients who are acutely responsive to either nitric oxide or prostacyclin. In this setting response is defined as a fall in mean PAP of at least 10 mmHg to near-normal levels and certainly less than a mean PAP of 40 mmHg [60]. Likewise, patients who do not have an acute vasodilatory response to short-acting agents and who are then placed on calcium channel blocker therapy are unlikely to benefit from this form of therapy [22]; 60–80 percent of children with severe pulmonary hypertension are nonresponsive to acute vasodilator testing and, therefore, require therapy other than calcium channel antagonists.

43.10.12 Prostacyclins

Adults with IPAH and children with congenital heart disease demonstrate an imbalance in the biosynthesis of thromboxane A_2 and prostacyclin. Likewise, adults and children with severe pulmonary hypertension show diminished prostacyclin synthase expression in the lung vasculature. Prostacyclin administered over the long term, utilizing intravenous epoprostenol, has shown to improve survival and quality of life in adults and children with idiopathic pulmonary arterial hypertension [53, 125].

Prostacyclin and prostacyclin analogs impact the cyclic-AMP pathway to increase pulmonary vasodilation. Intravenous epoprostenol-prostacyclin was first used in the 1980s, was FDA approved in 1995, and continues to be the gold standard

for treatment of severe disease. Although results from the treatment of patients with epoprostenol are encouraging, the therapy is cumbersome to administer. The prostacyclin must be infused 24-hours/day via a central venous catheter and kept cold with ice packs, and the half-life of the drug is 2–5 minutes placing the patient at risk for an acute pulmonary hypertensive crisis if there is an accidental discontinuation of the medication. In addition, the side effects of the drug include nausea, diarrhea, jaw pain, bone pain, and headaches.

The prostacyclin analog treprostinil was approved by the FDA initially for subcutaneous use (2002), followed by intravenous administration (2004), inhaled administration (2009), and oral treatment (2013). While subcutaneous treprostinil allows patients to remain free of central venous catheters, it can cause severe pain at the infusion site. Recent data has shown long-term efficacy in adults with PAH [126]. Treprostinil has also been given in the intravenous form. Intravenous treprostinil requires central line access and continuous infusion, but is easier for families to mix, and has a half-life of 4 hours. Intravenous treprostinil has fewer side effects than intravenous epoprostenol, but there are no studies comparing efficacy [127]. Treprostinil has also been studied in an inhaled form and is reasonably well tolerated by affected children [128, 129]. Oral treprostinil was shown to be effective as initial monotherapy treatment in adult PAH [130], but not as add-on therapy [131].

An inhaled prostacyclin analog, iloprost, received approval for the treatment of PAH in the United States in December 2004. This medication is administered by nebulization 6–9 times a day. Iloprost requires patient cooperation with the treatment administration lasting 10–15 minutes, which is difficult for young children [132–134]. The advantage of an inhaled prostacyclin is that it can cause selective pulmonary vasodilation without affecting systemic blood pressure. Additionally, inhaled prostacyclin analogs can improve gas exchange and intrapulmonary shunt in cases of impaired ventilation/perfusion matching by redistributing pulmonary blood flow from nonventilated to ventilated, aerosol-accessible lung regions [134, 135]. In children with congenital heart disease and PAH, inhaled iloprost may be as effective in lowering pulmonary artery pressure and resistance as inhaled nitric oxide, and thus may be useful in evaluation of acute vasoreactivity [134]. One randomized controlled trial of aerosolized prostacyclin therapy in children with acute lung injury demonstrated improved oxygenation [136]. Inhaled iloprost has also been studied in combination with bosentan and sildenafil, among others [137–139].

A recent publication has described early experiences with the oral prostacyclin analog selexipag in pediatric patients, targeting a goal dose of 1600 mcg twice per day [140, 141]. That study noted similar results with 9 of 10 patients reaching goal dose successfully and a reported trend toward improved hemodynamics [140].

Beraprost is an orally active prostacyclin analog with a half-life of 35–40 minutes. While beneficial effects have been noted in short-term trials, these may be attenuated with prolonged treatment [142, 143].

43.10.13 Endothelin-Receptor Antagonists

Another target for treatment of pulmonary hypertension is the vasoconstrictor peptide endothelin (ET) [144]. The endothelins are a family of isopeptides consisting of ET-1, ET-2, and ET-3. ET-1 is a potent vasoactive peptide produced primarily in the vascular endothelial cell, but also may be produced by smooth muscle cells. Two receptor subtypes, ET_A and ET_B, mediate the activity of ET-1. ET_A and ET_B receptors on vascular smooth muscle mediate vasoconstriction, whereas ET_B receptors on endothelial cells cause release of nitric oxide (NO) and prostacyclin (PGI2), and act as clearance receptors for circulating ET-1. ET-1 expression is increased in the pulmonary arteries of patients with pulmonary hypertension. Bosentan, a dual ET-receptor antagonist, lowers pulmonary artery pressure and resistance, and improves exercise tolerance in adults with pulmonary arterial hypertension [144]. These results can also be extrapolated to children [55, 142, 145–148]. In children with pulmonary arterial hypertension related to congenital heart disease or IPAH, bosentan lowers pulmonary pressure and resistance, and is well tolerated [142, 149]. Elevated hepatic aminotransferase levels occur in approximately 11% of adults treated with bosentan and 3% of children. In a 12-week study, children with IPAH or PAH related to congenital heart disease, bosentan was well tolerated and lowered the pulmonary artery pressure and resistance [142]. A more recent retrospective study of 86 children on bosentan for a median exposure of 14 months with and without concomitant therapy found that bosentan provided a sustained clinical and hemodynamic improvement, was overall well tolerated, and two-year survival estimates were 91% [146].

Macitentan, a dual endothelin-receptor antagonist with longer duration of action facilitating once daily dosing, was FDA approved in 2013 for adults with PAH. In adult patients, macitentan increased the time from the initiation of treatment to the first occurrence of a composite endpoint of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of pulmonary arterial hypertension [150]. Pediatric-specific studies of macitentan are ongoing [151].

Selective ET_A-receptor blockade is also possible using ambrisentan, an ET-receptor antagonist with high oral bioavailability, a long duration of action, and high specificity for the ET_A-receptor. Selective ET_A-receptor blockade may benefit patients with pulmonary arterial hypertension by blocking the vasoconstrictor effects of ET_A-receptors while maintaining the vasodilator/clearance functions of ET_B-receptors. Further studies using selective ET_A-receptor blockade with BQ 123 in postoperative congenital heart dis-

ease have been reported [152, 153]. Ambrisentan was approved by the U.S.A. FDA in June 2007. Adults showed significant improvements in 6-minute walk distance and significant delay in clinical worsening on ambrisentan. The incidence of elevated hepatic aminotransferase levels was 2.8% [154]. Initial experience with ambrisentan in children suggests that treatment is safe, with similar pharmacokinetics and adverse reactions to those seen in adults, and effective at improving PAH in many patients [155, 156].

43.10.14 Phosphodiesterase-5 Inhibitors

Specific phosphodiesterase-5 inhibitors, such as sildenafil [157–162], increase cGMP levels and thus promote pulmonary vasodilation and reverse remodeling. Sildenafil is as effective a pulmonary vasodilator as inhaled NO and may be preferred because it does not increase pulmonary wedge pressure in patients with LV diastolic dysfunction. Sildenafil may also be useful in the setting of inhaled nitric oxide therapy withdrawal [163–165] in postoperative pulmonary hypertension [166], or in the presence of pulmonary hypertension related to chronic lung disease [138]. In some settings, intravenous sildenafil may worsen oxygenation through increased V/Q mismatching [167, 168].

Sildenafil has been approved for the treatment of WHO functional class II-IV PAH adult patients [162], and has been extensively studied in children with PAH. In the 16-week, randomized, double-blind, placebo-controlled STARTS-1 study, the effects of oral sildenafil in pediatric PAH were evaluated [169]. Children (n = 235) with PAH (aged 1–17 yrs.; ≥8 kg) received low-, medium-, or high-dose sildenafil or placebo orally three times per day. The trial did not meet its primary endpoint (percentage change in pVO_2 for the low-, medium-, and high-doses combined versus placebo was 7.7% ± 4.0%, 95% CI, −0.2% to 15.6%; $P = 0.056$) [169]. After the initial 16 week study, an extension trial (STARTS-2) was performed: patients in the low-, medium-, and high-dose groups remained on their dose, while patients in the placebo group were randomized to low, medium, or high dose [170]. By 3 years, the hazard ratio for mortality was 3.95 (95% confidence interval, 1.46–10.65) for high vs. low dose. Most patients who died had idiopathic or heritable PAH (76% vs. 33% overall) and baseline functional class III/IV disease (38% vs. 15% overall). Kaplan-Meier estimated 3-year survival rates from the start of sildenafil were 94%, 93%, and 88% for patients randomized to low-, medium-, and high-dose sildenafil (Fig. 43.12). Based on this, the data-monitoring committee recommended that all patients down-titrate from the high dose. Review of the STARTS-1 and STARTS-2 by the FDA and the European Medicines Agency (EMA) resulted in disparate recommendations. Sildenafil was approved for pediatrics by the EMA in 2011, with a later warning to avoid use of the high dose. In August 2012, the FDA released a strong warning against the (chronic) use of sildenafil for pediatric patients (ages 1 through 17) with PAH (http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm317743.htm). In 2014, however, the FDA clarified the sildenafil warning, stating that there may be situations in which the risk-benefit profile may be acceptable in individual children and that sildenafil is still not recommended in children with PAH (http://www.fda.gov/Drugs/DrugSafety/ucm390876.htm).

Tadalafil, another selective PDE-5 inhibitor, has a longer duration of action allowing for once daily dosing. Data for tadalafil in pediatrics are limited. In one study of 29 children with PAH switched from sildenafil to tadalafil for convenience of dosing, the change was well tolerated (2 children discontinued due to headaches or allergic reaction) [171]. The average dose of sildenafil was 3.4 +/− 1.1 mg/kg/day and that of tadalafil was 1.0 +/− 0.4 mg/kg/day. For 14 of the 29 patients undergoing repeat catheterization, statistically significant improvements in PA pressure and PVR were observed after transition from sildenafil to tadalafil. A study of 391 children in Japan treated with tadalafil revealed WHO functional class improvement at 3 months, 1 year, and 2 years after the initiation of tadalafil and last observation in pediatric patients were 16.5%, 19.7%, and 16.3% [172].

Riociguat, a direct oral soluble guanylate cyclase (sGC) stimulator, increases cGMP directly in a non-NO-dependent manner and also increases the sensitivity of sGC to NO. [173] Riociguat was approved by the FDA in 2013 for treatment of adult PAH [174] and is the first FDA-approved drug for the treatment of chronic thromboembolic PH [174]. In the PATENT-1 and PATENT-2 trials riociguat was well tolerated in patients with repaired PAH-CHD, and treated subjects demonstrated improved 6MWD, PVR, WHO FC, and NT-proBNP [175]. A recent single-center case report also described a patient with severe IPAH who experienced significant improvement in PVR and WHO FC after changing from sildenafil to riociguat [176]. A phase 3 safety and tolerability trial of Riociguat, the PATENT-CHILD study, is currently enrolling children with PAH (Clinicaltrials.gov identifier NCT02562235).

43.10.15 Anticoagulation

In retrospective trials in adults with IPAH, the use of warfarin has been associated with improved survival. Although the use of chronic anticoagulation has not been studied widely in children, it is sometimes recommended. In IPAH, the aim is to maintain an INR between 1.3 and 2.0. The use of anticoagulation in patients with Eisenmenger syndrome is controversial, and the potential risks and benefits of anticoagulation in this setting must be carefully weighed. In general, fewer patients with PH are being treated with long-term warfarin than in prior eras unless there is a hypercoagulable state, central line, or history of thrombosis [177, 178].

43.10.16 Atrial Septostomy and Potts Shunt

The general indications for atrial septostomy include severe pulmonary hypertension, syncope, intractable heart failure refractory to chronic vasodilator treatment, and symptomatic low cardiac output states [22]. Risks associated with this procedure include worsening of hypoxemia with resultant right ventricular ischemia, worsening right ventricular failure, increased left atrial pressure, and pulmonary edema [179]. We favor a graded balloon dilation approach utilizing intracardiac echo and saturation monitoring to determine adequacy of shunt. We have frequently used a cutting balloon with the initial inflation followed by static balloon dilations.

An atrial shunt provides a diastolic pop-off, whereas a systemic to pulmonary connection (i.e., Pott's shunt) provides a systolic pop-off (Fig. 43.15). A Potts anastomosis, connection of the left pulmonary artery to descending aorta, has been used to allow a direct shunt allowing an immediate reduction in right ventricular afterload [180–182]. Palliation of severe PAH with the Potts shunt is increasing in prevalence, but data are limited and patient selection remains highly individualized.

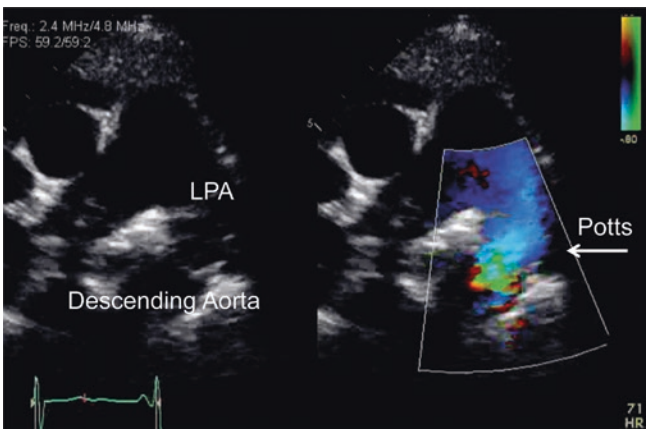


Fig. 43.15 Echocardiogram of Potts shunt

43.10.17 Transplantation

For patients who do not respond to prolonged vasodilator treatment, or with certain lesions, such as pulmonary vein stenosis, lung transplantation should be considered [183–186]. While cystic fibrosis accounts for the majority of pediatric lung transplants, IPAH is the second most common indication in some series, accounting for 15 percent of patients. The data on lung vs. heart-lung transplantation for "simple" congenital heart disease associated with PAH is controversial and center-dependent. A retrospective study found similar outcomes for children with congenital heart disease undergoing repair of congenital heart lesions combined with lung transplantation as compared with combined heart-lung transplantation [187]. There have been improved outcomes for pediatric lung transplantation in the recent years with a 5-year survival of approximately 60% (Fig. 43.16) [188].

43.11 Long-Term Outlook

Pulmonary hypertension in children previously carried a very poor prognosis. In a 1965 series of 35 patients with IPAH, 22 patients died within 1 year of the onset of symptoms, and none survived greater than 7 years [189]. In 1995, the prognosis was still poor, with the median survival in a

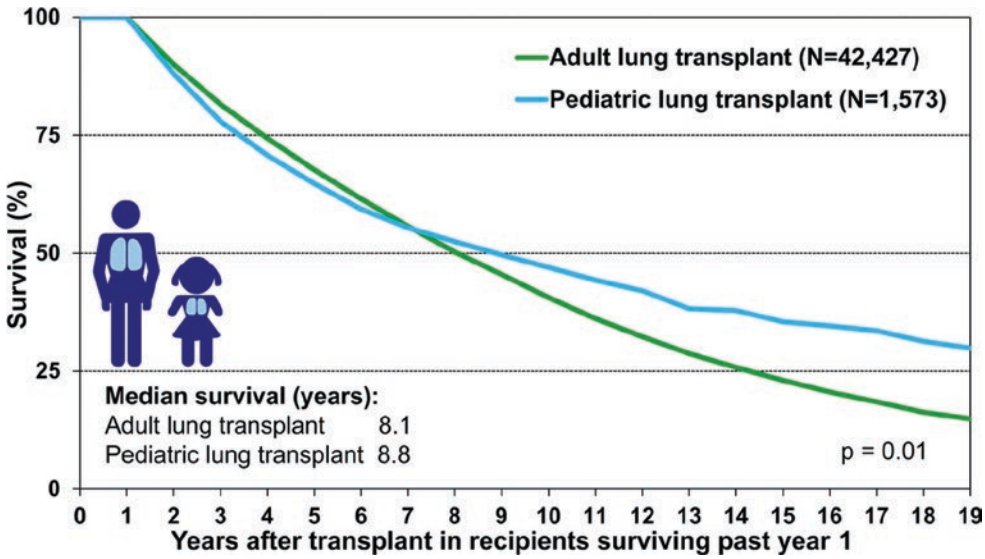


Fig. 43.16 Survival in pediatric lung transplantation. (Goldfarb et al. [188])

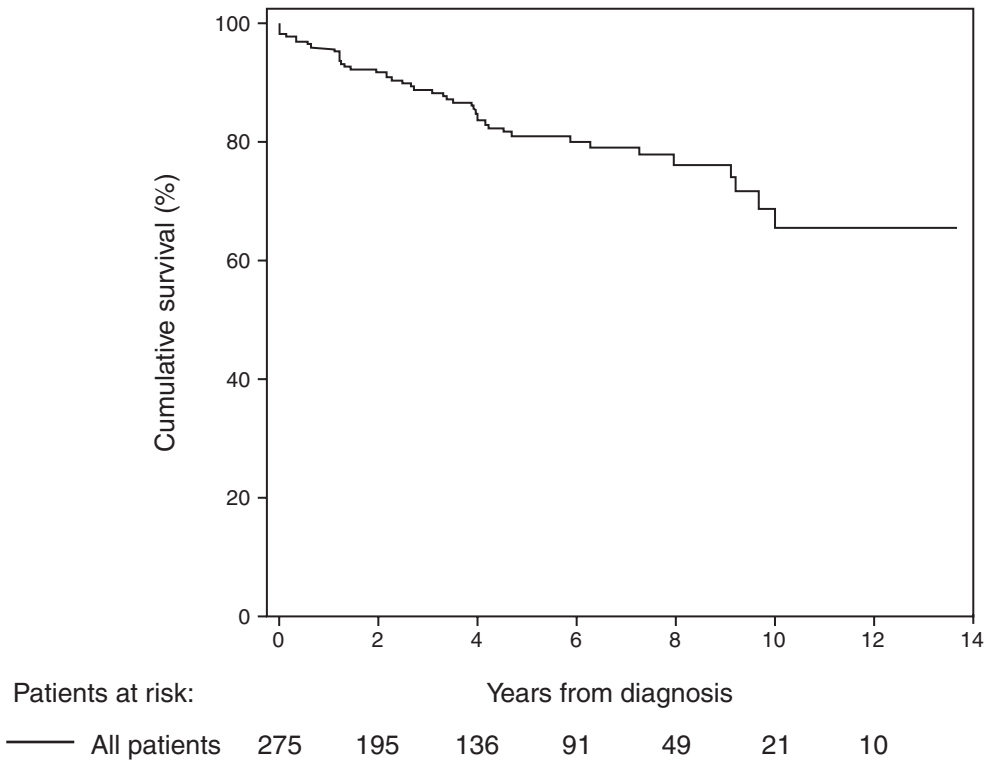


Fig. 43.17 Recent survival in pediatric PAH. (Zijlstra et al. [191])

series of 18 children with IPAH being 4.12 years [190]. However, recent advances in understanding the biology of the normal and hypertensive pulmonary circulations have led to a broader pharmacologic arsenal and improved prognosis of children with pulmonary hypertension. Recent survival in a cohort from three major PH centers revealed survival for pediatric PAH patients was improved with 1-, 3-, 5-, and 7-year transplantation-free survival rates of 96%, 89%, 81%, and 79%, respectively (Fig. 43.17) [191].

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Chapter 44
Acute Myocarditis and Cardiomyopathies

Brian Feingold and Steven A. Webber

Abstract The definition and classification of cardiomyopathies were recently revised by an expert panel of the American Heart Association (Maron et al., Circulation 113:1807–1816, 2006) following the initial classification by the World Health Organization in 1995 (Richardson et al., Circulation 93:841–842, 1996). Cardiomyopathies are considered "a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic" (Maron et al., Circulation 113:1807–1816, 2006). Cardiomyopathies are generally considered as primary (disease solely or predominantly confined to heart muscle) or secondary, showing pathological myocardial involvement secondary to a systemic or multiorgan disease process. Both forms are commonly seen in children, although primary forms predominate.

The definition and classification of cardiomyopathies was recently revised by an expert panel of the American Heart Association [1] following the initial classification by the World Health Organization in 1995 [2]. Cardiomyopathies are considered "a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic" [1]. Cardiomyopathies are generally considered as primary (disease solely or predominantly confined to heart muscle) or secondary, showing pathological myocardial involvement secondary to a systemic or multiorgan disease process. Both forms are commonly seen in children, although primary forms predominate.

Cardiomyopathies and myocarditis are significant contributors to end-stage heart failure in children, accounting for over 50% of all pediatric heart transplants [3]. They are also the commonest indication for ventricular assist device (VAD) support in childhood [4]. Pediatric cardiomyopathies have a reported incidence of 1.13–1.24 cases per 100,000 population in two recent large population-based studies [5, 6], though this is likely an underestimate. The true incidence of pediatric myocarditis is unknown. Many cases may be unrecognized and go on to experience clinical recovery. Some may be misdiagnosed as SIDS [7]. Others may present years later as chronic dilated cardiomyopathy with viral genome demonstrated in the myocardium but in the absence of active inflammation [8–10].

This chapter focuses on the role of the intensive care unit (ICU) in the management of the child with new-onset or established cardiomyopathy presenting with shock, heart failure, or arrhythmia. Management in the ICU comprises:

1. Determination of the form of cardiomyopathy and of the most likely etiology (most commonly discerning between acute myocarditis and an acute presentation of dilated cardiomyopathy (DCM))
2. Management of acute heart failure and / or arrhythmias
3. Estimation of prognosis and selection of patients for mechanical circulatory support and transplantation

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44.1 Dilated Cardiomyopathy and Myocarditis

44.1.1 Anatomy

DCM is characterized by dilation of one or both ventricles (most commonly the left ventricle) often with thinning of

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the left ventricle free walls. Varying degrees of hypertrophy may also be seen and left ventricular mass tends to be increased, even when the ventricular walls are thin. The left ventricle often takes on a globular shape and mitral regurgitation with annular dilation is frequently seen along with left atrial dilatation (Figs. 44.1a and 44.2a). Left ventricular systolic function is usually globally depressed, though varying degrees of ventricular dyssynchrony may be observed, even in the absence of bundle branch block. In contrast, right systolic ventricular function is often only minimally decreased or normal. Right ventricular dilation, when present, may be due to myocardial involvement from the primary disease process or secondary to tricuspid regurgitation and pulmonary hypertension.

In contrast, patients with acute myocarditis often show only a poorly functioning left ventricle with minimal dilation with, or without, regional wall motion abnormalities. There may be ventricular thickening secondary to myocardial edema, and left atrial enlargement may not be prominent, even when mitral regurgitation is present. These findings likely reflect the short duration of the disease process.

44.1.2 Etiology and Pathophysiology

Both acute myocarditis and DCM are characterized primarily by systolic ventricular dysfunction with resultant clinical signs and symptoms of heart failure. Diastolic dysfunction

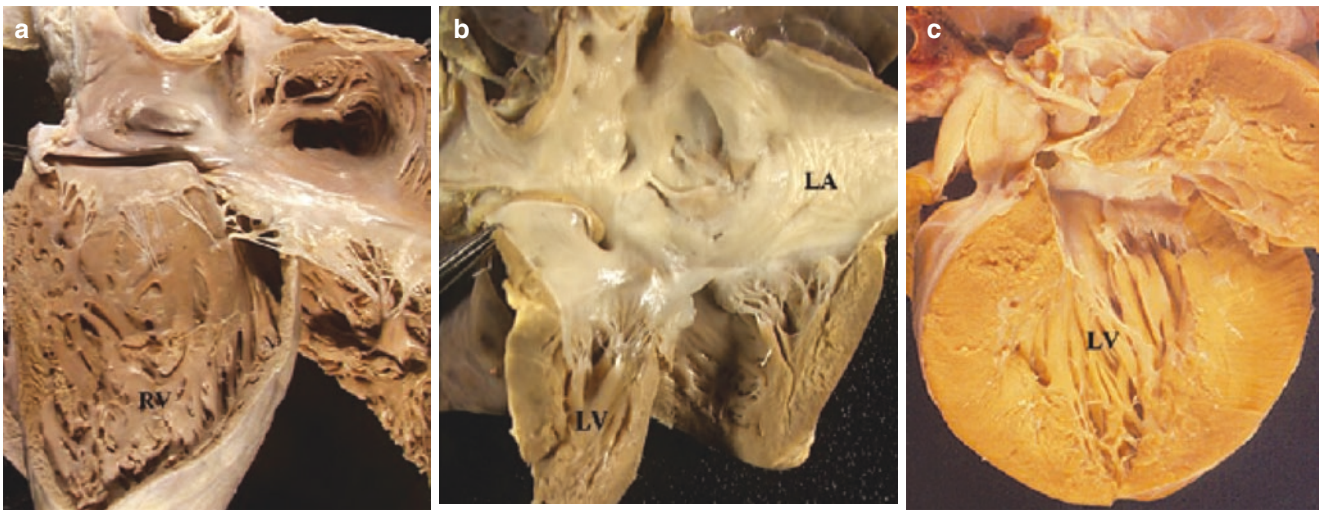

Fig. 44.1 Spectrum of pediatric cardiomyopathies. (**a**) Dilated cardiomyopathy (DCM) with marked ventricular dilation and wall thinning (shown from RV side). (**b**) Severe hypertrophic cardiomyopathy (HCM) with concentric hypertrophy, in this case secondary to Pompe's disease (glycogen storage disease type II). (**c**) Restrictive cardiomyopathy (RCM) with small left ventricular cavity size and marked dilation of the left atrium. (Courtesy of William Devine, Department of Pathology, Children's Hospital of Pittsburgh). LA left atrium, LV left ventricle, RV right ventricle

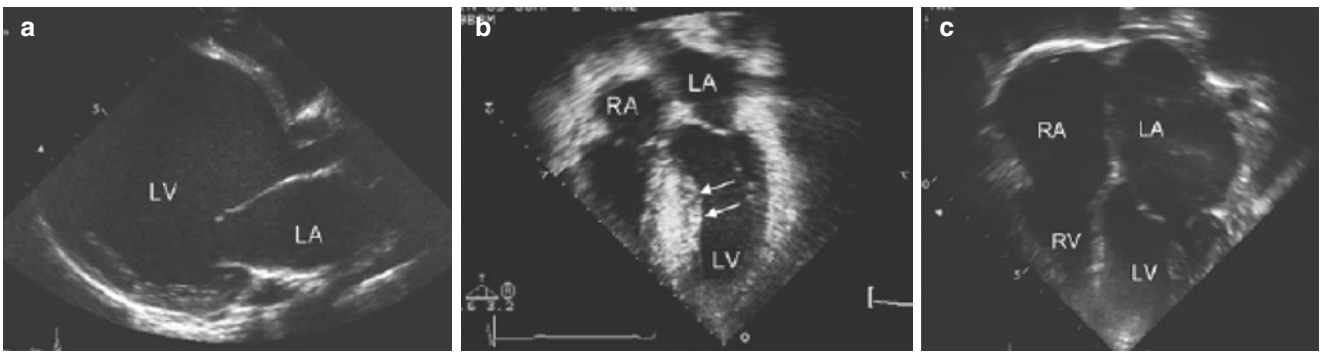

Fig. 44.2 Echocardiographic findings of pediatric cardiomyopathies. (**a**) Parasternal long-axis view demonstrates severe left ventricular dilation in a child with idiopathic DCM. (**b**) Asymmetric septal hypertrophy (arrows) in a child with HCM. (**c**) Apical four-chamber view demonstrates small ventricular chamber sizes and biatrial enlargement typical of RCM. LA left atrium, LV left ventricle, RA right atrium, RV right ventricle. (Courtesy of William Devine, Department of Pathology, Children's Hospital of Pittsburgh)

may also contribute to reduced myocardial performance in both settings, but particularly in acute myocarditis. In the latter, cardiac dysfunction may result from both direct viral invasion and myocyte lysis, as well as from the effects of myocardial inflammation. In clinical practice (beyond the neonatal period), symptoms are most often associated with (presumed) postviral lymphocytic infiltrates and autoimmunity. Adenovirus and enteroviruses (particularly Coxsackie B) are most frequent in children [11], although many other infectious and noninfectious causes have been identified, including viral, bacterial, fungal, and protozoal infections, as well as drug toxicities and various systemic disorders. The latter include Kawasaki disease and rheumatic fever.

Pediatric DCM encompasses a final common phenotype for a wide variety of etiologies. While the causes of most pediatric DCM are unknown, it is estimated that 30–40% of DCMs are inherited [12, 13], mostly in an autosomal-dominant fashion. Mutations in genes encoding myocyte cytoskeletal proteins as well as genes encoding sarcomere proteins have recently been identified as etiologies for DCMs [14]. Other genetic causes include inborn errors of metabolism (e.g., mitochondrial transport chain defects) [15] and neuromuscular syndromes (e.g., muscular dystrophies). Also, the finding of viral genome in patients with DCM suggests that at least some DCMs may result from prior myocarditis (either apparent or clinically unapparent) [9]. Other acquired forms of DCM include medication-related (e.g., anthracycline toxicity) and arrhythmia-induced (e.g., chronic, incessant supraventricular tachycardia).

44.1.3 Clinical Presentation

Heart failure in children from any cause often presents somewhat insidiously, after repeated evaluation and medical testing for other, more common conditions. Neonates and infants often present acutely unwell; yet, the diagnosis of a primary cardiac disorder may not be made on initial evaluation. It is not uncommon for cardiac disease to be considered only after ancillary studies fail to corroborate the presumed diagnosis or initial resuscitative attempts fail to improve the child's condition (e.g., shock due to sepsis). While much of the diagnostic difficulty results from the relative infrequency of primary cardiac disease in children, the inability of an infant or young child to verbally convey their symptoms also contributes. Also the frequency with which young children experience nasal, respiratory, or gastrointestinal symptoms, particularly during the winter and spring, often results in the initial symptoms of heart failure being attributed to these much more common maladies.

Infants with heart failure may present with a history of poor feeding, respiratory distress, listlessness, poor weight gain, or irritability. Common adult symptoms of paroxysmal nocturnal dyspnea and orthopnea are uncommon in pediatric patients. In older children, abdominal pain, anorexia, nausea, and vomiting are often observed and are likely due to liver capsule distention from hepatomegaly and/or intestinal venous congestion.

On physical examination, the child may appear anxious, and sinus tachycardia is usually present. Sweating is common in infants. Elevation of the jugular venous pulse may be present but is difficult to identify in the infant and toddler. Pallor and cool extremities may be present and are often associated with poor peripheral pulses and prolonged capillary refill. Resting tachypnea and retractions (suprasternal, intercostal, and subcostal) are common. Unlike adults, crackles are exceedingly rare in infants and young children with heart failure, even when pulmonary edema is present. Wheezes are more likely to be present. While hepatomegaly is a common finding, it is often overlooked or underappreciated by the inexperienced practitioner. Periorbital edema (infants and young children) with or without ascites (older children) is more common than peripheral edema in children. Failure to thrive may also be evident, particularly with chronic heart failure.

The clinical distinction between acute, fulminant myocarditis and acute presentation of chronic DCM is often difficult. At the time of presentation, many will have a history of an intercurrent or recent viral illness. In fact, viral syndromes are so common in early childhood that the etiologic relationship to the onset of acute heart failure is often not clear. However, the distinction between myocarditis and DCM is crucial. Many patients with fulminant myocarditis will recover completely if they are supported, whereas children with severely decompensated heart failure from DCM often will not recover without transplantation. Thus, the expectations from mechanical support (ECMO or VAD) and consideration for cardiac transplantation are directly impacted by the underlying diagnosis.

In many cases, clinical testing may help guide the diagnosis of acute myocarditis or acute presentation of DCM. The presence of marked cardiomegaly on *chest radiograph* and massive left-sided precordial forces on *ECG* suggest the underlying process occurred over time, favoring a diagnosis of chronic DCM over myocarditis. In contrast, absence of (or mild) cardiomegaly (Fig. 44.3a) and globally diminished voltages on electrocardiogram are more typical of acute myocarditis. Frank myocardial infarction may sometimes be observed on the 12 lead ECG of children with acute myocarditis. *Echocardiography* is very useful in the evaluation of infants and children suspected to have either myocarditis or cardiomyopathy and should be performed in all patients in whom these diagnoses are considered. *Endomyocardial biopsy* can generally be performed safely in children over the age of 1 year [16] and should be considered in the diagnostic

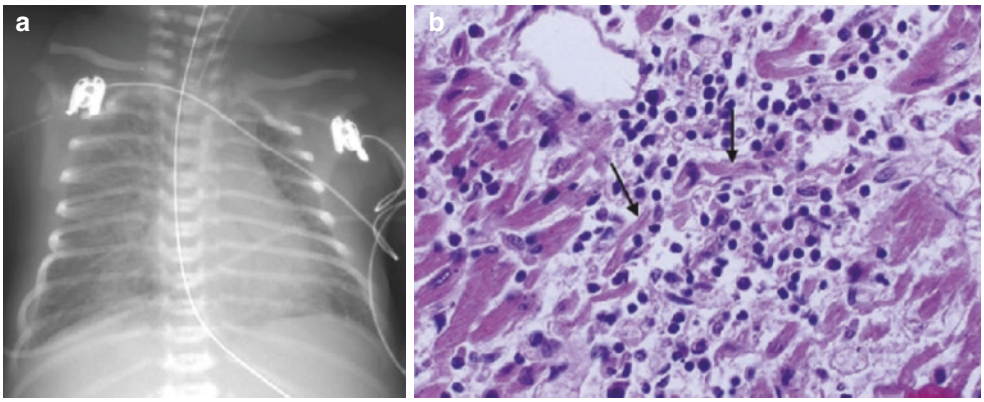

Fig. 44.3 Acute myocarditis. (**a**) Chest radiograph shows a small heart with pronounced pulmonary edema. (**b**) Endomyocardial biopsy specimen showing lymphocytic infiltrate with myocyte destruction (arrows). (Courtesy of William Devine, Department of Pathology, Children's Hospital of Pittsburgh)

evaluation, particularly when trying to distinguish between myocarditis and DCM. Biopsy samples from the right ventricle can be analyzed by routine hematoxylin and eosin staining for lymphocytic infiltrates with myocyte necrosis (Fig. 44.3b), consistent with a diagnosis of acute myocarditis [17] or for evidence of myocyte hypertrophy and/or interstitial fibrosis, favoring a diagnosis of DCM. A fresh-frozen sample should also be obtained for *PCR* analysis of common viral causes of myocarditis. *Viral cultures* of stool, urine, and respiratory secretions may contribute to the diagnosis, as may *polymerase chain reaction analysis* of blood, pericardial effusion, or cerebral spinal fluid. *Viral titers* (at presentation and during convalescence) are often performed, but are generally noncontributory to the diagnosis of childhood myocarditis.

Diagnostic *evaluation for inborn errors of metabolism* is generally reserved for patients presenting with dilated or hypertrophic cardiomyopathies in the first year of life. The presence of severe acidosis, hypoglycemia, elevated lactic acid, deranged liver function tests, and hyperammonemia should all lead to rapid metabolic and genetic evaluation although all of these may also be observed in the setting of cardiogenic shock from nonmetabolic causes. A full description of the evaluation of infants suspected of having an inborn error of metabolism is outside the scope of this text, but readers may refer to some excellent recent reviews [15, 18, 19].

44.1.4 Management

The critically ill patient, who presents on the verge of hemodynamic collapse, requires aggressive therapy to augment oxygen delivery while minimizing consumption. Intubation with mechanical ventilation and sedation (± paralysis) is useful to eliminate the work of breathing while improving pulmonary edema as a result of positive pressure ventilation. Placement of central venous and arterial monitoring lines is also facilitated by these maneuvers. In addition to being able to administer medications and monitoring hemodynamics, these lines serve to limit the need for repeated phlebotomy in infants and young children, in whom fear, agitation, and site availability are complicating issues. The use of pulmonary arterial catheters is less common in the pediatric age group than in adults and rarely improves management when it is apparent that pulmonary edema is of cardiac origin.

Intravenous diuretics are used to augment diuresis and improve congestive symptoms. Continuous infusions of furosemide have been used with success in pediatric patients when intermittent dosing has failed to result in adequate diuresis. Inotropes are used to augment cardiac function and output. Therapy often consists of low-to-moderate doses (2–5 μg/kg/min) of dopamine for renal perfusion and blood pressure support and milrinone (0.125–1 μg/kg/min) to diminish afterload and augment cardiac output. Augmented inotropy can be achieved with dobutamine (1–10 μg/kg/min), while further afterload reduction may be achieved with sodium nitroprusside (0.3–4 μg/kg/min), if blood pressure tolerates. Rarely do patients require support with infusions of high doses of epinephrine or norepinephrine. In these cases (except when pathology is believed to be rapidly reversible), serious consideration should be given to early institution of mechanical circulatory support (see below). Caution must also be taken with regard to the arrhythmogenic potential of all inotropes, particularly with escalating doses. Appropriate monitoring is essential and care must be taken to aggressively correct all electrolyte disturbances, particularly hypo or hyperkalemia and hypomagnesemia.

Only limited data exists regarding the use of nesiritide for the treatment of acute heart failure in the pediatric population. Our experience has primarily involved its use in children who were otherwise recalcitrant to diuretics [20]. With appropriate monitoring of blood pressure and serum sodium, no complications were noted and some success was achieved in inducing diuresis. Others have reported use of nesiritide immediately after cardiac surgery, reporting no adverse hemodynamic effects or arrhythmias [21].

With stabilization and improvement in end-organ perfusion, gradual weaning of therapies is indicated. When oral medications can be safely tolerated and adequately absorbed, digoxin is often initiated, though of unproven benefit in pediatric patients. Intravenous diuretics are changed to oral forms and angiotensin-converting enzyme (ACE) inhibitors are begun for afterload reduction while weaning milrinone. Beta-blockers (other than as antiarrhythmic agents) only play a limited role in the ICU care of the child with DCM. Indeed, during acute deterioration requiring use of intravenous inotropes, beta-blockers will generally need to be withdrawn. Institution of beta-blockers for new-onset DCM is generally not performed in the ICU, since benefits (if they exist) are long-term and patients in the ICU are often hypotensive or being aggressively diuresed and vasodilated. Introduction of beta-blockers is part of the long-term management of chronic heart failure and is of unproven benefit (though widely performed) at this time [22]. Usually, beta-blockers are commenced after transition to oral diuretic therapy and once ACE inhibitor dosing is optimized. This generally occurs on the medical floors or in the outpatient setting.

When acute heart failure is unresponsive to aggressive medical management, institution of mechanical circulatory support must be considered. This is discussed in detail in Chap. 6. In general, ventricular assist devices are most appropriate when used as a bridge to transplantation, since prolonged periods of support may be required. Recovery from acute (including fulminant) myocarditis is often rapid, so ECMO or short-term use of VADs is more appropriate.

In acute myocarditis, therapy is primarily supportive. Only rarely is infection caused by a specific agent for which there is established antimicrobial therapy of proven efficacy. Intravenous immunoglobulin and corticosteroids have both been used [23], though there is no proof of their efficacy in randomized clinical trials. Steroids are contraindicated when there is evidence of active viral infection. More potent immunosuppressive agents, including T cell cytolytic agents and calcineurin inhibitors, have been used in some programs. There is no data to support a specific risk/benefit ratio and most programs do not use these agents.

Avoidance of dysrhythmias is a key component in the management of all patients with acute and chronic heart failure. In addition to careful attention to maintaining normal serum electrolyte concentrations, control of tachyarrhythmias (both supraventricular and ventricular) is important. Amiodarone is commonly used for treatment and prophylaxis of ventricular tachycardia, as well as for refractory atrial tachycardias.

The role of implanted cardioverter-defibrillators (ICDs) in the management of children and adolescents has not been as well defined as in adults. Evidence suggests children with DCM have a lower risk of sudden death as compared to adults with similar degrees of ventricular dysfunction [24]. Nonetheless, in children with DCM, particularly those with evidence of ventricular tachycardia, ICDs have been utilized and are likely indicated in patients with syncope and aborted sudden death. Factors that may complicate placement of ICDs in children include greater risk of complications such as lead fracture (possibly due to growth or greater levels of activity in children as compared to adults), greater risk of inappropriate discharge due to ability to achieve higher (sinus) heart rates, and the inability to use endovascular leads in smaller children (<15 kg), necessitating epicardial lead placement [25].

44.1.5 Long-Term Outlook

Traditionally, long-term outlook in children with DCM was said to follow the "rule of thirds" with 1/3 improving, 1/3 remaining the same, and 1/3 demonstrating progressive deterioration in cardiac function. Recent population data from several groups has improved our understanding of the natural history of DCM. The National Australian Childhood Cardiomyopathy Study showed 5-year freedom from death or transplantation of 63% for children with DCM [26, 27]. The Pediatric Cardiomyopathy Registry showed a 5-year survival of 54% for DCM in North America [28, 29]. These data include outcomes for those followed with a diagnosis of DCM that may never have required intensive care. It is, therefore, of interest to note a recent important publication that focused on epidemiology and outcomes for new-onset heart failure from myocardial (nonstructural) disease. In a population-based study for the United Kingdom and Ireland, 82% of children presenting with new-onset heart failure (most due to DCM) were in NYHA (or Ross) class III or IV and 41% required mechanical ventilation during first admission. One-year transplant-free survival was only 66% [30]. This is far worse than outcomes for new-onset heart failure in adults. Predictors of survival for DCM vary considerably between series. In a recent systematic review [31], it was noted that the most consistent findings associated with improved outcome were younger age at diagnosis, better fractional shortening and ejection fraction at diagnosis, and presence of myocarditis.

In general, the outcomes of acute myocarditis in children are good. A number of studies have shown survival rates of between 75% and 100% for acute myocarditis in childhood [23], including fulminant cases that may require mechanical circulatory support. This emphasizes the benefit of knowing the diagnosis of myocarditis, since acute transplantation should be avoided even if mechanical support is required. This will provide the opportunity for cardiac recovery, as well as minimize the risks of transplantation during recent or active viral infection.

44.2 Hypertrophic Cardiomyopathy

44.2.1 Anatomy

In hypertrophic cardiomyopathy (HCM), it is most common for patients to show asymmetric hypertrophy of the interventricular septum, with varying degrees of obstruction to left ventricular outflow due to prominence of the subaortic septum and/or systolic motion of the anterior leaflet of the mitral valve (Fig. 44.2b). Less commonly, children with HCM may demonstrate concentric left ventricular hypertrophy (Fig. 44.1b). In infant presentation, involvement of both the left and right ventricles is common, and biventricular obstruction may occasionally be observed. As ventricular hypertrophy may not be apparent until puberty, children with a family history of HCM in whom no genetic diagnosis/marker has been established should undergo serial evaluation with electrocardiography and echocardiography before, during, and after puberty to assess for development of abnormal cardiogram and ventricular hypertrophy.

44.2.2 Etiology and Pathophysiology

HCM is most commonly an inherited disorder (autosomal dominant) with marked variability in clinical expression. Nearly all mutations identified to date are in ten genes that encode cardiac sarcomere proteins [32]. It is likely that many other disease-causing mutations are yet to be identified. When there is a known familial mutation, testing of relatives can rule out disease. However, in many families, no mutation is identified, or testing has not been performed. It is estimated that current screening panels for sarcomeric protein mutations reveal mutations in approximately 70% of cases. Other causes of pediatric HCM include conditions associated with left ventricular hypertrophy such as glycogen or lysosomal storage diseases, mitochondrial defects, and Noonan, LEOPARD, and Beckwith–Wiedemann syndromes.

Patients with HCM generally have thickened left ventricle walls with normal or decreased cavity size and preserved or hyperdynamic systolic function. A subgroup with pronounced restrictive physiology and atrial dilatation has been reported [33]. In some cases, there appears to be overlap of phenotype with restrictive cardiomyopathy (RCM). Cases of classical HCM and RCM have been observed in different members of the same family due to cardiac Troponin I mutations [34].

Heart failure symptoms are very rare in children and adolescents with HCM, and are most commonly a result of diastolic dysfunction. The exception is the infant with severe disease, often with biventricular hypertrophy with or without outflow obstruction. These infants commonly present with heart failure. Metabolic and genetic work-up is warranted in these cases.

Syncope and aborted sudden death may be observed in patients with HCM. The pathophysiology is often hard to define. Tachycardia and hypovolemia (e.g., due to dehydration and fever) may be poorly tolerated; impaired myocardial perfusion, severe obstruction, inappropriate peripheral vasomotor tone, and atrial and ventricular arrhythmias may all contribute to syncope and mortality in HCM.

44.2.3 Clinical Presentation

Patients with HCM may present in the absence of symptoms (e.g., for evaluation of a murmur) or due to a family history. Progressive activity intolerance and syncope are also common presenting complaints; however, it should be noted that in clinical practice, most children with these symptoms do not have cardiomyopathy. Affected infants may show tachypnea, hepatomegaly, and/or failure to thrive. In older children, chest pain may also be a symptom and suggests myocardial ischemia [32]. Unfortunately, it is not uncommon for sudden death (or aborted sudden death) to be the initial presentation of HCM in adolescents and young adults [35]. Undiagnosed HCM is a leading cause of sudden death in young, healthy individuals and athletes.

44.2.4 Management

Most children with HCM are asymptomatic and thus are not often encountered in the ICU. While progression to end-stage heart failure occurs, the diagnosis is relatively rare in children, accounting for only 2.5% of pediatric heart transplant listings in a recent analysis of over 3000 pediatric transplant candidates from a large, multicenter database [36]. With advancing symptoms of heart failure, patients may be admitted to the hospital for treatment. Although so-called burned-out HCM occurs in children in which there is progressive systolic dysfunction and left ventricular dilation, heart failure from HCM results predominantly from diastolic dysfunction. Thus, many of the therapies employed in the treatment of heart failure from DCM are not useful or are only of limited benefit.

An ideal agent for management of heart failure due to HCM would possess positive lusitropic effects, enabling relaxation of the ventricular myocardium and thus achieving improved stroke volume at lower filling pressures. Unfortunately, this agent does not yet exist and therapies directed primarily at management of diastolic ventricular

dysfunction are scant. Most common is the use of negative inotropic agents, such as non-dihydropyridine calcium channel blockers (e.g., verapamil) or beta-blockers (e.g., propranolol, atenolol). In the ICU setting, esmolol may be preferred due to its short half-life. Due to the exquisite sensitivity/dependence of the neonatal and infant heart to serum calcium levels, use of intravenous calcium channel blockers in infants less than 1 year of age is usually contraindicated. Milrinone, a phosphodiesterase III inhibitor, possesses some positive lusitropic effect [37] and thus may be of theoretical benefit in select patients with HCM and advanced heart failure symptoms in the absence of significant subaortic obstruction. As milrinone can be arrhythmogenic, careful consideration must be given to balance any potential benefits against the risks of induced tachyarrhythmias. Furthermore, vasodilatation may exacerbate any left ventricular outflow obstruction. Diuretics are often used in the outpatient setting for patients with congestive symptoms. These agents must also be used with caution in the setting of diastolic dysfunction as cardiac output and myocardial perfusion can be compromised with insufficient preload and again outflow obstruction may be increased.

The role of ICDs in the management of children with HCM is unclear. Data from a multicenter registry of pediatric and congenital heart disease patients showed HCM was the second most common diagnosis for which subjects received an ICD [38]. In patients with HCM who experience syncope or aborted sudden death, implantation of an ICD is likely indicated. Use of ICDs for primary prevention in patients with HCM is not established.

44.2.5 Long-Term Outlook

Although the natural history of HCM in adults is quite variable [32], survival tends to be worse the younger a patient presents. In particular, infants who present with heart failure have a poor prognosis. Patients who present older than 1 year of age are unlikely to die of progressive heart failure from HCM, but may succumb to sudden death [39]. Sudden death predominates in adolescents and young adults with HCM and is thought to be more likely in those with a family history of sudden death or personal history of recurrent syncope, ventricular tachycardia, or massive left ventricular hypertrophy [35].

Hypertrophy often progresses (or may first become apparent) during periods of rapid growth (i.e., puberty), and thus, patients with HCM should be monitored closely during adolescence. In a small percentage of patients, there may be a regression of hypertrophy, with ultimate development of left ventricular dilation and poor systolic function. This so-called end-stage or "burned-out" HCM typically requires treatment for systolic heart failure much like DCM and may necessitate transplantation [40]. It is rare in childhood.

Our knowledge of outcome in pediatric HCM has recently been greatly advanced through analyses from the two large multicenter registries. In the National Australian Childhood Cardiomyopathy Study [27, 41], less than 10% presented with heart failure, most presenting with a murmur for family screening. A third were syndromic (mostly Noonan syndrome). Freedom from death or transplant was 83% at 5 years and 76% at 10 years. Presentation by 1 year of age was an important predictor of mortality. Annual mortality for patients presenting beyond this age was only 1.5%. In the Pediatric Cardiomyopathy Registry [29, 42], survival for idiopathic HCM (n = 634) was 82% at 5 and 10 years for infantile presentation and 94% and 86% at the same time intervals for presentation beyond infancy.

44.3 Restrictive Cardiomyopathy

44.3.1 Anatomy

Restrictive cardiomyopathy (RCM) is a rare form of cardiomyopathy characterized by normal or decreased volume of both ventricles associated with atrial enlargement (often massive) and with normal LV wall thickness (Figs. 44.1c and 44.2c). As mentioned earlier, there is some phenotypic overlap seen with HCM, and mild left ventricular hypertrophy is sometimes observed. Systolic function is generally normal [1].

44.3.2 Etiology and Pathophysiology

Overall, RCM is a rare diagnosis, accounting for approximately 5% of pediatric cardiomyopathies [5, 6]. The underlying cause(s) are generally unknown [43–45]. This is in contrast to adult patients with RCM, in whom infiltrative diseases such as amyloidosis and sarcoidosis are sometimes identified. While some children may present with familial forms, most cases are sporadic. Cardiac troponin I mutations have been reported as a cause of restrictive (and hypertrophic) cardiomyopathy [34]. The severe restrictive physiology leads to decreased cardiac output, elevated filling pressures, and atrial stretch that may lead to arrhythmias. Some patients demonstrate presumptive evidence of ischemia based on ST segment depression, especially during tachycardia. Elevation of pulmonary vascular resistance is frequently seen (even at presentation) and may contribute to right heart failure. Loss of systolic function is rare, although it is occasionally seen in advanced disease.

44.3.3 Clinical Presentation

Exercise intolerance, exertional angina, syncope, tachyarrhythmias, or sudden death may all occur. Atrial tachycardias are not uncommon and likely result from severe atrial dilation due to poor ventricular compliance. These are poorly tolerated in the setting of diastolic compromise.

Much like those with HCM, children and adolescents with RCM often present incidentally for evaluation of a murmur or for follow-up of an atypical cardiac silhouette on chest radiography obtained for unrelated reasons. Patients may also present with symptoms of heart failure, angina, palpitations, or syncope. Syncope may be precipitated by atrial or ventricular tachycardia, both of which are poorly tolerated in the setting of limited ventricular compliance. Similar to HCM, sudden death is also not an uncommon presentation of RCM [44].

44.3.4 Management

Therapeutic options for pediatric RCM are very limited. Many of the same physiologic considerations (and thus limitations in management) discussed for patients with HCM are also pertinent for those with RCM. Gentle diuresis is indicated if there is pulmonary venous congestion or pulmonary edema, but excessive diuresis may lead to reduction in cardiac output. Vasodilators may lead to hypotension, since augmented cardiac output may not occur when stroke volume is fixed. The role of beta-blockers is unclear. Slowing of the heart rate will prolong diastolic filling time, but since stroke volume is relatively fixed, increasing heart rate may be an important mechanism for augmenting cardiac output.

As short-term survival is poor after a diagnosis of RCM, many centers recommend early evaluation for cardiac transplantation. Cardiac catheterization should be performed during the evaluation process because of the high likelihood of increased pulmonary vascular resistance. Hemodynamic assessment may also help with the distinction from constrictive pericarditis. Computed tomography is indicated if pericardial disease is suspected. Although secondary causes of RCM, such as amyloidosis and sarcoidosis, are exceedingly rare in children, biopsy should be considered in older children presenting with RCM to assess for these systemic diseases.

For patients managed out of hospital, implantation of an ICD in combination with antiarrhythmic agents may be considered, especially if prior near-syncope, syncope, or tachyarrhythmia has occurred.

44.3.5 Long-Term Outlook

Children with RCM have very poor prognosis in the absence of heart transplantation. Survival at 5 and 10 years after diagnosis was 39% and 20%, respectively, at our center [43], and others have reported similar outcomes [46]. A minority of patients has been reported to survive upward of 8–12 years [45, 47–49]; however, strong, independent predictors of prolonged survival remain to be identified. The presence of symptoms at diagnosis did not correlate with survival in our cohort. Since excessive elevation in pulmonary vascular resistance may necessitate heart–lung transplantation, progressive elevation in pulmonary resistance should also lead to consideration of early transplantation.

44.4 Noncompaction Cardiomyopathy

44.4.1 Anatomy

In left ventricular noncompaction (LVNC) cardiomyopathy, the left ventricle shows prominent trabeculations and deep intertrabecular recesses (Fig. 44.4a, b). These findings are most commonly observed at the apex of the left ventricle but can be seen in an isolated fashion along the lateral wall. There is often dilation of the left ventricle with associated depressed systolic function. There may also be coincident ventricular hypertrophy, or at least lack of expected ventricular wall thinning for the degree of chamber dilation. Noncompaction can also occur in the setting of congenital heart disease, particularly hypoplastic left heart syndrome, ventricular septal defects, and pulmonary stenosis [50].

44.4.2 Etiology and Pathophysiology

LVNC has been increasingly diagnosed over the last 10 years. Previously, cases of LVNC may have been classified as HCM or DCM in part because of a lack of awareness of the diagnosis, limited resolution of earlier generations of echocardiography machines, and lack of standardized diagnostic criteria. LVNC may account for up to 9% of pediatric cardiomyopathies [6]. It can occur in isolation or with other congenital cardiac disease, and both sporadic and familial forms have been described [51]. When LVNC is inherited, X-linked inheritance appears to be most common, but autosomal-dominant, autosomal-recessive, and mitochon-

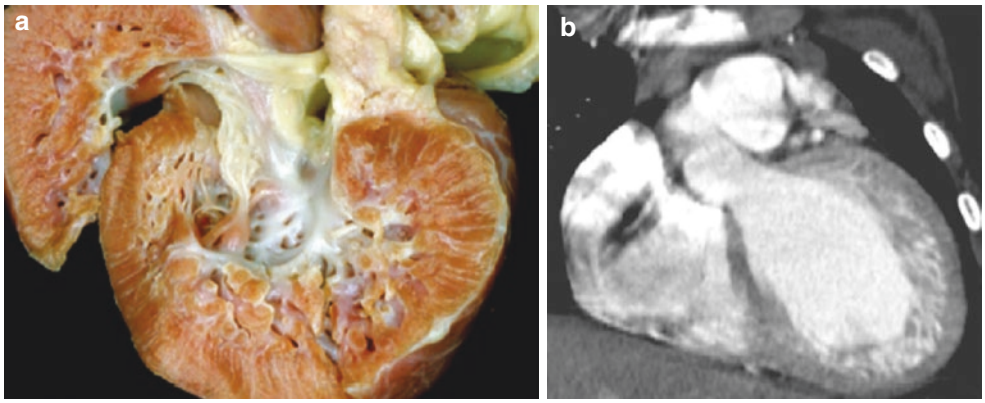

Fig. 44.4 Left ventricular noncompaction (LVNC) cardiomyopathy. (**a**) Pathologic specimen showing typical "spongiform" myocardium of left ventricle. (Courtesy of William Devine, Department of Pathology, Children's Hospital of Pittsburgh). (**b**) Intertrabecular recesses and dilation of the left ventricle in a teenager with noncompaction cardiomyopathy as shown by computed tomography. (Courtesy of William Devine, Department of Pathology, Children's Hospital of Pittsburgh)

drial inheritance may also occur. Mutations in the G4.5 gene at Xq28 (that encodes tafazzin) are responsible for X-linked LVNC [52] and also some other infantile DCMs, including Barth syndrome, which is characterized by cardiomyopathy (often with LVNC), intermittent neutropenia, peripheral myopathy, and growth delay [53, 54]. LVNC has been postulated to result from an arrest in early embryonic endomyocardial morphogenesis, resulting in a spongy meshwork of fibers and myocardial sinusoids [55]. Patients often have features most consistent with DCM, including symptomatic heart failure and arrhythmias, although some are found to have only asymptomatic LV dysfunction. Waxing and waning of ventricular function has also been described. Some series also report relative high prevalence of ventricular thrombosis and/or systemic embolic events, particularly in adults [56–58].

44.4.3 Clinical Presentation

Approximately half of children with LVNC who present for evaluation have signs and symptoms of heart failure. Others may come to evaluation incidentally for cardiomegaly on chest X-ray, abnormal ECG findings, or for assessment of a murmur. Patients may also present with arrhythmias. Most series show a tendency to progression in heart failure symptoms over time [58, 59], although a waxing and waning course is not rare. Presentation in infancy with heart failure due to severe systolic ventricular dysfunction is not unusual, and some of these cases show marked improvement over time, though this may be transient.

44.4.4 Management

Discerning LVNC from the broader category of DCM can require a high index of suspicion. Echocardiographic diagnostic criteria have been described [60] and recently called into question [61]. Adjunctive imaging modalities such as CT or MRI may provide better diagnostic information [62] but are less readily accessible and may be impractical during the initial diagnostic evaluation of a critically ill child with heart failure. Genetic testing for mutations in the G4.5 gene may help lead to a specific diagnosis, especially when the family history suggests X-linked inheritance.

Patients who manifest primarily with heart failure due to depressed systolic ventricular function are treated in a fashion similar to those with DCM. Therapy with diuretics and ACE inhibitors, with or without beta-blockers, is often employed during long-term follow-up. Although systemic embolism and arrhythmias (atrial fibrillation and ventricular tachycardia) are relatively common in the adult LVNC population, these are relatively rare in pediatric series. Ventricular ectopy may also be observed. Systemic anticoagulation is indicated when there is severe systolic ventricular dysfunction.

44.4.5 Long-Term Outlook

The relative infrequency of LVNC does not allow for proper characterization of the clinical course of children with this diagnosis, as in patients with DCM. Ichida and colleagues [59] report the longest follow-up in their series

of patients with childhood LVNC (median 6 years, range 0–17 years) and described the development of ventricular dysfunction or death in 75% of those followed for ≥10 years. In another series, transplant-free survival in infants with LVNC and no congenital heart defect was 52% at 3 years [50]. This was almost identical to transplant-free survival of 53% among 29 subjects with LVNC in the National Australian Cardiomyopathy Study [27]. Although these studies of LVNC in childhood report median ages at presentation of between 3 months and 7 years [50, 58, 59], there are various reports in adults that describe initial diagnosis as late as 70–75 years [56, 57] with absence of depressed cardiac function in some cases. This suggests that LVNC may be more common than has been observed, with some having only the morphologic findings (deep trabeculations) without overt ventricular dysfunction until much later in life.

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Chapter 45
Pericardial Diseases

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Abstract Pericardial diseases are defined as structural or functional abnormalities of the visceral or parietal pericardium that may impact cardiac function. Diseases of the pericardium include a spectrum of acquired and congenital problems consisting of infectious and inflammatory processes, neoplastic lesions, as well as congenital structural defects.

45.1 Introduction

Pericardial diseases are defined as structural or functional abnormalities of the visceral or parietal pericardium with potential impact on cardiac function. Diseases of the pericardium include a spectrum of acquired and congenital problems consisting of infectious and inflammatory processes, neoplastic lesions, as well as congenital structural defects. Treatment is aimed at addressing the underlying cause.

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45.2 Anatomy of the Pericardium

The pericardium is a sac-like structure surrounding the heart, consisting of two layers: a thin inner visceral layer made up of mesothelial cells and a thick outer layer made up of collagen and elastic fibers, separated by a virtual space containing a small amount of fluid (about 20 ml), which serves as lubricant [1]. The pericardial fluid is produced by the visceral pericardium and is essentially an ultrafiltrate of plasma. The pericardial fluid normally drains through the right lymphatic duct via the right pleural space and by the thoracic duct via the parietal pericardium [2]. The arterial supply of the pericardium is via a branch of the internal thoracic artery, and the venous drainage is through tributaries of the brachiocephalic veins.

The pericardium envelops the heart and great vessels, but is not attached to them. Instead, it reflects around the great vessels forming the pericardial recesses and sinuses. The pericardium is anchored to the diaphragm by the pericardiophrenic ligament and to the sternum by the sterno-pericardial ligament, providing support for the heart within the thoracic cage. It has been speculated that the presence of the parietal pericardium helps maintain a functionally optimal cardiac shape, since the heart tends to be more spherical after pericardiectomy.

45.3 Physiology and Pathophysiology

Although an intact pericardium is not critical to cardiovascular function, it assumes some minor functions including:

- Limitation of intrathoracic cardiac motion
- Preservation of diastolic and systolic interactions between the right and left ventricles, balancing right and left ventricular output
- Limitation of acute cardiac dilatation

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– Lubricant effect that minimizes friction between cardiac chambers and surrounding structures
– Lymphatic and immunological functions, acting as anatomic barriers that help prevent spread of infection from contiguous structures, especially the lungs

The normal pericardium limits cardiac distention, thereby coupling the ventricles and enhancing their interactions [3, 4]. Pressure or volume overload of one ventricle influences the compliance and filling of the contralateral ventricle via septal-mediated diastolic interactions, called interventricular coupling. By influencing the effects of diastolic pressure and dimensions between the ventricles, the pericardium facilitates a balance between the right and left ventricular output.

The normal intrapericardial pressure is subatmospheric, nearly equal to intrapleural pressure and varies with pleural pressure. The inspiratory decrease in pleural pressure slightly reduces pericardial, right atrial, right ventricular, pulmonary capillary wedge, and systemic arterial pressures. Under physiologic conditions, respiratory variations influence cardiac filling and hemodynamics. However, the effects on the right and left heart are distinct, secondary to differences in the anatomic relationship of the systemic and pulmonary venous return to the intrapleural space [5]. The systemic venous system is extrapleural as opposed to the pulmonary venous system, which is intrapleural. As a consequence, decreases in intrathoracic pressure during inspiration have a different effect on systemic and pulmonary venous return. The systemic venous return is augmented by about 50%, which increases right heart filling and output. Since pleural pressure changes are evenly distributed to the left heart chambers and pulmonary veins, there is minimal change in the pressure gradient between the pulmonary veins and the left ventricle. Therefore, left heart filling is essentially unchanged throughout the respiratory cycle [6].

Abnormal pericardial fluid production is usually secondary to injury or inflammation (postoperative pericardial effusion, acute pericarditis, post-pericardiotomy syndrome). Transudative fluid results from obstruction of fluid drainage, while exudative fluid is secondary to inflammatory, infectious, malignant, or autoimmune processes. The normal pericardium has a small capacitance volume (about 150 ml) limited by the relative noncompliance of the parietal pericardial layer. When reserve capacitance has been reached, further increases in intrapericardial volume will result in a steep increment of intrapericardial pressure. The hemodynamic repercussion of pericardial fluid accumulation is highly dependent upon the rate of accumulation of fluid in the pericardial sac. Rapid accumulation of pericardial fluid causes a sudden increase in intrapericardial pressure with hemodynamic compromise. Slow accumulation of pericardial fluid can be asymptomatic even when large fluid volumes are present (Fig. 45.1) [7].

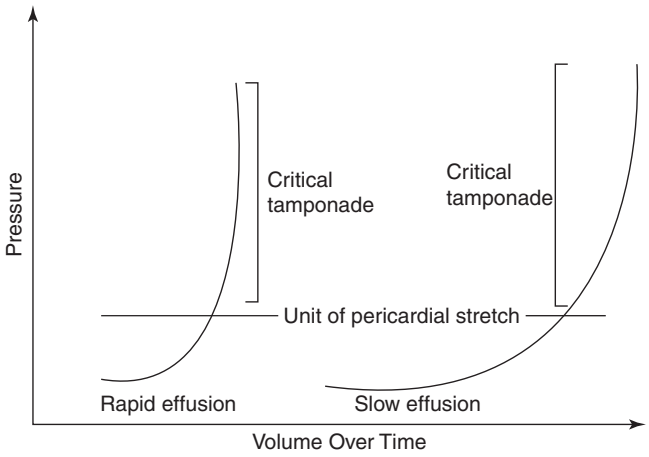

Fig. 45.1 Pericardial pressure–volume curve showing rapid and slow increase of pericardial volume over time. (From [7])

Cardiac tamponade is a consequence of markedly diminished diastolic filling that occurs when transmural distending pressures are insufficient to overcome the increased intrapericardial pressure. In tamponade, inspiration augments inflow to the right ventricle, causing an abrupt expansion of the right ventricle during diastole at the expense of the left ventricle (Fig. 45.2) [8]. Conversely, during expiration, left ventricular expansion causes right ventricular and atrial diastolic collapse. This reciprocating behavior of the ventricles during respiration is responsible for a paradoxical pulse [9].

The pericardium also serves as a protective barrier from the spread of infection or inflammation from adjacent structures. Pericardial inflammation manifests as a fibrinous reaction with an exudative effusion. This can lead to fibrosis, thickening, calcification, and obliteration of the space between the visceral and parietal layers; adhesions can occur between the pericardium and myocardium, leading to decreased pericardial compliance and constrictive pericarditis. This results in diminished ventricular distensibility, inability to maintain adequate preload, and biventricular diastolic dysfunction. As opposed to a pericardial effusion, early ventricular filling is not altered in constrictive pericarditis. However, as the ventricles fill, they meet the inelastic resistance of the stiff pericardium, at which time filling pressure rises rapidly to an elevated plateau. This late diastolic phenomenon is due to a change in the volume–elasticity curve, a small increase in volume resulting in a considerable increase in end-diastolic pressure. Atrial filling pressures are elevated, reflecting both ventricular noncompliance and atrial constraint from the thick pericardium. Because of the isolated encasement of the pericardium and not the systemic veins or lungs, there is dissociation between intrathoracic and intracardiac pressures with marked respiratory variation and discordance in right and left heart filling [10, 11].

Through analysis of the atrial waveforms, improved understanding of the physiology of the venous circulations, the

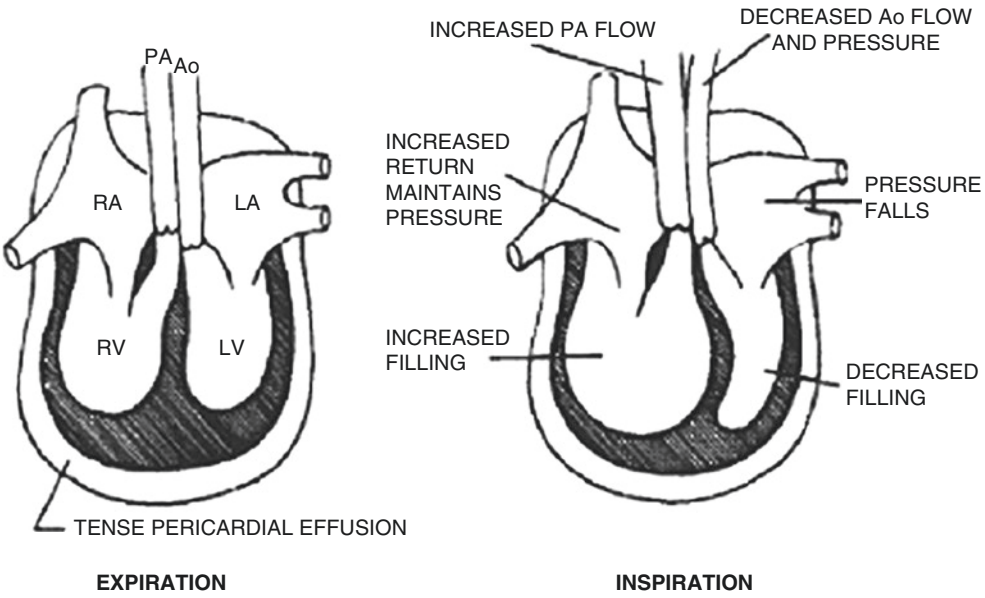

Fig. 45.2 Ventricular interdependence and mechanism of pulsus paradoxus. (From [6]). LA left atrium; LV left ventricle; RA right atrium; RV right ventricle

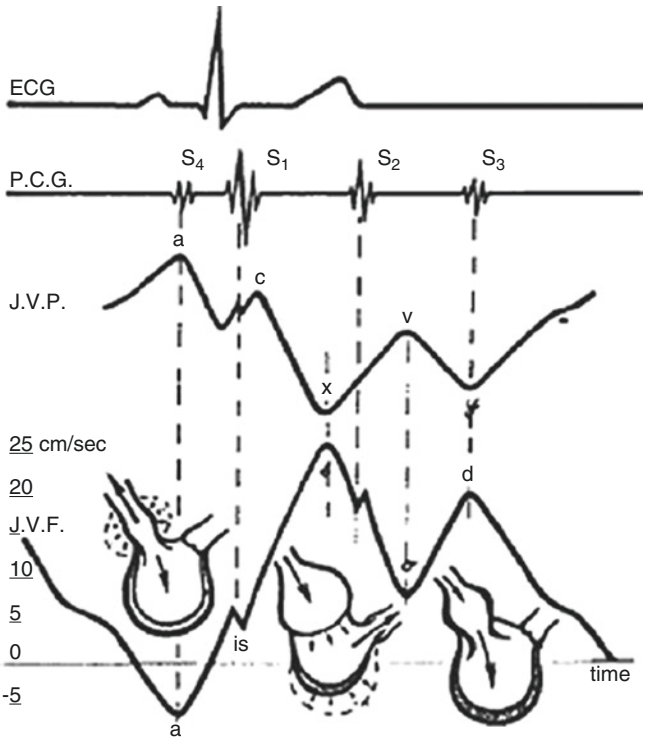

Fig. 45.3 Mechanics of atrial wave form. (From [6]). a atrial systole; c atrial contraction; d ventricular diastole; JVP jugular venous pulse; P.C.G. phonocardiogramm; S heart sound; x atrial relaxation; v ventricular systole; y atrial emptying

dynamic effect of intrapericardial and intrathoracic pressures, and respiratory variations during the cardiac cycle is possible [12]. The atrial waveforms are constituted by two positive deflections, the A and V waves, and two negative waves, the x and y descents (Fig. 45.3). The atrial A wave is generated by atrial systole following the P wave of the electrocardiogram. The strength of atrial contraction is reflected in the rapidity of the A wave upstroke and peak amplitude. The x descent follows the A wave and is a function of atrial relaxation which is influenced by pericardial compliance. The V wave reflects venous return, resulting in atrial filling and increased atrial pressure during ventricular systole. The height of the V wave correlates with atrial compliance. The subsequent diastolic y descent represents atrial emptying. The steepness of the y descent is influenced by the volume and pressure in the atrium just prior to atrioventricular valve opening and by the resistance to atrial emptying (atrioventricular valve narrowing, ventricular compliance, and pericardial compliance).

45.4 Epidemiology and Etiology

Pericardial effusions can be associated with pericarditis or secondary to cardiac surgery (Table 45.1) [13]. Common causes of pericardial effusions in children include prior cardiac surgery, infectious pericarditis, malignancy, and connective tissue disorders. In a significant number of children, however, despite extensive investigation, it is not possible to identify a clear etiology. A viral cause is often considered, though rarely confirmed [14].

Postoperative pericardial effusions can occur in isolation or be secondary to post-pericardiotomy syndrome. In the postoperative period, even small amount of loculated pericardial fluid, particularly when localized along the free wall of the right atrium or ventricle, can have significant hemodynamic repercussions [15]. In developing countries, tuberculosis is responsible for approximately 70% of cases of large pericardial effusions and most cases of constrictive pericarditis.

Table 45.1 Noninfectious causes of pericardial effusion

Idiopathic	
Uremia	
Hypothyroidism	
Neoplasia	Metastases
	Leukemia
	Lymphoma
Postcardiac surgery (post-pericardiotomy syndrome)	
Acute myocardial infarction	
Postradiation	
Rheumatic fever	
Collagen vascular disease	Rheumatoid arthritis
	Systemic lupus erythematosus
Trauma (hemopericardium)	
Hypercholesterolemia	
Chylopericardium	
Sarcoidosis	
Whipple disease	
Drug-induced	

Table 45.2 Infectious causes of pericarditis

Viral	Coxsackie virus A and B
	Adenovirus
	Cytomegalovirus
	Epstein–Barr virus
	Varicella-Zoster virus
	Mumps virus
	Influenza virus
	Hepatitis virus
	Human immunodeficiency virus
	Variola and vaccinia viruses
Pyogenic	*Streptococcus pneumoniae*
	Streptococcus pyogenes
	Staphylococcus aureus
	Haemophilus influenzae
	Neisseria meningitidis
	Neisseria gonorrhoeae
	Pseudomonas aeruginosa
	Francisella tularensis
	Bartonella henselae
	Cardiobacterium hominis
	Salmonella spp.
	Actinomyces spp.
	Nocardia spp.
	Coxiella burnetii
	Legionella spp.
Tuberculous	*Mycobacterium tuberculosis*
Fungal	Histoplasmosis
	Coccidioidomycosis
	Candidosis
	Aspergillosis
	Blastomycosis
	Echinococcosis
	Amebiasis
Parasites	*Entamoeba histolytica*
	Echinococcus spp.
Miscellaneous	Mycoplasma
	Chlamydia
	Rickettsiae
	Spirochetes

However, in industrialized countries, tuberculosis accounts for only 4% of cases of pericardial effusion and an even smaller proportion of constrictive pericarditis [16].

Post-pericardiotomy syndrome is more common in older children and can occur in any patient in whom the pericardial sac has been opened. Patients usually present within 1–6 weeks of a surgery involving a pericardiotomy. An autoimmune etiology has been postulated.

Acute pericarditis is most commonly secondary to viral infections, particularly enteroviruses and Cocksackie virus B (Table 45.2) [17]. Effusive-constrictive pericarditis is usually secondary to infections creating a thick exudate, such as pyogenic bacteria or tuberculosis. Purulent pericarditis is a medical and surgical emergency and requires prompt antibiotic treatment and pericardial drainage, to prevent adhesions and eventual constriction. The incidence of tuberculous pericarditis is increasing in underdeveloped countries, particularly in Africa, as a result of the human immunodeficiency virus (HIV) epidemic [18].

Constrictive pericarditis is rare in children in developed countries, but as mentioned above, the incidence in underdeveloped countries is much higher due to higher rates of tuberculosis. Clinical presentation depends on etiology and the rate of onset and severity of disease (Table 45.3) [19, 20].

Pericardial cyst is a rare mediastinal abnormality, usually congenital but may also be acquired after cardiothoracic surgery. Cysts are typically located at the right cardiophrenic angle (50–70%) or at the left cardiophrenic angle (28–38%). A rare complication is associated with pericardial tamponade.

Congenital absence of the pericardium can be complete or partial and can be isolated or associated with other congenital anomalies in one-third of the cases, such as patent ductus arteriosus, mitral stenosis, or Tetralogy of Fallot. Life-threatening complications include herniation of a cardiac chamber through the defect, most commonly the left atrial appendage.

Hemopericardium should be suspected in any patient complaining of severe chest pain following traumatic injury.

Chylopericardium is a pericardial effusion comprised of chyle, the normal content of the thoracic duct. Chylopericardium may be primary (idiopathic), or secondary to conditions like failing Fontan physiology or to injury of the thoracic duct and associated with chylothorax (post-surgery). Complications include cardiac tamponade, acute pericarditis, or chronic constriction.

45.5 Clinical Presentation

The clinical presentation of pericardial diseases differs according to their etiology and will be discussed separately.

Table 45.3 Causes of constrictive pericarditis

Idiopathic			
Postacute pericarditis			
Tuberculosis			
Infectious	Virus	Bacteria: *Staphylococci*, *streptococci*	Fungi: Histoplasmosis
Rheumatoid disease			
Sarcoidosis			
Mediastinal radiation (Hodgkin's lymphoma)			
Trauma (hemopericardium)			
Status postcardiac surgery (post-pericardiotomy syndrome)			
Uremia			
Neoplasia with pericardial infiltration			
Metabolic and genetic disorders			

45.5.1 Pericardial Effusion and Tamponade

Chest pain or discomfort relieved by sitting up and leaning forward and intensified by lying supine is typical. Respiratory symptoms of cough and dyspnea can dominate the clinical picture. The physical exam reveals a pericardial friction rub heard most frequently during expiration with the patient upright and leaning forward [21]. The friction rub may not be heard in patients with large effusions. Tachypnea, tachycardia, widened pulse pressure, and hepato-jugular reflux are the signs of impending hemodynamic compromise. The Classic Beck triad of pericardial tamponade includes hypotension, muffled heart sounds, and jugular venous distension [22]. Pulsus paradoxus, defined as a decrease in systolic blood pressure of more than 10 mmHg with inspiration, is a sign of falling cardiac output. Late findings are cyanosis and decreased level of consciousness.

45.5.2 Post-pericardiotomy Syndrome

Post-pericardiotomy syndrome typically occurs 1–6 weeks after cardiac surgery. The patient can suffer from fatigue and low-grade fever. Anterior precordial chest pain that increases on deep inspiration is common. The typical clinical finding is that of a pericardial friction rub. When a pericardial effusion is associated, the friction rub may disappear, the heart sounds are attenuated, and tamponade is a possibility.

45.5.3 Acute Pericarditis

With bacterial pericarditis, the patient is febrile and appears toxic. In the setting of viral or autoimmune pericarditis, fever and evidence of toxicity are generally milder. Chest pain is common, usually retrosternal or precordial. The pain is usually described as sharp or stabbing, and is made worse with inspiration or movement. Pain may be of sudden or gradual onset and may radiate to the back, neck, or left shoulder. Associated signs and symptoms include low-grade intermittent fever, dyspnea, tachypnea, cough, and dysphagia. Acute abdominal pain is not uncommon in children. The most common and important physical finding is a pericardial friction rub, best heard at the lower left sternal border or apex when the patient is sitting forward, and may be transient.

45.5.4 Constrictive Pericarditis

The history reveals symptoms of congestive heart failure, such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea, diaphoresis, easy fatigability, and tachycardia. Precordial pain is unusual in chronic constrictive pericarditis, as opposed to acute pericarditis. The hallmarks of physical diagnosis include absence of a drop in jugular venous pulsations during inspiration (Kussmaul's sign) and elevated jugular pressure with prominent y descent (Friedreich's sign). Unlike other forms of pericardial disease, such as acute pericarditis, a friction rub is usually not audible. A protodiastolic knock, usually heard along the left sternal border, corresponds to the abrupt cessation of ventricular filling during diastole. As the systemic venous pressure becomes elevated, signs of right-sided heart failure develop, such as neck vein distention, hepatomegaly, ascites, hepato-jugular reflux, and peripheral edema [23, 24]. Signs of diminished cardiac output include diminished pulse pressure, pulsus paradoxus, and a prominent third heart sound.

45.5.5 Pericardial Cyst

Although most pericardial cysts are asymptomatic, patients may present with atypical chest pain, dyspnea, or persistent cough [25].

45.5.6 Absence of the Pericardium

Complete congenital absence of the pericardium is often an incidental finding with chest imaging demonstrating deviation of the heart into the left chest. In those with symptoms, paroxysmal stabbing chest pain, largely nonexertional and mimicking coronary artery disease, and dyspnea can be associated [26]. Displacement of the left ventricular impulse on clinical exam is the most common feature.

45.6 Preoperative Management

45.6.1 Pericardial Effusion and Tamponade

45.6.1.1 Laboratory

Blood work should be directed toward identifying the etiology (Tables 45.1 and 45.2). Diagnostic studies can be performed on the pericardial fluid including cell count and differential, protein, lactate dehydrogenase, glucose, gram stain, bacterial and fungal cultures, viral PCR, mycobacterial acid fast stain, and tumor cytology. When connective tissue disease is suspected, rheumatoid factor, antinuclear antibodies, and complement levels can be measured.

45.6.1.2 Chest X-Ray

An increased cardiac silhouette that is globular (water bottle-shaped heart) can be seen with excessive pericardial fluid accumulation (Fig. 45.4) [27]. Another finding is visualization of the pericardial fat stripe within the cardiac silhouette. The lung fields are usually oligemic, and a pleural effusion is often associated.

45.6.1.3 Electrocardiogram

Low voltage QRS with diffuse nonspecific ST segment changes are present with large effusions (Fig. 45.5). Electrical

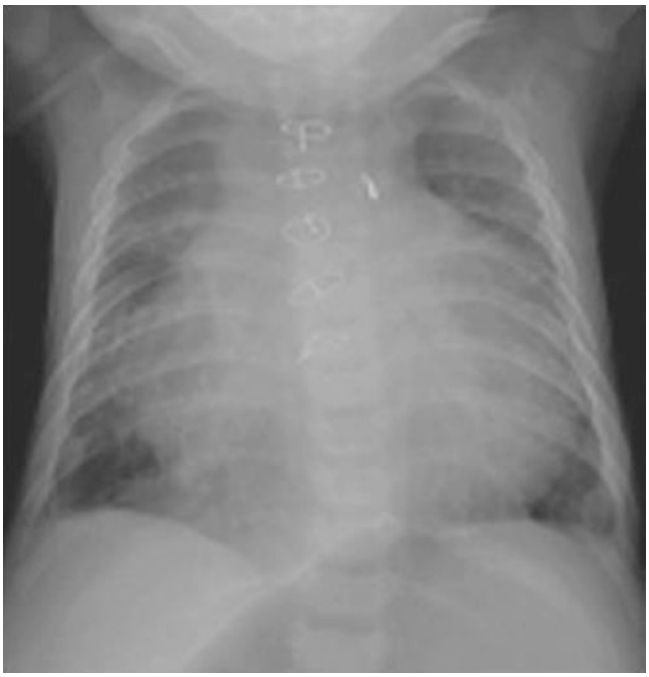

Fig. 45.4 Chest X-ray in pericardial effusion: water bottle shaped heart

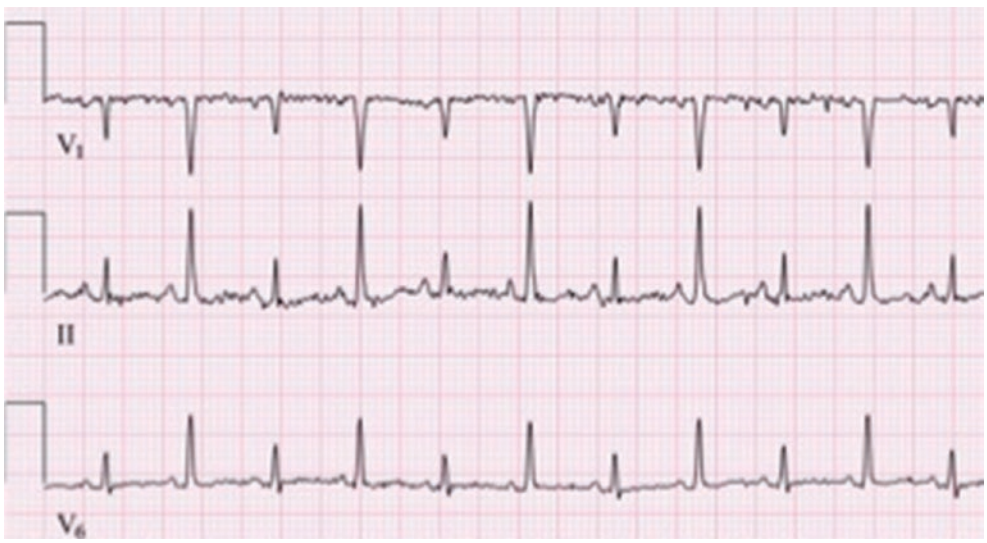

Fig. 45.5 Electrocardiogram in pericardial effusion: low voltage QRS with nonspecific ST segment changes and electrical alternans

alternans is pathognomonic of cardiac tamponade and is characterized by alternating P wave, QRS complex, and T wave voltages attributable to swinging motion of the heart [28, 29].

45.6.1.4 Echocardiography

Pericardial effusion appears as an "echo-free" space between the visceral and parietal pericardium on M-mode echocardiography (Fig. 45.6) [30]. Effusions tend to accumulate posterior and inferior to the left ventricle initially. However, on echocardiographic imaging, fluid visualized above the right atrium in the four-chamber view is the most sensitive indication as this is the first place where a pericardial effusion is seen. Moderate effusions (10–20 mm in size) extend toward the apex of the heart, and large effusions (more than 20 mm) circumscribe the heart (Fig. 45.7) (Table 45.4).

The rapidity of fluid accumulation and the compliance of the pericardium influence the hemodynamic significance for a given fluid volume. As pericardial fluid accumulates, intrapericardial pressure increases until it exceeds normal filling pressure of the heart, leading to tamponade. The first sign of hemodynamic compromise is expiratory right ventricular free wall collapse early in diastole, reflecting the brief period when intrapericardial pressure is greater than the right ventricular transmural distending pressure (Table 45.5) [31, 32]. The right ventricle is the first to collapse due to its lower intracardiac pressure compared to the left ventricle. Although right ventricular collapse is generally a specific indicator of tamponade, the sensitivity can be reduced in conditions with increased right ventricular pressure [33].

Expiratory right atrial collapse occurs in late diastole (Fig. 45.8) and is seen as an indentation of the normally rounded anterosuperior right atrial wall. The sensitivity of expiratory right atrial collapse for diagnosing tamponade is low (55%), but the specificity is high (90%). Extension of collapse greater than 1/3 of the cardiac cycle increases the sensitivity of this finding to more than 90% [34, 35]. Absence of expiratory right atrial collapse virtually excludes tamponade. Another sensitive marker of tamponade by echocardiogram is absence of inspiratory collapse (plethora) of the inferior vena cava, defined by less than 5 mm decrease in diameter during inspiration [36]. The sensitivity of inferior vena cava plethora is high (97%), but the specificity is low (66%). Diastolic collapse of the left atrium and rarely the left ventricle occurs during inspiration, related to the increased right heart inflow and abrupt expansion of the right ventricle.

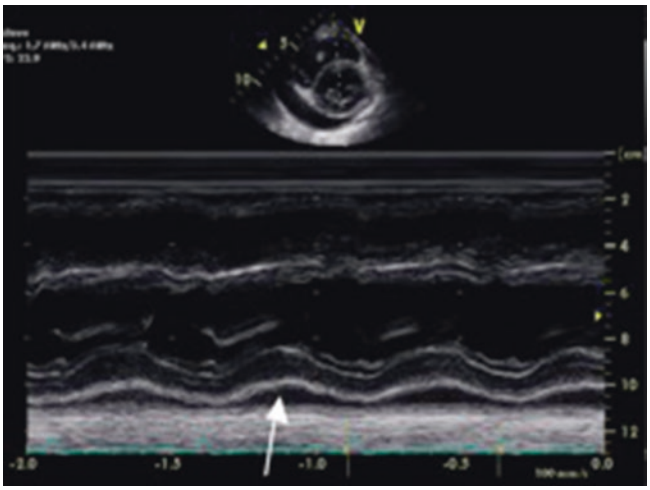

Fig. 45.7 M-mode echocardiography of a patient with a large pericardial effusion: echo-free space (arrow) between the visceral and parietal pericardium

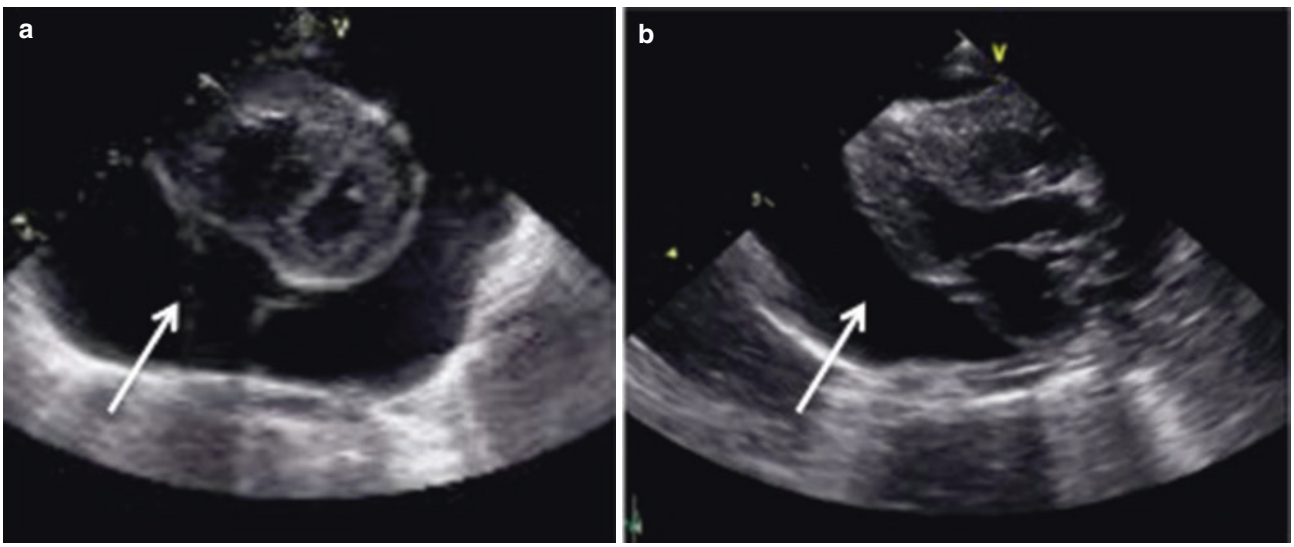

Fig. 45.6 (**a**) Parasternal 2D short-axis echocardiography showing a large pericardial effusion circumscribing the heart. (**b**) Parasternal 2D long-axis echocardiography showing a large pericardial effusion circumscribing the heart

Table 45.4 Echocardiographic findings in pericardial tamponade and constrictive pericarditis

Parameters	Tamponade	Constrictive pericarditis
RAP	↑	↑
RV and LV filling pressure	↑ RV = LV	↑ RV = LV
PAP	Normal	Mild ↑ RVSP <40 mmHg
RV diastolic pressure plateau		>1/3 peak RV pressure
2D echo	Pericardial effusion	Pericardial thickening, Septal shudder Interventricular dependence: IVS diastolic shift toward LV during inspiration and toward RV during expiration
M-mode		Septal notch
Doppler MV and TV	Reciprocal respiratory changes in RV and LV filling ↑ TV E during inspiration ↑ MV E during expiration	Respiratory variation (>10%) in RV and LV filling, ↑ MV E during expiration Respiratory variation in IVRT
	LV inflow: E > A	LV inflow: E > A ↑ TR peak velocity, VTI and duration during inspiration
Doppler Pv		Respiratory variation in Pv flow ↑ D during expiration Pv flow: ↑ AR ↓ S S/D > 0.65 during inspiration
TDI		Em >8 cm/s E/Em <15
Color M-mode		Vp >100 cm/s

Adapted from Otto [87] and Tam et al. [88].
A Doppler late diastolic wave; AR Doppler A wave reversal: D Doppler diastolic wave; E Doppler early diastolic wave; Em Tissue Doppler early diastolic wave; IVRT isovolumic relaxation time; IVS intervenricular septum; LV left ventricle; MVmitral valve; PAP pulmonary artery pressure; Pv pulmonary vein; RAP right atrial pressure; RV right ventricle; RVSP right ventricular systolic pressure; S Doppler systolic wave; TR tricuspid regurgitation; TDI Tissue Doppler imaging; TV tricuspid valve; Vp color M-mode propagation flow; VTI velocity time integral

Doppler echocardiography shows large swinging amplitudes of the mitral and tricuspid inflow, the aortic and pulmonary outflow, and the hepatic veins. Normally, there is no more than 10% variation in the amplitude of inflow and outflow signals with respiration, but this exceeds 30% in tamponade (Fig. 45.9).

The classic Doppler patterns of cardiac tamponade include (Fig. 45.10) [37, 38]:

- Mitral inflow: During inspiration, E wave velocity decreases by more than 30% compared with expiration.
- Pulmonary veins: During inspiration, D wave velocity decreases.

Table 45.5 Assessment of hemodynamic compromise in cardiac tamponade

Effusion	Clinical and echo signs
Insignificant effusion	Flat neck veins Normal BP, HR, RR, good perfusion Effusion on echo, no chamber compression
Significant, compensated	Increased JVP No hypotension, tachycardia Mild pulsus paradoxus Good perfusion Effusion on echo with mild RV collapse
Severe, compensated	Increased JVP Prominent pulsus paradoxus Tachycardia, no hypotension Good perfusion Chamber collapse on echo
Severe, decompensated	Increased JVP Tachycardia, tachypnea Hypotension, pulsus paradoxus Chamber collapse, swinging heart on echo

BP blood pressure; HR heart rate; JVP jugular venous pulse; RR respiratoy rate; RV right ventricle

- Tricuspid inflow: During inspiration, E wave velocity increases by more than 50% compared with expiration.
- Hepatic veins: During inspiration, S is greater than D. During expiration, there is a very limited or absent D wave with prominent reversal.

45.6.1.5 Cardiac CT and MRI

CT can potentially suggest composition of fluid and may detect as little as 50 ml of fluid.

MRI can detect as little as 30 ml of pericardial fluid and may be able to distinguish hemorrhagic and nonhemorrhagic effusions. Both MRI and CT scan may be superior to echocardiography in detecting loculated pericardial effusions and pericardial thickening.

45.6.2 Post-pericardiotomy Syndrome

45.6.2.1 Laboratory

Elevated white blood cell count with a left shift and elevated erythrocyte sedimentation rate (ESR) are usual.

45.6.2.2 Chest X-Ray

Radiographic evidence of pleural effusions and cardiac enlargement secondary to a pericardial effusion are common.

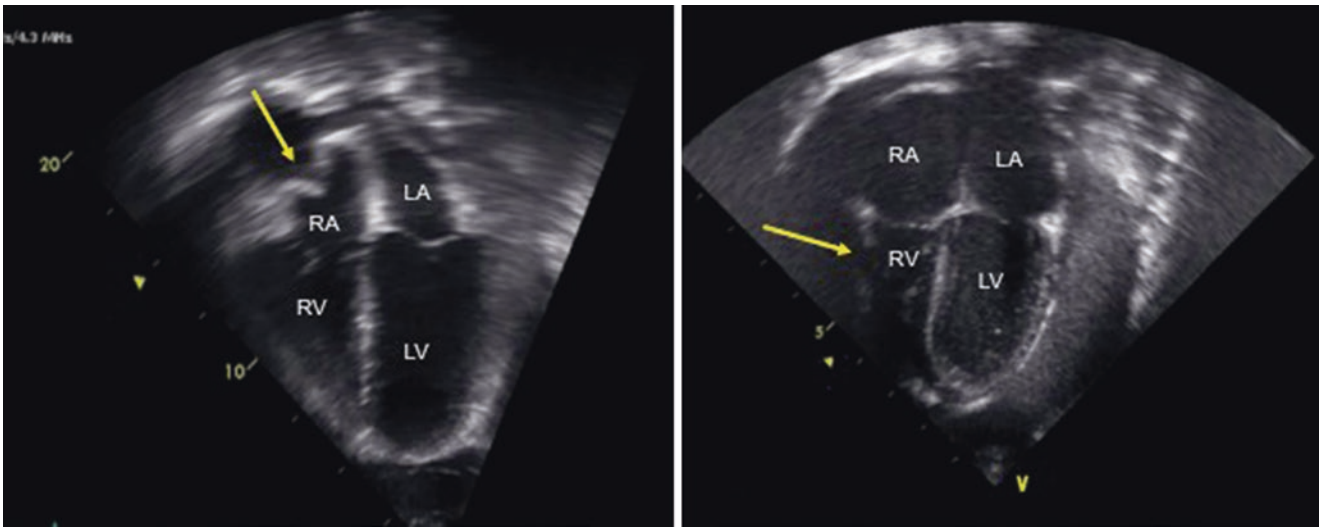

Fig. 45.8 Apical four-chamber 2D-echocardiography views in pericardial effusion: right diastolic atrial collapse (arrow, left-sided picture) and right ventricular diastolic collapse (arrow, right-sided picture)

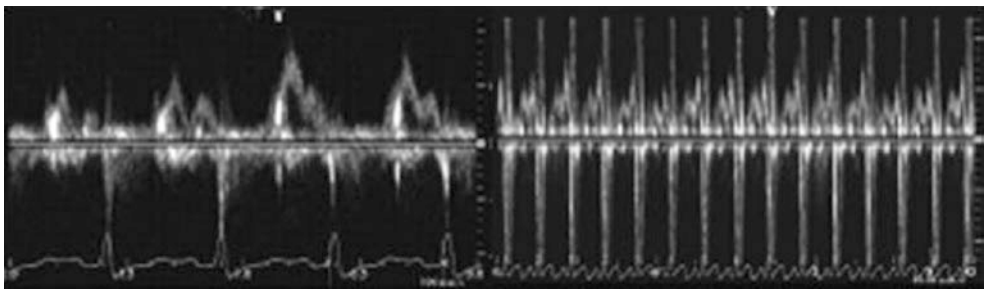

Fig. 45.9 Respiratory variation in mitral inflow by 2D-echocardiography in cardiac tamponade

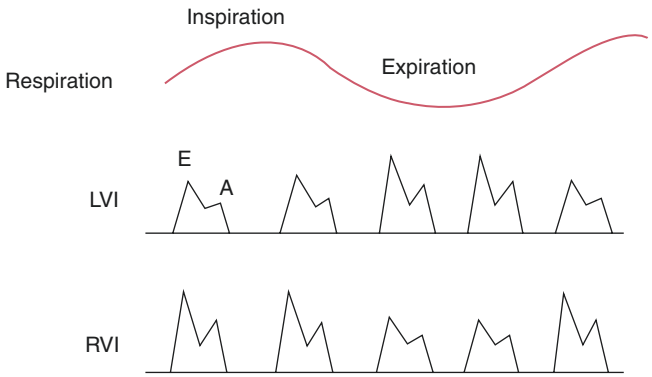

Fig. 45.10 Respiratory variations in mitral and tricuspid inflow in cardiac tamponade. A Doppler late diastolic wave; E Doppler early diastolic wave; LVI left ventricular inflow; RVI right ventricular inflow

45.6.2.3 Electrocardiogram

Nonspecific abnormalities of the T waves (flattening in leads I and lateral chest) and decrease in voltage with a large pericardial effusions are common findings.

45.6.2.4 Echocardiography

Pericardial effusion is documented and its hemodynamic repercussion evaluated as described above.

45.6.3 Acute Pericarditis

45.6.3.1 Laboratory

Inflammatory markers are usually elevated (C-reactive protein, ESR). Cardiac Troponin I rise has been described as detectable in acute pericarditis in about 30% of patients and is associated with ST segment elevation and presence of a pericardial effusion [39].

45.6.3.2 Chest X-Ray

The chest X-ray is unremarkable in the absence of a pericardial effusion.

45.6.3.3 Electrocardiogram

The ECG can be diagnostic in acute pericarditis. It evolves four stages. The first stage is characterized by ST-segment elevation and concave upward ST segments noted in all leads except V_1 (Fig. 45.11). In the second stage, normal ST segments with T-wave flattening are noted. T-wave inversion without Q-wave formation is noticed in the third stage. The fourth stage is characterized by ECG normalization.

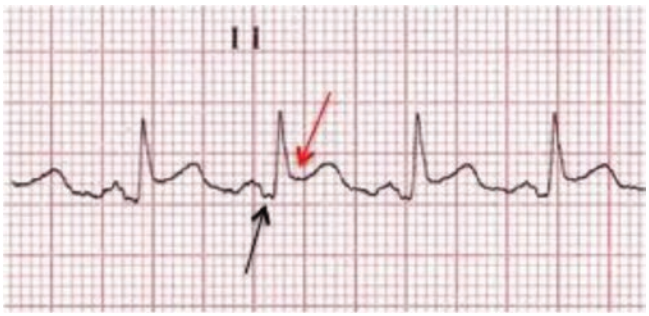

Fig. 45.11 ECG in acute pericarditis: diffuse concave upward ST-segment elevation Red arrow) and PR segment depression (black arrow)

Another important ECG finding is PR-segment depression.

45.6.3.4 Echocardiography

The echocardiogram is often normal, unless acute pericarditis is associated with a pericardial effusion. While the finding of a pericardial effusion supports the diagnosis of acute pericarditis, its absence does not exclude it. In pericarditis, the pericardium may have a normal appearance.

45.6.3.5 Cardiac CT Scan and MRI

The normal thickness of the pericardium as measured by CT scanning is less than 2 mm and 4 mm by MRI. The limitation of CT scan is the difficulty in differentiating fluid from thickened pericardium.

45.6.4 Constrictive Pericarditis

45.6.4.1 Laboratory

Brain natriuretic peptide (BNP) is usually normal or just above normal in patients with constrictive pericarditis as opposed to elevated (>600 pg/ml) in patients with restrictive cardiomyopathy, helping differentiate between these two conditions [40]. No data on BNP levels in this setting are available in children.

45.6.4.2 Chest X-Ray

The chest X-ray is usually unremarkable. Pericardial calcifications are present in 40–50% of patients, giving an egg-shell appearance to the cardiac silhouette [41] (Fig. 45.12).

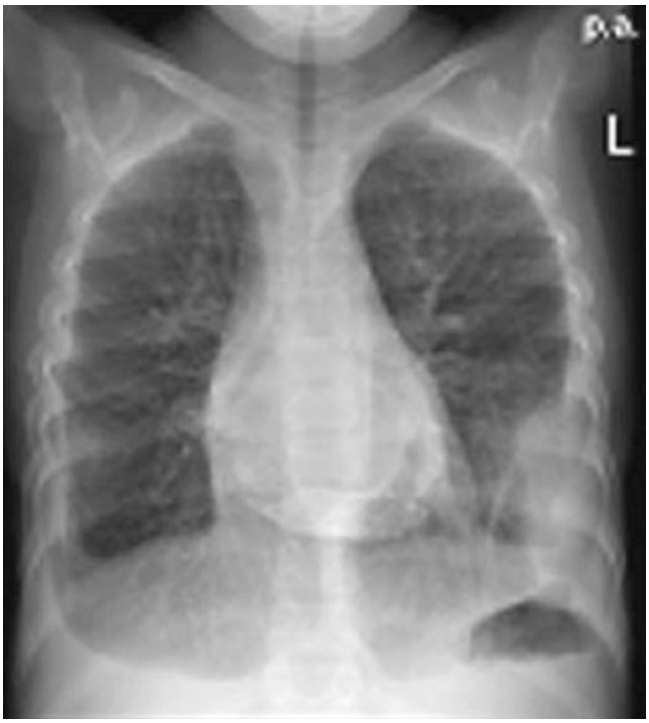

Fig. 45.12 Chest X-ray in constrictive pericarditis: Egg-shell appearance of the cardiac silhouette

The right superior mediastinum may be enlarged owing to dilation of the superior vena cava. Pleural effusions may be present, reflecting chronic elevation of right heart filling pressures. Pulmonary infiltrates are uncommon.

45.6.4.3 Electrocardiogram

ECG is nonspecific but usually demonstrates diffuse low voltage and nonspecific ST-T wave changes. Atrial dysrhythmias are common.

45.6.4.4 Cardiac Catheterization

The hallmark finding in constrictive pericarditis is the elevation and near-equalization of end-diastolic pressures in the right atrium, right ventricle, pulmonary capillary wedge, and left ventricle. The right atrial pulse waveform is characterized by a prominent A wave, reflecting rapid early diastolic filling of the ventricle, a sharp x descent, due to accelerated atrial relaxation, and a sharp y descent reflecting the early resistance-free right ventricular filling. The mean jugular venous and right atrial pressures are elevated.

The right ventricular waveform is distinctive, with a "dip and plateau" or "square root sign" pattern (Fig. 45.13), reflecting the rapid relaxation, followed by a sharp increase

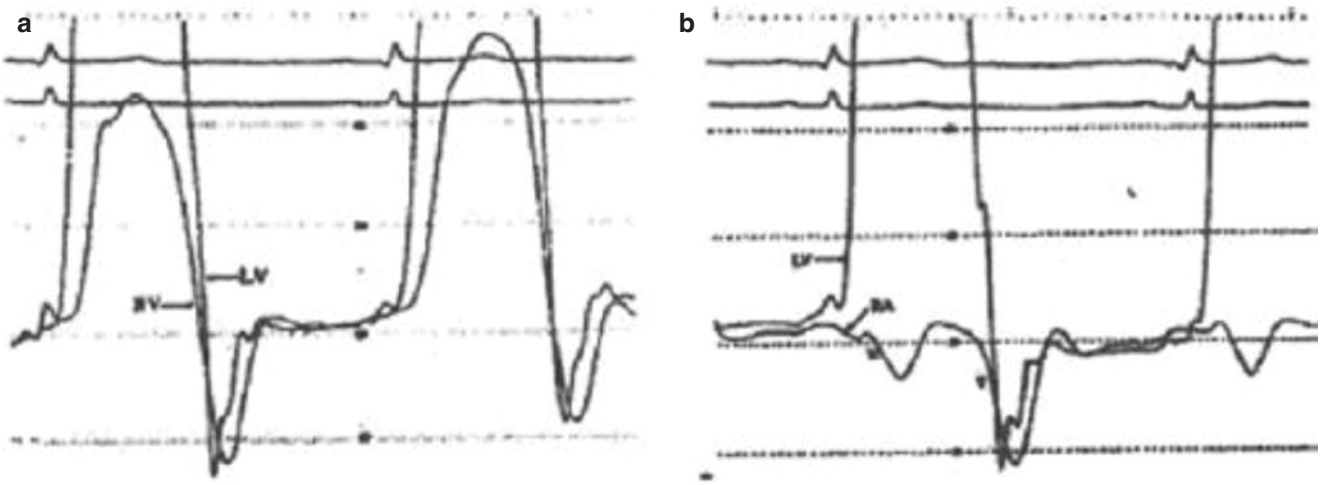

Fig. 45.13 (**a**) Simultaneous right and left ventricular pressure showing equalization of diastolic pressures and characteristic "dip and plateau" contour in constrictive pericarditis. (**b**) Simultaneous right atrial and left ventricular pressure recordings demonstrating equalization during diastole with prominent x and y descent of the atrial tracing. (From [6])

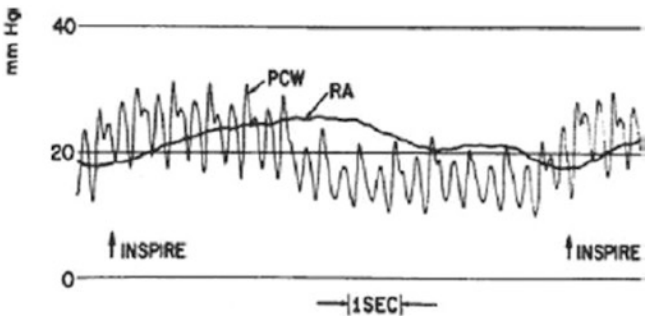

Fig. 45.14 Differential changes in the hemodynamic tracing of mean right atrial (RA) and pulmonary capillary wedge pressure (PCWP) during respiration in constrictive pericarditis. Mean RA pressure increases during inspiration (Kussmaul sign) and PCWP decreases. (From Grossman [89])

in filling pressure as the expanding ventricle meets the constraints of the pericardium [42]. The left ventricular pressure tracing is usually similar. Other hemodynamic findings include a right ventricular diastolic pressure exceeding one-third of the right ventricular systolic pressure, and a pulmonary artery pressure of less than 50 mmHg [43].

Another hallmark of constriction is increased ventricular interdependence. Because pericardial constraint limits total cardiac volume, there is a reciprocal relation between left and right heart filling due to enhanced septal interaction. There is opposite directional changes in ventricular systolic pressure and reciprocal changes with respiration, with inspiration inducing an increase in right ventricular but a decrease in left ventricular pressure, a phenomenon called ventricular discordance. The opposite changes occur during expiration, with increased left heart filling and reduced right heart filling (Fig. 45.14). This may be the most reliable hemodynamic indicator of constriction [44].

When hemodynamic studies are equivocal, a bolus fluid can be administered and reveals striking elevation of the filling pressures in the case of constrictive pericarditis [45, 46].

45.6.4.5 Echocardiography

Echocardiography remains the most utilized noninvasive tool in the initial assessment of constrictive pericarditis [47]. A thickened pericardium with some degree of pericardial effusion may be observed by 2D-echocardiography [48]. Transthoracic echocardiography is insensitive, as mildly increased pericardial thickening can be missed, and false-positives can be obtained if the gain is set too high. Pericardial calcifications with localized tethering of atrial or ventricular cavities may be noted, while separation of the entire pericardium by a small fixed space is known as the "halo sign." The systemic veins are usually dilated, with the inferior vena cava showing absent collapse with inspiration (plethora). Septal "bounce" is typical, defined as abrupt posterior movement of the interventricular septum in early diastole during inspiration, and is caused by underfilling of the left ventricle and redistribution of blood from the left to the right ventricle. This "bounce" represents the first and best clue for the presence of constriction [49].

The right and left ventricular size is decreased, and both atria are mildly enlarged, related to the compliance abnormality of the ventricles. The ventricles have an elongated appearance giving the heart a tubular shape. The biventricular systolic function is usually normal. Interventricular septal motion may be paradoxical or flat as a sign of ventricular interdependence. A characteristic septal notch has been described in early diastole, corresponding to the septal bounce

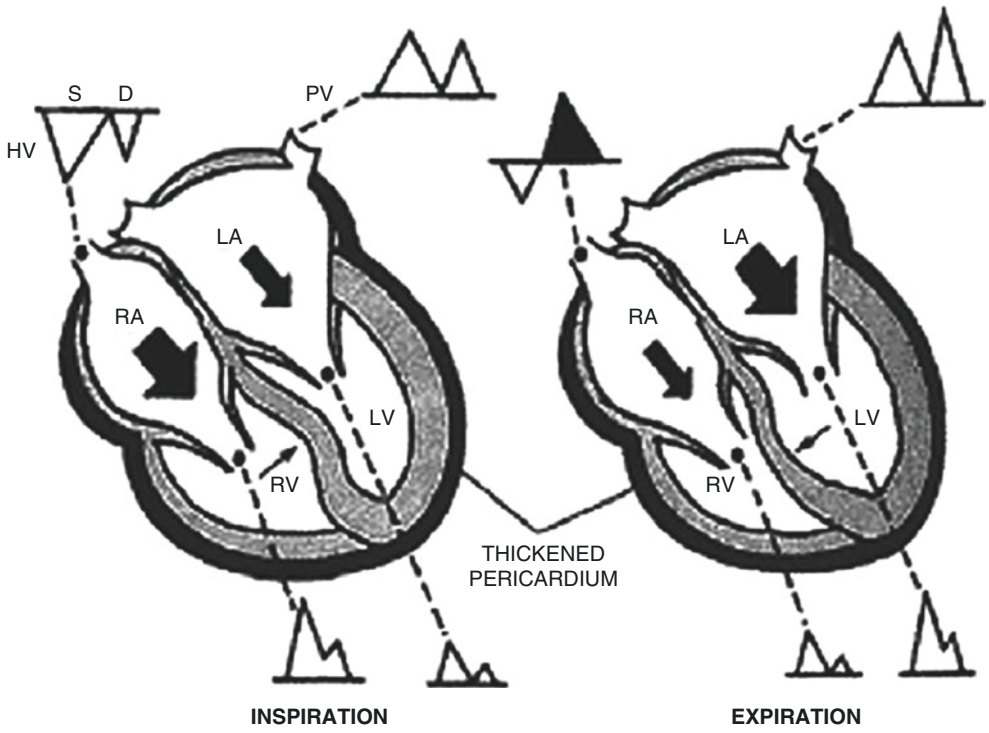

Fig. 45.15 Respiratory variation of transvalvular and central venous flow velocities in constrictive pericarditis. With inspiration, the driving pressure gradient from the pulmonary bed to the left cardiac chambers decreases, resulting in a decrease in mitral inflow and diastolic pulmonary venous velocities. Decreased left ventricular filling results in ventricular septal shift to the left, allowing increased flow to the right-sided cardiac chambers, resulting in increased tricuspid inflow and diastolic hepatic venous velocities. The opposite changes occur during expiration. (From Oh [90]). D Doppler diastolic wave; HV hepatic vein; LA left atrium; LV left ventricle; PV pulmonary vein; RA right atrium; RV right ventricle; S Doppler systolic wave

seen by 2D-echocardiography [50, 51]. Extensive areas of adhesions seen posteriorly by M-mode provide evidence for generalized pericardial thickening and constriction.

The hallmark of Doppler examination is reciprocal respiratory variation of right and left heart flows caused by interventricular dependence. The classical Doppler pattern consists of the following (Fig. 45.15) [52–54]:

- Mitral inflow: During inspiration, E wave to A wave ratio (E > A) is lower, while during expiration, there is larger E wave to A wave (E > A) ratio. E wave is typically increased more than 25% with expiration and the IVRT increased more than 25% with inspiration.
- Pulmonary veins: During inspiration, S and D waves are near equal in size. During expiration, larger S and D waves are noted.
- Tricuspid inflow: Shows the same pattern with reciprocal changes compared to the mitral inflow. During expiration, smaller E wave to A wave (E > A) ratio is noted, while during inspiration, there is larger E wave to A wave (E > A) ratio. E wave is typically increased more than 40% with inspiration.
- Hepatic veins: During inspiration, S wave is greater than D wave, with a small A wave reversal. During expiration, S wave is greater than D wave, with small or absent D wave and larger A wave reversal.

Also described in constrictive pericarditis is an inspiratory increase in the tricuspid regurgitant jet velocity and duration of the signal [44]. As opposed to restrictive cardiomyopathy, respiratory variation in the filling phase is more pronounced in constrictive pericarditis. Tissue Doppler echocardiography shows a normal or high early mitral annular velocity (Em wave) in constrictive pericarditis, as opposed to restrictive cardiomyopathy where it is reduced [55]. The usually positive linear relation between mitral Doppler E and tissue Doppler Em (E/Em) is useful to assess left atrial pressure and is found to be reversed in constrictive pericarditis [56]. The propagation velocity (vp) of early diastolic transmitral flow on color M-mode is normal or increased in constrictive pericarditis [57].

45.6.4.6 Cardiac MRI and CT

Both CT and MRI can detect a thickened pericardium (≥4 mm), but this is an insensitive finding. An advantage of CT is the ability to detect calcification, indicative of constrictive pericarditis (Fig. 45.16) [58, 59]. However, CT may have difficulty in differentiating pericardial fluid from thickened pericardium. The absence of pericardial thickening does not rule out hemodynamically significant restrictive pericarditis.

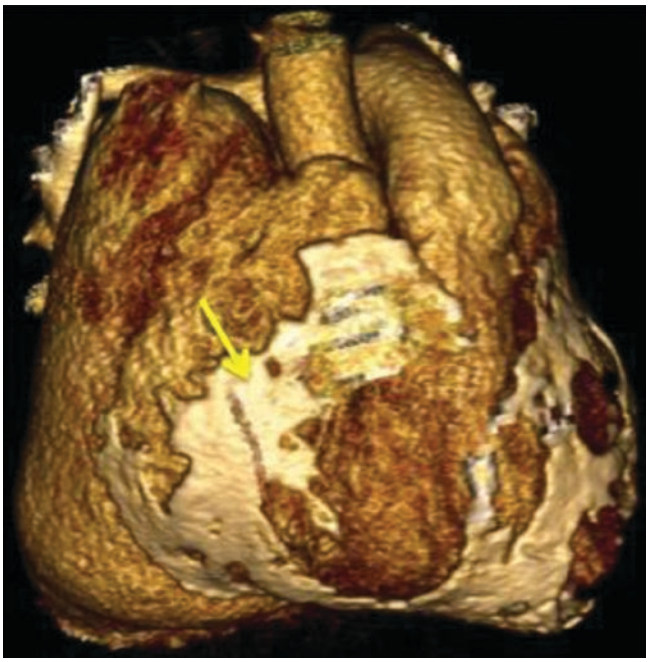

Fig. 45.16 Cardiac Computed Tomography (CT) with 3D-reconstruction showing calcified pericardium (yellow arrow)

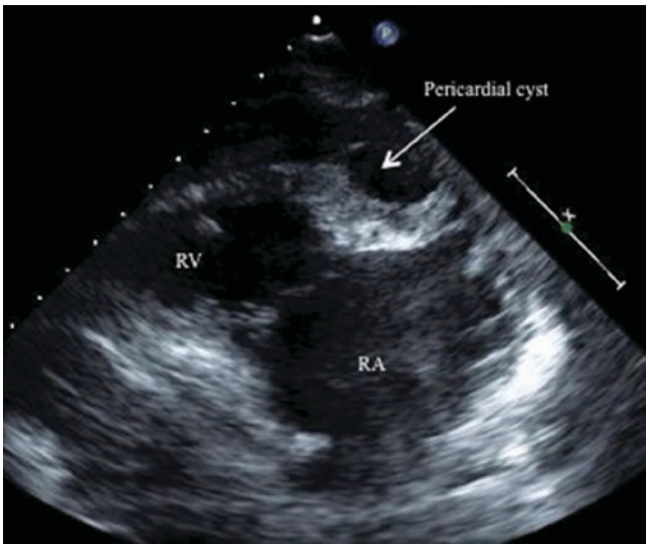

Fig. 45.17 Echocardiography parasternal long axis view showing a pericardial cyst, anterior to the right heart chambers (courtesy of MS. Cohen, MD). RA right atrium, RV right ventricle

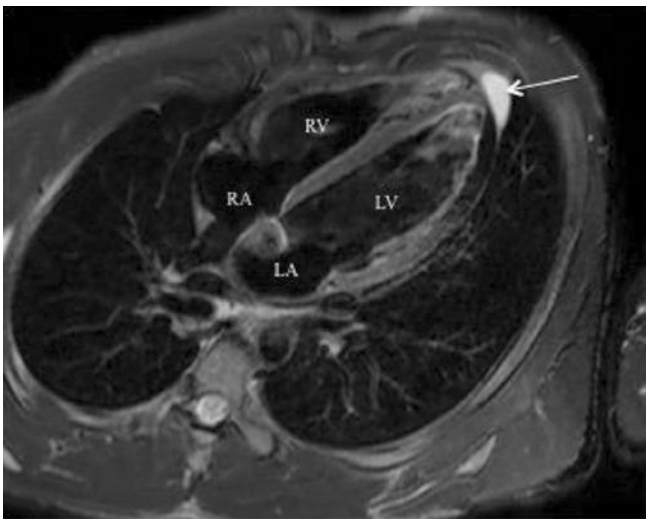

Fig. 45.18 Cardiac MRI of a pericardial cyst (white arrow), anterior to the right heart chambers. RA right atrium, RV right ventricle (courtesy of MS. Cohen, MD). LA left atrium, LV left ventricle, RA right atrium, RV right ventricle

45.6.5 Pericardial Cyst

45.6.5.1 Chest X-Ray

A pericardial cyst is typically suspected after an abnormal chest X-ray consisting of a round, discrete mass in the right cardiophrenic angle, which is the most common location of these cysts [60].

45.6.5.2 Echocardiography

Pericardial cysts are difficult to detect with transthoracic echocardiography. They present as an echo-free space that is more localized and spherical than a pericardial effusion (Fig. 45.17) [61].

45.6.5.3 Cardiac CT and MRI

CT and MRI are the preferred methods to confirm a suspected diagnosis of pericardial cyst (Fig. 45.18) [25, 62]. On CT scan, pericardial cysts are thin-walled, sharply defined, oval homogeneous masses. Their attenuation is slightly higher than water density, 30–40 HU, and the cyst fails to enhance with intravenous contrast [63].

45.6.6 Absence of the Pericardium

45.6.6.1 Chest X-Ray

The chest X-ray reveals levoposition of the heart with loss of the right heart border hidden by the spine [26]. Prominence of the main pulmonary artery and interposition of a tongue of lung tissue between the pulmonary artery and the aorta (opacification of the aortopulmonary window) or between

the inferior border of the heart and the left hemidiaphragm are other findings.

45.6.6.2 Electrocardiogram

Right bundle branch block is common. Right axis deviation with leftward displacement of the transition zone in the precordial leads can be seen.

45.6.6.3 Echocardiography

Complete absence of the pericardium leads to enlargement of the right ventricle, excessive motion of the posterior left ventricular wall, paradoxical motion of the interventricular septum, and a shift of the heart to the left resulting in more of the right ventricle being seen on the left parasternal long axis view. All of these findings mimic right ventricular volume overload, and thus this diagnosis should be excluded [64]. Partial absence of the pericardium sometimes results in herniation of a chamber through the defect, with the false appearance of wall motion abnormality. The biventricular function is usually normal. True wall motion abnormality is seen if a coronary artery is compressed.

45.6.6.4 Cardiac MRI

The most reliable finding is interposition of lung tissue between the main pulmonary artery and the aorta. The heart can be completely displaced in the left hemithorax and its apex elevated (Fig. 45.19). The main pulmonary artery and the left atrial appendage can be seen extending far beyond the mediastinal margins.

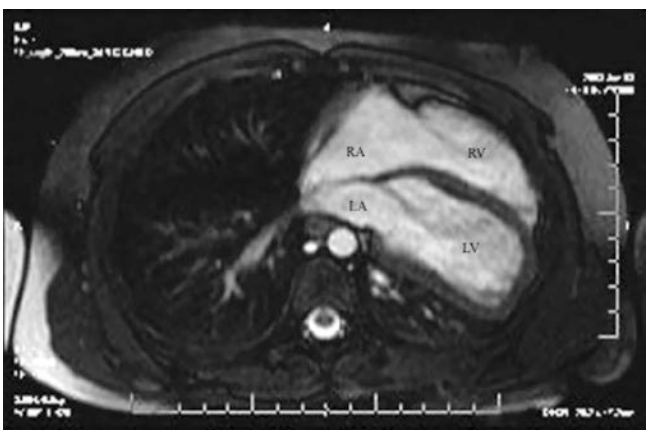

Fig. 45.19 Cardiac MRI of absent pericardium with unusual leftward and posterior shift of the heart and absence of a visible pericardium. On cine imaging, the ventricles are unusually mobile and the typically seen pericardial fluid (normally clearly visible during systole) is absent (courtesy of MS. Cohen, MD). *LA* left atrium; *LV* left ventricle; *RA* right atrium; *RV* right ventricle

45.7 Medical Management

45.7.1 Post-pericardiotomy Syndrome

Post-pericardiotomy syndrome is usually self-limited, but relapses can occur. Medical treatment includes bed rest and anti-inflammatory drugs:

- Acetylsalicylic acid (Aspirin 100 mg/kg/day or 800 mg every 6 hours in adults) is thought to reduce inflammation and fever and is administered for 10 days, then gradually tapered down over 3 weeks. High-dose Aspirin should be associated with a gastroduodenal prophylaxis (proton-pump inhibitor).
- Nonsteroidal anti-inflammatory drugs (NSAIDs): Ibuprofen (10 mg/kg/day) is an alternative to aspirin therapy.
- Corticosteroids (Prednisone 1–2 mg/kg/day) are preferably avoided, but they can be used in severe or recurrent cases during 2–4 weeks followed by gradual tapering off.
- High-dose intravenous immunoglobulins (IVIGs) have been described in the treatment of recurrent post-pericardiotomy syndrome [65].

45.7.2 Pericarditis and Pericardial Effusion

If an infectious cause of pericarditis or a pericardial effusion is identified, obviously, appropriate antimicrobial therapy should be started. In the case of a small pericardial effusion in the postoperative period, an increase in the diuretic regimen can be attempted. NSAIDs or acetylsalicylic acid are usually used to decrease the inflammatory reaction. Aspirin (100 mg/kg/day) during 7–10 days, tapered down over 3–4 weeks, is usually the first-line treatment. Steroids are reserved for severe and recurrent cases, as cases of corticoid-dependant pericardial effusion has been described. It is uncertain whether adjunctive corticosteroids are effective in reducing mortality or pericardial constriction in tuberculous pericarditis, and their safety in HIV-infected patients has not been conclusively established.

45.7.3 Constrictive Pericarditis

The treatment is essentially symptomatic, with diuretics to reduce right heart failure and pulmonary edema. The only curative treatment is pericardiectomy.

45.7.4 Recurrent Pericarditis

Colchicine has been shown to be safe and effective in the treatment and prevention of recurrent pericarditis after failure of conventional treatment, especially in idiopathic cases [66]. The dose for adults is 1.0–2.0 mg for the first day, followed by a maintenance dose of 0.5–1.0 mg daily for 3 months. Although colchicine is well established for the treatment of pericarditis in adults, it is not routinely used in children and there is not enough evidence to support or discourage its use in that patient population [67].

45.8 Procedures

45.8.1 Echocardiography-Guided Pericardiocentesis

The approach is to assess the size, distribution, and ideal needle entry site and trajectory to safely evacuate the pericardial fluid. The echocardiographic transducer is placed approximately 3–5 cm from the parasternal border, and the area of maximal pericardial fluid accumulation is identified. The needle trajectory is established by the angle of the transducer [68–70]. The precordium is entered in the angle formed between the xyphoid process and the left costal cartilages using an 18-mm gauge needle directed at an approximate 15° posterior angle toward the shoulder. The needle is advanced with the tip bent downward, while continuous suction is performed with a syringe until fluid is obtained. Adequate drainage of the pericardial fluid is assessed by echocardiography. Echocardiography-guided pericardiocentesis is simple, safe, and effective for primary treatment of clinically significant pericardial effusion, even in the postoperative period [71]. Complications include transient arrhythmia and hemopericardium.

45.8.2 Percutaneous Pericardial Drainage

Frequently, pericardiocentesis is accompanied by insertion of a drainage catheter to reduce the rate of recurrence that may complicate simple needle drainage. The precordium is entered from the standard subxyphoid approach using an 18-mm gauge needle until fluid is obtained. To assess the position of the needle in the pericardial sac, saline solution can be injected and monitored via echocardiography [72]. A 0.035′ guide wire is advanced into the pericardial space, under echo-guidance. The needle is subsequently removed, and the tract is dilated with a 7F or 8F dilator. A 7F or 8F pigtail catheter is then inserted over the guide wire, positioned in the posterior pericardial space at the level of the left atrioventricular groove (Fig. 45.20).

45.8.3 Percutaneous Balloon Pericardiotomy

The initial part of the procedure is similar to percutaneous pericardial drainage but is performed in the catheterization laboratory under fluoroscopic guidance. The parietal pericardium is dilated using a 10F dilator. Further dilation is

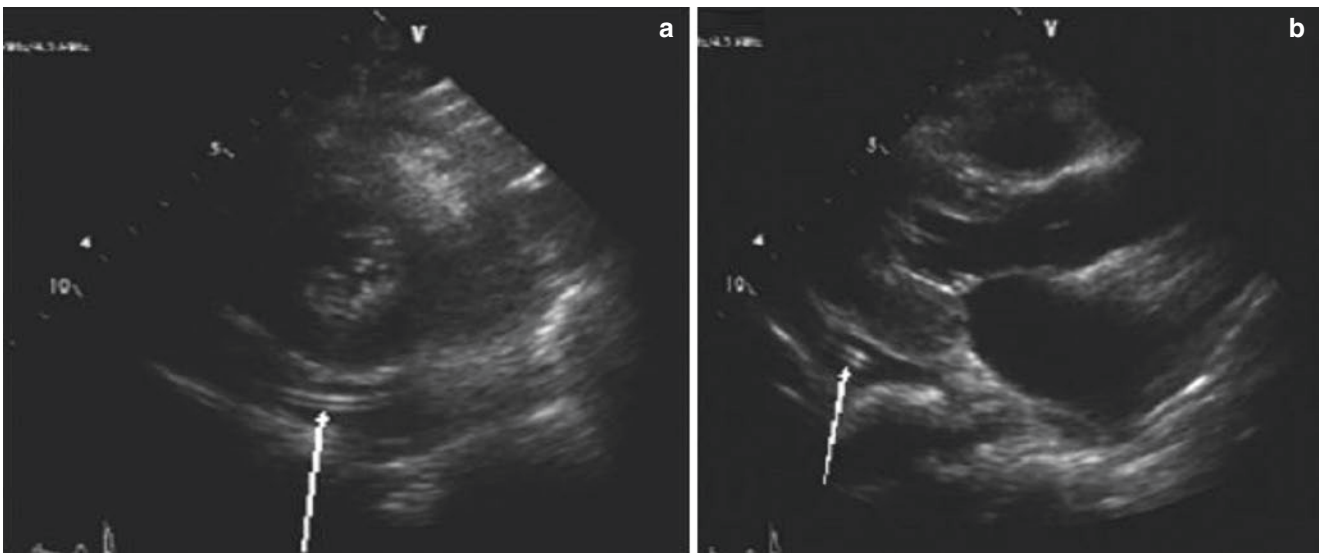

Fig. 45.20 (**a**) 2D-echocardiography in parasternal short axis view showing a pericardial drain in the posterior pericardium (arrow). (**b**) 2D-echocardiography in parasternal long axis view showing a pericardial drain in the posterior pericardium (arrow)

performed using either a single balloon (20 mm wide, 3 cm long) or trefoil (triple) balloons. The balloon is filled with a mixture of contrast and saline, and is manually inflated to a maximum pressure of 3.5 atm until the balloon "waist" disappears. Three inflations of 15 seconds each are recommended. At the end of the procedure, a pigtail catheter is exchanged over the wire and left in place to allow complete drainage of the effusion [73]. Complications include fever, pneumothorax, pleural effusion, and severe chest pain. The success rate of this procedure is very high [74].

45.8.4 Pericardial Sclerosing Therapy

When significant pericardial effusion recurs, a more definitive intervention is needed. Pericardiocentesis with instillation of sclerosing agents has been shown to be successful for malignant pericardial effusions, with a low recurrence rate. Most commonly used drugs are tetracycline or bleomycin, instilled through a pigtail catheter [75, 76]. Common side effects include transient pyrexia, severe retrosternal chest pain, and transient atrial arrhythmia. Few data are available in children [77].

45.9 Surgical Management

45.9.1 Pericardial Effusion

45.9.1.1 Subxyphoid Pericardial Drainage

Subxyphoid pericardiotomy is often preferred to percutaneous pericardiocentesis in critically ill patients or when echo-guided pericardiocentesis fails. It is performed via a midline incision from the xyphosternal junction to 6–8 cm below the tip of the xyphoid. The xyphosternal junction is split and the xyphoid process removed to expose the diaphragm. The sternum is lifted so the pericardium can be reached. The pericardium is incised allowing the fluid to drain freely and a pericardial drain is left in place [72]. Minor complications include wound dehiscence and transient pneumothorax.

45.9.1.2 Pleuro-Pericardial Window

Limited pericardiectomy is performed via a left thoracotomy. No attempt is made to excise all pericardial tissue; the main objective is to provide drainage of the pericardial sac into the left pleural space. This procedure can also be performed under direct thoracoscopic vision with excellent visualization of the pericardium and pleura.

45.9.2 Constrictive Pericarditis

45.9.2.1 Pericardiectomy

Pericardiectomy is the treatment of choice for symptomatic patients with typical constrictive hemodynamics. Limited pericardiectomy is usually performed via a left thoracotomy, but does not allow access to the right atrium and vena cava. Total pericardiectomy is defined as a wide excision of the pericardium from around the both ventricles, the great vessels, the vena cava, and the right atrium. It is usually performed via a median sternotomy or bilateral transsternal anterior thoracotomy. A median sternotomy with cardiopulmonary bypass stand-by is usually the preferred approach as it offers better exposure to the right side of the heart [78].

Poor results with persistent elevation of ventricular filling pressures have been attributed to inadequate decortication and remodeling of the ventricles after pericardiectomy. Complications include excessive bleeding and low cardiac output syndrome, thought to be secondary to fibrosis and atrophy of the myocardial fibers. Reoperation for recurrent constrictive pericarditis after partial pericardiectomy is common [79]. Improvement of symptoms and normalization of the intracardiac pressures occurs more quickly after extensive pericardiectomy [80].

45.9.3 Congenital Absence of the Pericardium

Surgical procedures employed for patients with absence of the pericardium include left atrial appendectomy, division of adhesions, pericardiectomy, or pericardioplasty. The latter is usually reserved for symptomatic patients, as the symptoms are thought to be secondary to excessive cardiac motion. It is controversial as to whether asymptomatic patients with moderate-sized pericardial defects should undergo prophylactic operation to reduce the risk of death from cardiac structure herniation or incarceration [81].

45.9.3.1 Pericardioplasty

Surgical reconstruction of the pericardium can be performed with Gore-Tex material or xenograft pericardium. The lateral and anterior surfaces of the newly reconstructed pericardium are then sutured to the lateral and medial aspect of the diaphragmatic surface, to avoid excessive cardiac motion. Careful attention must be paid to the left phrenic nerve [26].

45.9.4 Pericardial Cyst

Surgical excision is recommended only in symptomatic patients, while asymptomatic patients can be managed conservatively [82]. Minimally invasive thoracoscopic resection of the cyst is a good alternative, as it minimizes postoperative pain and has a better cosmetic outcome [83].

45.10 Postoperative Management

Among the pericardial disease processes, a common postoperative strategy may be employed. In large part, postoperative care is supportive with additional treatment directed at the underlying etiology of the disease. Management of the patient in ICU consists of fluid balance monitoring, sedation and analgesia, respiratory management, inotropic and vasodilator therapy, and recognition of anticipated complications.

In many patients, the duration of the pericardial disease process will impact their postoperative course.

45.10.1 Monitoring

Continuous cardiorespiratory monitoring remains standard for these patients. Attention should be paid to alterations in heart rate, blood pressure, and respiratory rate. Most patients should be maintained in the physiologic range after returning to the intensive care unit.

45.10.2 Fluid Management

The fluid status of a patient with pericardial disease returning to the ICU environment should be monitored carefully. Many postoperative patients may have been on very high doses of diuretics prior to surgery and a few may be diuretic dependent. Maintenance intravenous fluid therapy should be initiated on patients unless contraindicated by concurrent illness. Most will not need the aggressive fluid management of other postoperative cardiac patients. The exceptions are those patients with restrictive physiology in whom fluid balance will become important as their disease process progresses.

45.10.3 Sedation and Analgesia

Most patients should be extubated in the operating room or upon return to the ICU. Sedation should not be a significant issue in the postoperative period. Pain control can be achieved with continuous narcotic infusion or boluses. Pain from thoracotomy should not be underestimated, especially in the older patients, as atelectasis secondary to shallow breathing can be a serious complication. The transition to oral pain management should occur when the patient is capable of tolerating an oral diet. In the older child or adolescent, intermittent oral or intravenous benzodiazepines may be used for anxiolysis. Additionally, intravenous ketorolac or NSAIDs may be useful in patients with an inflammatory component to their pericardial disease.

45.10.4 Respiratory Management

Most patients are extubated in the operating room or immediately upon return to the intensive care unit. Adequate pain control helps avoid atelectasis, one of the most common complications after thoracotomy or sternotomy.

45.10.5 Inotropic and Vasodilator Therapy

A low cardiac output state may be treated with volume resuscitation, inotropic support, and afterload reduction. Additionally, vasoactive medications may be used depending upon the clinical state of the patient.

45.10.6 Anticipated Complications

In-hospital mortality after pericardiectomy for constrictive pericarditis is not negligible, reported around 15%. Complications after surgery include low cardiac output syndrome and hemorrhage. Patients should be monitored after surgical intervention for persistent effusion or restrictive physiology.

45.11 Long-Term Outcomes

Pericardiectomy improves symptoms in the majority of patients during late follow-up. A subgroup of patients does not experience an amelioration in clinical symptoms, probably because myocardial function does not completely recover [84]. This is particularly true for patients with long-standing constriction, especially in the setting of tuberculosis. Right ventricular dysfunction has been associated with myocardial involvement and absence of clinical improvement after pericardiectomy [85]. Recurrence is the most troublesome complication of pericarditis, occurs in 15–50% of patients, and is probably an autoimmune process (e.g., Dressler's syndrome).

The overall prognosis in idiopathic recurrent pericarditis is excellent, and complications are uncommon. Even after numerous recurrences of pericarditis, constrictive pericarditis as a complication is extremely rare. The risk of evolution to constrictive pericarditis in idiopathic acute pericarditis is estimated to be around 1% [86]. The risk of progression to constriction is higher in tuberculous, neoplastic, or purulent pericarditis.

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Chapter 46
Infective Endocarditis

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Abstract Infective endocarditis (IE) is defined as a microbial infection of the endocardial surface of the heart. Native and prosthetic valves are the most frequently involved sites. Studies have shown that the incidence in the pediatric population has trended upward mostly due to the increased survival rate of patients with congenital heart disease (CHD) and premature newborns. The infecting organism may be bacterial, or fungal. Despite medical and technological advances to facilitate early diagnosis, prevention, and treatment of IE, it still carries substantial risk of mortality and morbidity.

46.1 Introduction

The incidence of infective endocarditis (IE) in the adult population has ranged approximately 2–6 cases per 100,000 patients per year according to the most recent studies [1, 2]. The incidence in the pediatric population has varied among the studies but has shown an upward trend [3, 4]. This is mostly due to the increased survival rate of patients with congenital heart disease (CHD) and premature newborns [3, 4]. Underlying etiology and risk factors for IE have also evolved over the years. Rheumatic heart disease, once a leading predisposing risk factor for IE, no longer plays a predominant role in the development of IE in children, especially in developed countries. Repaired or unrepaired CHDs, with or without prosthetic material/device, are now the predominant factors predisposing to IE. IE can also occur in the absence of structural heart disease especially in neonates requiring prolonged indwelling central lines [3, 5]. Despite recent medical and technological advances to facilitate early diagnosis, prevention, and treatment of IE, it still carries substantial risk of mortality and morbidity [5, 6].

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46.2 Pathogenesis

While the intact endocardium is a poor surface as a stimulant for platelet aggregation and bacterial adhesion, any injury to the endothelium serves as a potent nidus for thrombogenesis giving rise to a site of potential nonbacterial thrombotic endocarditis (NBTE) [3, 7]. Integrity of cardiac endothelium is disturbed when there is turbulent flow either at the native or repaired structures, or when it comes into contact with foreign materials. The presence of foreign cardiac device can also indirectly lead to turbulent blood flow by adversely affecting the cardiac structure's function [3, 7]. NBTE then serves as a site for bacterial or fungal adhesion leading to formation of vegetation. Once the site is colonized with bacteria or fungus, it functions as a source of constant bacteremia and reseeding/growing of the vegetation [3, 7]. Sources of bacteremia include but are not limited to dental procedure, poor dental hygiene, or body piercing/tattoos [3, 7]. Right-sided endocarditis, especially in a structurally

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normal heart, is frequently associated with intravenous drug use and the presence of indwelling catheter or pacemaker leads. The cardiac device can be a direct site and source of infection when it is inadvertently infected at the time of placement [3, 7]. IE can occur either at native or prosthetic valves. Percutaneous pulmonary valve implantation has gained popularity over the years and now offers an excellent alternative to surgery especially among high-risk surgical candidates to treat the right ventricular outflow disease. There have been reports of increased incidence of endocarditis with percutaneously placed pulmonary valve [8, 9].

The two most common pathogens responsible for IE in the pediatric population are the viridans group of *Streptococci* and *Staphylococcus aureus*, which together account for about 80% of cases [3, 7, 10]. Coagulase-negative *staphylococci* (CoNS) and *enterococci* are the next most common organisms [3, 11]. Although the viridans group of *streptococci* has been a leading organism associated with IE in patients with CHD or rheumatic heart disease, many studies are now showing *S. aureus* as a leading cause of IE especially with increasing prevalence of nosocomial infections [3, 12]. *S. aureus* is frequently responsible for acute rapidly progressive bacterial endocarditis with high mortality [3, 7]. It is also more common in the presence of prosthetic valve or device. Coagulase-negative *staphylococci* (CoNS) also play a major role in endocarditis affecting prosthetic valves as well as native valves and can lead to both valvar and perivalvar lesions [3, 7].

Endocarditis due to Gram-negative bacteria in the pediatric population is rare and accounts for about 10% of cases in this cohort. Fastidious coccobacilli of the HACEK group (*Haemophilus parainfluenzae, H. aphrophilus*, *H. paraphrophilus*, *Actinobacillus (Hemophilus) actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* species, and *Kingella kingae*) are slow growing and often are thought to be responsible for at least some episodes of culture-negative endocarditis. Among the HACEK group, *H. parainfluenzae* and *K. kingae* are the prevalent causes of endocarditis. Other Gram-negative bacteria, which have rarely caused endocarditis, include *Neisseria gonorrhoeae*, *Escherichia coli*, *Pseudomonas aeruginosa*, or *Serratia marcescens* [3, 7].

Fungal pathogens are a relatively unusual cause of endocarditis in children. However, fungal endocarditis is associated with a high mortality even with the aggressive treatment. Fungal pathogens typically associated with IE include *Candida* species, *Aspergillus* species, *Histoplasma*, and *Cryptococcus* [3, 4, 7].

Culture-negative endocarditis accounts for anywhere between 5 and 20% of cases of IE [3, 13]. In the setting of culture-negative endocarditis, blood cultures are persistently negative even when diagnosis criteria are met either by clinical symptoms or imaging modalities. Prior exposure to antibiotics is the most frequent explanation for culture-negative endocarditis though the HACEK group of bacterial pathogens is often responsible for this syndrome due to their poor growth [3, 7].

46.3 Clinical Findings and Diagnosis

46.3.1 Clinical Manifestation

The clinical presentation of a pediatric patient with infective endocarditis can be quite variable. In general, the presentation may be indolent (previously called subacute). This may involve a history of long-standing, low-grade fever associated with a number of nonspecific symptoms. These symptoms can include weight loss, fatigue, night sweats, and arthralgias. The presence of these symptoms in a child with underlying congenital or acquired heart disease should raise concern for the possibility of IE. In contrast, some children may present with the acute onset of high-grade fevers and evidence of systemic toxicity. Such children may have evidence of metastatic infection and/or embolic disease and are more likely to have infection due to *S. aureus* rather than to have viridans group of *streptococci* or HACEK organism. In both circumstances, clinical findings might include the presence of a new or changing heart murmur, development of congestive heart failure, renal abnormalities (due to the presence of immune complex disease or embolic phenomenon), or other findings related to embolic phenomenon.

In the past wherein new/changing murmur was a necessity for diagnosis, this is no longer considered a major component in making the diagnosis. The classic extracardiac findings of IE such as Janeway lesions and Osler nodes are much less commonly seen in children compared to adults with IE.

It should be noted that the acute presentation of infective endocarditis in the neonatal/infant population may not be as described above. Often times, neonates do not mount a fever, and they may present with hypothermia and "shock-like" symptomatology with hypotension and low cardiac output state. Therefore, one has to have a high index of suspicion to diagnose IE in this group of patients. Mortality rate is quite high in neonates/infancy.

46.3.2 Evaluation: Laboratory Tests and Imaging

The key component of the laboratory assessment for infectious endocarditis is the performance of multiple blood cultures. Accordingly, clinicians evaluating children with a pre-existing history of congenital or acquired heart disease presenting with an illness that is potentially compatible with IE should obtain 3 blood cultures separated in time on the first day of evaluation. For children presenting with an acute illness and systemic

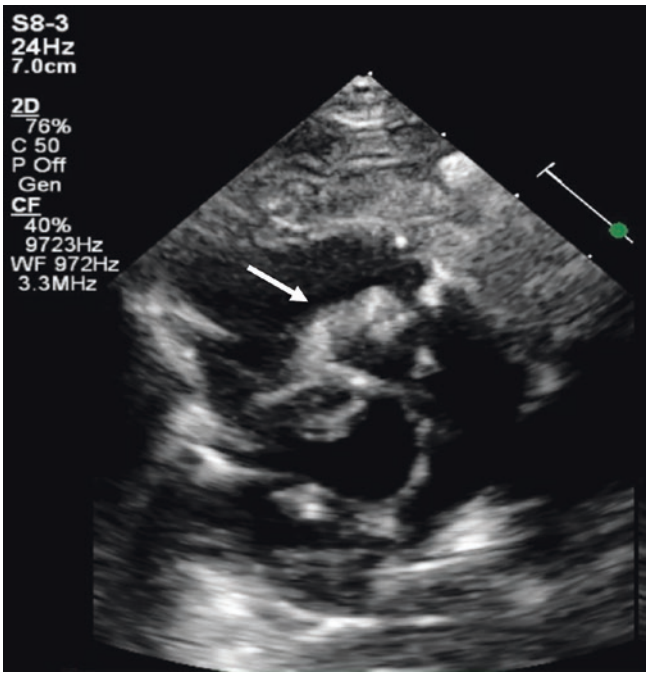

Fig. 46.1 TTE image – parasternal short-axis view of pulmonary valve vegetation (white arrow)

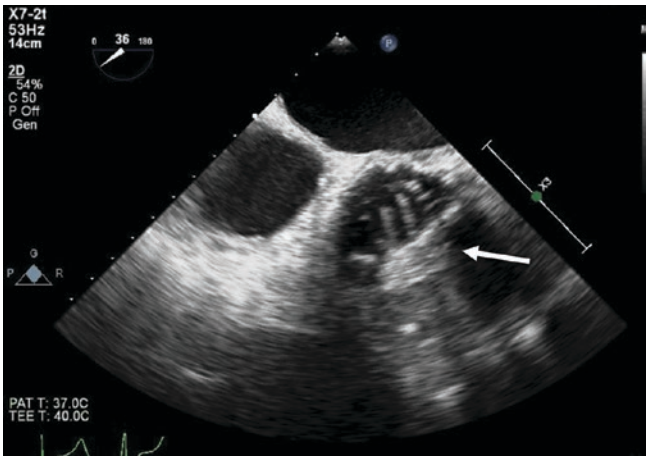

Fig. 46.2 TEE image – midesophageal view of vegetation on mechanical aortic valve (white arrow) .(Image courtesy of Dr. Jeremy Steele, Cleveland Clinic Children's Hospital)

toxicity, these cultures should be obtained over a 1–2 hour time period followed by initiation of empiric antimicrobial therapy. The 2015 Pediatric IE guidelines also suggest potentially obtaining 2–3 more cultures the following day for those with a subacute illness whose cultures are negative the next day. Hence, if the initial blood cultures are negative on day 2, it is recommended to get two additional sets of cultures irrespective of concurrent use of antibiotics/antimicrobial therapy.

Performance of an echocardiogram is also an essential component in the diagnosis of IE. The use of transthoracic echocardiography (TTE) has much greater sensitivity in children less than 60 kg compared to adults. Accordingly, this is generally recommended as the first step in the effort to confirm the presence of IE by echocardiography (Fig. 46.1). However, for larger children or those with potentially more subtle changes (i.e., paravalvular leakage, prosthetic valve endocarditis), a transesophageal echocardiogram (TEE) will likely be more sensitive than a TTE (Fig. 46.2). Of note, neither a TTE nor a TEE has perfect sensitivity or specificity in the diagnosis of IE.

Additional laboratories can support the diagnosis of IE in children. Performance of a complete blood count with differential and platelet count may identify the presence of anemia, leukocytosis, and/or thrombocytopenia. Anemia may occur due to chronic illness or hemolysis – so if present, other tests to investigate the anemia may be performed. Elevated acute phase reactants (e.g., sedimentation rate and C-reactive protein) also support the diagnosis of IE. Rheumatoid factor elevation is also present in cases of infective endocarditis. A urinalysis may identify the presence of hematuria, as well as red blood cell casts and/or proteinuria. This is due to embolic manifestation of IE and the formation of immune complexes in glomeruli. Finally, performance of an electrocardiogram (EKG) may identify abnormalities or new changes, but there are no specific EKG findings in a patient with infective endocarditis.

46.3.3 Diagnostic Criteria

Most experts use the modified Duke Criteria when considering the diagnosis of IE [14]. The diagnosis of IE using these criteria considers the presence of a combination of major and minor criteria. The first major criteria is the presence of a positive blood culture with a typical organism (e.g., viridans *Streptococci* or *S. aureus*) associated with IE from at least 2 blood cultures drawn 12 hours apart ideally or multiple positive cultures taken over time for less common organisms. The second major criterion is the presence of evidence of endocardial involvement documented by echocardiogram. Endocardial involvement may include the presence of an abscess, new mass on valve, or dehiscence of the valve. It should be noted that while new valvar regurgitation is considered a major criteria, worsening valvar regurgitation does not count to meet this requirement. Minor criteria include the presence of an underlying heart condition or history of drug use that predisposes to IE, the presence of fever (temperature > 38 degrees), vascular phenomenon (e.g., arterial emboli, pulmonary infarcts, conjunctival hemorrhage, Janeway lesion), immunologic phenomenon (e.g., Osler nodes, Roth spots, rheumatoid factor), and microbiologic phenomenon (e.g., a positive blood culture that does not meet the definition for major criteria or serologic evidence of active infection with organism consistent with IE).

Using these criteria, a patient is felt to have definitive IE in the presence of 2 major criteria or 1 major and 3 minor criteria or 5 minor criteria. A patient is felt to have possible IE in the presence of findings that are consistent with IE that fall short of definite but are not rejected. Finally, using the modified Duke Criteria, the diagnosis is rejected if there is (1) a firm alternative diagnosis for the manifestations suggestive of IE, (2) resolution of these manifestations with antibiotic therapy for ≤4 days, or (3) no pathologic evidence of IE at surgery or autopsy when antibiotics have been used for ≤4 days.

46.4 Treatment

Successful treatment of presumed or confirmed IE is dependent on eradication of responsible pathogen with antibiotic treatment alone or combined with surgery. Bactericidal agents via the intravenous route are the preferred choice for bacterial IE to prevent treatment failures and relapse. Surgery is indicated in the presence of hemodynamic instability or failure of medical therapy.

46.4.1 Antimicrobial Therapy

The American Heart Association (AHA) task force and the European Society of Cardiology provide and update a detailed set of guidelines for the treatment of IE in pediatric patients including recommended therapeutic agents and durations [3, 15]. Current guidelines recommend that an infectious disease expert should always be consulted to determine the antimicrobial agent and duration of therapy for patients with IE. Antimicrobial management is determined by clinical symptoms/presentation, causative agent, location of IE, and patient's history including underlying anatomy and surgical history, presence of prosthetic material or indwelling lines, as well as prior history of endocarditis. It is also important to note any recent or current antibiotic exposures [1, 11, 15].

Prolonged treatment, usually 4–6 weeks, with high serum concentration of bactericidal agents is desired to ensure penetration into vegetation as pathogens are often embedded in high concentration within vegetation. Serum peak and trough levels should be monitored when using vancomycin or aminoglycosides to avoid toxic side effects. Eradication of bacteremia should be documented after initiation of antimicrobial therapy with at least two negative blood cultures that are 24–48 hours apart to determine the adequacy of therapy [3, 11, 15].

The most common pathogens associated with IE are Gram-positive cocci including *streptococci, staphylococci* (both *S. aureus* and coagulase-negative *staphylococci*), and *enterococci*.

46.4.1.1 Native Valve Endocarditis

Endocarditis involving a native cardiac valve secondary to penicillin-susceptible *streptococci* (a minimal inhibitory concentration (MIC) to penicillin ≤0.1 μg/mL) including the viridans group of *streptococci* (α-hemolytic *Streptococci*), *S. bovis*, or β-hemolytic *streptococci* can be treated with either parental penicillin or ceftriaxone for a 4-week duration which achieve bacteriologic cure rates of greater than 98%. Ampicillin is an alternative treatment option to penicillin. This treatment regimen avoids the use of aminoglycosides, which are nephrotoxic. In the adult population, a 2-week treatment with penicillin, ampicillin, or ceftriaxone plus an aminoglycoside has proven to carry bacteriologic cure rates of more than 98% in uncomplicated native valve endocarditis due to *streptococcus* species. For relative penicillin-resistant *streptococci* (MIC >0.1–0.12 to <0.5 μg/mL), a 4-week course with penicillin or ceftriaxone combined with 2 weeks of daily gentamicin is a recommended therapy. Endocarditis caused by penicillin-resistant strain (MIC >0.5 μg/mL) should be treated with vancomycin combined with gentamicin for 4–6 weeks. The same treatment applies to those who are allergic or unable to tolerate β-lactam antibiotic drugs. When treating with vancomycin and gentamicin, close monitoring of blood levels of drugs and renal function is warranted, given their possible side effects.

Staphylococci, which may be either coagulase-positive *(S. aureus)* or coagulase-negative *(S. epidermidis* and other species), have now been identified as a leading cause of endocarditis in recent studies [3, 12]. Almost all *staphylococci* are resistant to penicillin. Those that are susceptible to β-lactamase-resistant penicillin are termed methicillin susceptible or MSSA and can be treated with penicillinase-resistant penicillin such as oxacillin or nafcillin for 4–6 weeks. The potential role of the use gentamicin in this setting is controversial. While the Pediatric IE Guidelines state that the addition of gentamicin for the first 3–5 days is optional, the updated adult guideline from the same year specifically recommends against the use of gentamicin based on the absence of demonstrated benefit and toxicity of this drug in this patient population [3, 11]. At Children's Hospital of Pittsburgh, it is our practice not to use gentamicin for native valve endocarditis. Endocarditis due to methicillin-resistant *staphylococci* (MRSA) should be treated with vancomycin for 6 weeks. Similar differences exist in recommendations relating to the use of gentamicin in the pediatric and adult evidenced-based

treatment guidelines for patients with native valve endocarditis due to MRSA as for MSSA. Daptomycin is considered the alternative regimen for patients with endocarditis due to MRSA who are allergic to or cannot tolerate vancomycin.

Endocarditis secondary to *enterococci* that are susceptible to penicillin should be treated with a combination of penicillin or ampicillin and aminoglycosides (gentamicin) for 4–6 weeks. For patients whose *enterococci* are resistant to or are unable to tolerate penicillin or ampicillin, vancomycin combined with gentamicin should be used for 6 weeks. Gentamicin should be administered to achieve a peak serum concentration of 3–4 μg/mL and a trough serum concentration of <1 μg/mL. Trough levels of vancomycin should be targeted to 10– 20 μg/mL. Vancomycin-resistant *enterococci* may cause endocarditis although rarely. They should be treated with linezolid or daptomycin.

The fastidious group of HACEK organisms is the most common Gram-negative bacteria to cause endocarditis. Infections due to the HACEK organisms can be treated with ceftriaxone, other third-/fourth-generation cephalosporin, or ampicillin-sulbactam for 4–6 weeks. Other Gram-negative organisms such as *Escherichia coli, Pseudomonas aeruginosa,* or *Serratia marcescens* are rare causes of endocarditis and require individualized therapy based on responsible organism and susceptibility by guidance from infectious disease experts. They usually require therapy with an extended-spectrum penicillin or cephalosporin combined with an aminoglycoside for 6 weeks. Surgical consult is often required as well due to frequently associated complications including embolic events and abscess.

Prognosis for fungal endocarditis usually is poor with evidence of high mortality and morbidity. *Candida* species are the most common organism, while *Aspergillus* endocarditis is rare. With the exception of neonates with mural endocarditis, treatment with antifungal agents alone is usually unsuccessful and surgery is required in conjunction with medical treatment. Amphotericin B has been the first line of therapy with the therapy duration of more than 6 weeks. Studies have shown that caspofungin or voriconazole could be used as alternatives [16, 17]. Due to the high rates of relapse and the prolonged delay in relapse, long-term (lifelong) suppressive therapy with oral imidazoles is often recommended [2, 3, 7].

46.4.1.2 Prosthetic Valve Endocarditis

Treatment for infective endocarditis involving prosthetic valves or other prosthetic materials warrants a therapy that lasts 6 weeks or longer. Endocarditis due to penicillin-susceptible *streptococci* can be treated with penicillin or ceftriaxone for 6 weeks combined with a 2-week course of gentamicin while that of penicillin-resistant strain requires a 6-week course of penicillin or ceftriaxone with gentamicin. If infection is caused by *staphylococci*, the treatment consists of a combination of oxacillin/nafcillin for MSSA or vancomycin (for MRSA) with rifampin for the whole 6-week course and gentamicin for the first 2 weeks.

46.4.2 Surgery

Major indications for surgical intervention for endocarditis include the presence of congestive heart failure/cardiogenic shock, embolic events, or progressive valve disease. Studies have shown that early surgical intervention in both pediatric and adult populations has been associated with low mortality and morbidity rates as well as improved overall outcomes [18–20]. However, surgery is deferred in the presence of other comorbid conditions or complications that carry poor prognosis. Those with fungal endocarditis, poor response to antibiotic treatment, and acute *staphylococci* endocarditis should be evaluated for surgical intervention along with antibiotics treatment. IE affecting a prosthetic valve due to MRSA is associated with the high mortality, and the valve replacement is usually necessary. Other indications of surgical intervention include echocardiographic evidence of persistent or enlarging vegetation, valve dehiscence or perforation, as well as large perivalvular abscess [3, 21, 22].

46.4.3 Anticoagulation

The use of oral anticoagulation therapy should be discontinued when endocarditis is suspected or diagnosed as it is associated with increased risks for hemorrhagic stroke [3, 11, 15]. Should patients need anticoagulation therapy for other underlying reasons, they can be bridged to heparin therapy if deemed safe from neurological standpoints. Antiplatelet therapy has shown to make no difference in overall associated complications [23, 24].

46.5 Long-Term Management

Complications of endocarditis include recurrent infection, valvular sequela, and extension of infection. Extensive disruption of valvular integrity and function can lead to heart failure. Damage to the conduction system can occur as well. Embolization is one of major extracardiac complications and can involve any location including the brain, kidneys, lungs, and spleen. A higher risk of embolization is associated with infection due to *staphylococci*, HACEK organisms, and fungi

and vegetations involving left-side structures, especially the mitral valve [3, 25]. Signs for antibiotics toxicity including nephrotoxicity and ototoxicity should be closely monitored. Patients receiving aminoglycoside therapy should undergo hearing evaluation before and after the completion of treatment with gentamicin.

At the end of the antibiotic treatment, an echocardiogram should be performed to serve as a baseline for follow-up. Relapse remains as a great concern, and patients should be educated about the signs and clinical symptoms of recurrent endocarditis such as fever and evidence for congestive heart failure with instructions to seek professional help immediately. On a long-term basis, patients need ongoing observation and follow-up not only with cardiology but also with infectious disease specialists with thorough examination and education regarding recurrent infection, and delayed or worsening valvular function. The antibiotic prophylaxis regimens for endocarditis have been modified over the years, and both AHA and ESC have limited its use to dental procedures on patients who are deemed to have an increased risk of IE [26]. The importance of meticulous dental hygiene should be stressed, and patients should get regular evaluations by a dentist.

Infectious endocarditis still carries a high rate of mortality and morbidity, and it is important to develop an individualized diagnosis and treatment plan involving multidisciplinary team members to promote more efficient and comprehensive management strategies.

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Chapter 47
Heart Failure

Stephanie J. Nakano, Eduardo M. da Cruz, Cécile Tissot, and Shelley D. Miyamoto

Abstract Following an initial cardiac insult, a cascade of compensatory mechanisms are activated in an attempt to preserve cardiac output. Nevertheless, prolonged activation of initially adaptive processes ultimately become maladaptive and precipitate the syndrome of heart failure. Medical heart failure therapies focus on symptom management, augmentation of cardiac output and prevention of adverse myocardial remodeling.

47.1 Definition

Heart failure is defined as the inability of the heart's output to meet the metabolic demands of the body, or the heart is able to meet these demands only in the setting of an abnormally elevated filling pressure. The clinical appearance of a patient with heart failure can vary from a well-compensated state, which can be associated with minimal signs or symptoms, to fulminant cardiogenic shock. Heart failure is often a result of myocardial failure, but it may also occur in the presence of near-normal cardiac function under conditions of extremely high demand. Irrespective of etiology, the end result of heart failure is circulatory failure.

47.2 Pathophysiology

Inadequate adaptation of the cardiac myocytes to increased wall stress in order to maintain adequate cardiac output is the inciting event in cardiac failure. The most important adaptations are outlined below:

- Frank–Starling mechanism is the ability of the heart to alter its contractility based on the degree of venous return. In the failing heart, increasing preload can increase stroke volume to maintain cardiac output [1, 2].
- Activation of neurohumoral systems including increased activity of the (1) sympathetic nervous system [3] and (2) renin–angiotensin–aldosterone system along with increased release of (3) vasopressin and (4) natriuretic peptides acts to maintain blood pressure and end-organ perfusion [4–6].
- Myocardial remodeling results in augmentation of contractile tissue (ventricular hypertrophy) [7].
- When these compensatory mechanisms are excessively and chronically activated in an attempt to preserve cardiac output, detrimental effects on the heart and circulation ensue.

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47.2.1 Frank–Starling Mechanism

The Frank–Starling mechanism allows augmentation of cardiac output by the failing myocardium at the expense of elevated end-diastolic volume. As heart failure worsens, elevations in end-diastolic volume are associated with an increase in end-diastolic pressure resulting in pulmonary edema. Circulatory failure as a result of heart failure occurs when further increases in end-diastolic volume no longer result in increased ventricular performance and end-organ perfusion is inadequate.

47.2.2 Neurohumoral Activation

The transition to symptomatic heart failure is accompanied by further activation of the sympathetic/adrenergic system and activation of the renin–angiotensin–aldosterone system (RAAS) to preserve cardiac output and maintain perfusion to vital organs early in heart failure. However, chronic activation of these compensatory mechanisms results in adverse remodeling and can even block the beneficial effects of other peptides.

47.3 Sympathetic Nervous System

The purpose of sympathetic nervous system activation of the heart is to promote a rapid increase in performance for immediate, short-term gain. Activation of the sympathetic nervous system results in increased release and decreased uptake of norepinephrine (and to a lesser degree epinephrine), resulting in vasoconstriction to maintain arterial pressure and preserve end-organ perfusion. This sympathetic stimulation also increases afterload and myocardial cytosolic calcium entry [3]. Increased calcium entry into the myocytes augments myocardial contractility (inotropy) while impairing myocardial relaxation (lusitropy). The combination of an increase in afterload and inotropy and impairment of myocardial lusitropy leads to an increase in myocardial energy expenditure and oxygen demand. Elevations in plasma norepinephrine are responsible for downregulation of β_1-adrenergic receptors, and the adrenergic reserve of the heart is diminished [8]. Additionally, heightened sympathetic drive results in direct damage to the cardiac myocyte [9–11]. In adult heart failure, elevated plasma norepinephrine levels are inversely correlated with left ventricular function and accompany progressive clinical deterioration [3, 12]. In children with a left-to-right shunt, the increase in afterload (systemic vascular resistance) worsens the left-to-right shunt, leading to an increase in the pulmonary to systemic flow ratio (Q_p:Q_s) and worsening symptoms of pulmonary overcirculation.

47.4 Renin–Angiotensin–Aldosterone System

The renin–angiotensin–aldosterone system (RAAS) regulates the cardiovascular system through modulation of systemic blood pressure, water and electrolyte balance, and hormones. Increase in RAAS activity is initially an adaptive process to increase blood pressure and intravascular volume in the setting of low cardiac output. However, prolonged RAAS activation becomes maladaptive, leading to excessive vasoconstriction, fibrosis, and pathologic cardiac remodeling. Activation of the renin–angiotensin–aldosterone system (RAAS) leads to increased circulating levels of renin, angiotensin II, and aldosterone. Release of these RAAS mediators occurs secondary to decreased perfusion and sympathetic stimulation of the kidney. Renin is responsible for cleaving angiotensinogen to form angiotensin I which is converted into angiotensin II with the action of angiotensin-converting enzyme (ACE). Angiotensin II is a potent vasoconstrictor, which enhances norepinephrine release and is associated with myocyte hypertrophy and cell death [13]. Aldosterone causes salt and water retention, resulting in increased preload, which further increases in myocardial energy expenditure and peripheral edema [4–6].

47.5 Vasopressin

Vasopressin is a pituitary hormone that is essential for the maintenance of normal plasma osmolality. Vasopressin levels are increased in heart failure and probably contribute to poor free water clearance (V_2 receptors) and systemic vasoconstriction via the V_1 receptors [14].

47.6 Natriuretic Peptides

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are released in response to changes in atrial and ventricular wall tension, respectively, as a result of volume/pressure expansion. Both peptides promote vasodilation and natriuresis, owing to reductions in cardiac preload and afterload. BNP produces afferent arteriolar vasodilation and

inhibits sodium reabsorption in the proximal convoluted tubule. BNP also inhibits renin and aldosterone release, is an important diagnostic tool, and has therapeutic implications discussed later in this chapter [15–17].

47.6.1 Myocardial Remodeling

Chronic neurohumoral activation eventually leads to increased myocardial volume and mass. This myocardial remodeling process is responsible for early adaptive mechanisms such as augmentation of stroke volume (Starling mechanism) and decreased wall stress (Laplace mechanism). However, persistent activation of neurohumoral systems is eventually harmful as maladaptive mechanisms such as increased myocardial oxygen demand, myocardial ischemia, impaired contractility, and arrhythmogenesis result. At the cellular level, chronic stimulation of the sympathetic nervous system results in myocyte hypertrophy, myocyte cell death, and eventually cardiac norepinephrine depletion [18]. For these reasons, the neurohumoral system is an important target of therapy resulting in improved long-term heart failure outcomes in adults. While therapies targeting the neurohormonal system in children with heart failure are used, there are very few data supporting their efficacy in this population [19]. In addition, there is an evolving body of evidence that adaptation of the failing pediatric heart is distinct from the adult failing heart, supporting the need for future pediatric-focused research [20–25].

47.7 Etiology

The causes of cardiac failure in the intensive care unit are varied, but are best classified by the time course of onset (acute or chronic) and mechanism of failure – systolic, diastolic, or a combination (Table 47.1).

47.7.1 Acute Heart Failure

One of the most common causes of acute cardiac failure in the pediatric population is myocarditis. Myocarditis is usually viral in origin and patients with fulminant myocarditis present in shock with rapid onset of hemodynamic deterioration. Endocarditis, rheumatic heart disease, and rarely trauma can result in severe valve injury, which can present acutely in the intensive care unit.

47.7.2 Chronic Heart Failure

Patients with chronic heart failure can decompensate and present with signs and symptoms requiring intensive care management. Although it is not always possible to determine the cause, decompensated heart failure can be preceded by an acute infection, noncompliance with medical therapy, or onset of arrhythmias.

Table 47.1 Causes of cardiac failure in pediatrics

Systolic heart failure			Diastolic heart failure
Arrhythmias	Intrinsic heart disease	High output failure	
Supraventricular tachycardia	Myocarditis (infectious, autoimmune)	Anemia	Infiltrative cardiomyopathy (amyloidosis, hemochromatosis, eosinophilic cardiomyopathy)
Bradycardia (complete heart block)	Ischemic heart disease (ALCAPA, Kawasaki, transplant vasculopathy)	Thyrotoxicosis	Hypertrophic cardiomyopathy
Ventricular tachycardia (arrhythmogenic right ventricular dysplasia – ARVD)	Rheumatic heart disease	Arteriovenous malformations	Restrictive cardiomyopathy
	Valvular heart disease (endocarditis)	Sepsis	Systemic hypertension
	Toxin-induced (anthracyclines, carbon monoxide)		Heart transplant rejection
	Dilated cardiomyopathy (idiopathic, metabolic, postinfectious, genetic)		Sarcoidosis
	Congenital heart disease (right- or left-sided obstruction, chronic valvar insufficiency)		Endomyocardial fibrosis
	Myocardial noncompaction		
	Heart transplant rejection		

ARVD arrhythmogenic right ventricular dysplasia, *ALCAPA* anomalous left coronary artery from the pulmonary artery

47.7.3 Systolic Heart Failure

Most forms of cardiac failure consist of a combination of systolic and diastolic failure. Systolic heart failure is defined by inadequate ventricular inotropy to meet the body's physiologic needs. Systolic heart failure occurs in the setting of myocarditis, dilated cardiomyopathy, ischemia (congenital coronary artery anomalies, Kawasaki disease, posttransplant coronary vasculopathy, coronary injury after cardiac surgery), excessive pressure (left-sided obstructive lesions) or volume overload (long-standing valve insufficiency, intracardiac shunts), and prolonged arrhythmia. Inadequate perfusion of vital end organs results in presenting signs and symptoms such as mental status changes, poor end-organ function (kidney and liver), and vomiting or feeding intolerance.

47.7.4 Diastolic Heart Failure

Diastolic heart failure is defined by inadequate lusitropy or abnormalities of ventricular relaxation. Isolated diastolic heart failure is rare and as mentioned above usually occurs in combination with systolic heart failure. Restrictive and hypertrophic cardiomyopathies are common causes of diastolic heart failure, while systolic function is initially preserved. Presentation of diastolic heart failure is related to the extent of elevation in atrial pressure, as a result of ventricular stiffness. Elevated right atrial pressure results in jugular venous distention, hepatic congestion, and lower extremity edema. Elevated left atrial pressure is associated with pulmonary edema and orthopnea; exercise intolerance and dyspnea are common. Diastolic heart failure should not be confused with other causes of impaired ventricular filling such as constrictive or restrictive pericarditis, large pericardial effusions, mitral or tricuspid stenosis, or obstruction of systemic or pulmonary venous return. Despite their similar presentation to true diastolic heart failure, ventricular relaxation is usually normal in these settings.

47.8 Staging

The New York Heart Association (NYHA) classification is based on the relation between symptoms and the amount of effort required to provoke them. Because of the inability to use this classification in small children, R.D. Ross has proposed to grade the severity of heart failure in infants based on feeding, respiratory pattern, and clinical parameters [19, 26] (Table 47.2).

Table 47.2 The New York Heart Association (NYHA) and modified Ross classifications of cardiac failure

	NYHA classification	Modified Ross classification
Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitations	No limitations or symptoms
Class II	Slight limitation of physical activity, comfortable at rest. Ordinary physical activity results in fatigue, palpitations, and dyspnea	Mild tachypnea or diaphoresis with feeding
Class III	Marked limitation of physical activity. Although comfortable at rest, less than ordinary activity leads to fatigue, dyspnea, and palpitations	Infants with growth failure and marked tachypnea or diaphoresis with feedings, older children with marked dyspnea on exertion
Class IV	Symptomatic at rest. Discomfort increases with any physical activity	Symptoms at rest such as tachypnea, retractions, grunting, or diaphoresis

47.9 Clinical Features

In the infant, clinical history can reveal failure to thrive, poor feeding associated with diaphoresis, vomiting, increased work of breathing, and irritability. The older child can present with dyspnea, orthopnea, paroxysmal nocturnal dyspnea, poor appetite and growth, fatigue, or weakness.

Although some of the physical signs of heart failure described in this section may be seen in the compensated patient, the focus here will be on the expected features of a patient with decompensated or severe acute heart failure as would be seen in the ICU setting.

- General appearance
  - Central cyanosis.
  - Diminished pulse pressure, dusky discoloration of the skin with delayed capillary refill time due to poor peripheral perfusion.
- Reduced systolic arterial pressure, weak, rapid, and thready pulse
  - Evidence of increased adrenergic activity manifested by tachycardia, diaphoresis, pallor, peripheral cyanosis with pallor, and coldness of the extremities.
- Tachycardia or arrhythmia
- Tachypnea, increased work of breathing
- Pulmonary rales over the lung bases, frequently accompanied by wheezing, especially in the infant

- Pleural effusion, usually bilateral, and/or ascites
- Jugular venous distention and peripheral edema – due to systemic venous hypertension – may be difficult to appreciate or absent in infants
- Hepatojugular reflux, found in older children with right-sided heart failure
- Hepatomegaly, most reliable sign of cardiac failure in the infant
- Gallop rhythm, with a protodiastolic (S_3) and/or telediastolic (S_4) gallop, one of the earliest cardiac physical finding in decompensated heart failure
- Accentuated second heart sound if associated with pulmonary hypertension
- Cardiomegaly with a displaced apical impulse
- Systolic murmurs
  - Mitral and tricuspid regurgitation murmurs are often present in patients with decompensated heart failure because of ventricular dilatation.
- Failure to thrive and cachexia
  - Related to increased total metabolism secondary to augmentation of myocardial oxygen consumption and excessive work of breathing.

47.10 Laboratory Studies

- Complete blood count
  - Useful to assess anemia, which may cause or aggravate heart failure. Leukocytosis may result from stress or signal an underlying infection.
- Electrolytes
  - Hyponatremia reflects an expansion of extracellular fluid volume in the setting of a normal total body sodium.
  - Hypokalemia and hypochloremia can be the result of prolonged administration of diuretics.
  - Hyperkalemia can be the result of impaired renal perfusion and marked reductions in glomerular filtration rate (GFR) or from intracellular potassium release due to impaired tissue perfusion.
- Renal function tests
  - Elevated BUN and BUN/creatinine ratios are seen in decompensated heart failure.
- Liver function tests
  - Congestive hepatomegaly is often associated with impaired hepatic function, which is characterized by elevation of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), and other liver enzymes.
  - Hyperbilirubinemia (both direct and indirect) is related to acute hepatic venous congestion and is common with severe right heart failure. Elevated alkaline phosphatase, and prolongation of the prothrombin time can be seen. In children with long-standing heart failure and poor nutritional status, hypoalbuminemia results from hepatic synthesis impairment.
- B-type natriuretic peptide
  - BNP is a natriuretic peptide released in response to ventricular volume expansion and pressure overload. In normal individuals, BNP levels are elevated immediately after birth, but fall to adult levels by 3 months of age [27]. In the setting of heart failure, BNP levels correlate closely with the NYHA Classification of Heart Failure and with ventricular filling pressures [28–31]. BNP levels of more than 80 pg/ml have a good specificity and sensitivity in diagnosing heart failure [16].
- *CK-MB, troponin I and T* can be useful if the clinical scenario is suggestive of an ischemic process.
- Lactate
  - Elevated lactate is seen in patients with decompensated heart failure as a result of decreased tissue perfusion and/or decreased metabolism due to secondary liver dysfunction and can be a useful serologic marker for monitoring response to therapeutic interventions. Abrupt elevations on lactate levels may occur early in the process of decompensation and should motivate caregivers to aggressively treat patients trying to reverse or to compensate the acute changes leading to the cardiac failure.
- Infectious serologies
  - Viral infections (Table 47.3) are the most common cause of infectious myocarditis, but bacterial, rickettsial (e.g., Q fever), fungal, spirochetal (e.g., Lyme disease), and protozoal (e.g., Chagas, malaria) infections are other possibilities.

Table 47.3 Viral etiologies of myocarditis

Viral etiologies of myocarditis			
Coxsackie virus	Respiratory syncytial virus	Cytomegalovirus	Herpes virus (herpes simplex and human herpes virus 6)
Adenovirus	Mumps	Echovirus	HIV
Parvovirus B19	Rubella	Epstein–Barr virus	Parainfluenza
Influenza A virus	Varicella	Hepatitis C virus	Measles

- Metabolic work-up
  - Metabolic evaluation of a patient presenting to the intensive care unit with cardiac failure should be dictated based on patient age, history, and clinical suspicion.
  - Total carnitine level and an acylcarnitine profile can demonstrate carnitine transporter defects.
  - Urine organic and amino acids. Specifically, quantitative 3-methylglutaconic aciduria should be obtained in boys with clinical suspicion for Barth syndrome. This X-linked disorder is associated with dilated cardiomyopathy, failure to thrive, neutropenia, and muscle weakness.
  - Thiamine deficiency is a rare problem in developed countries, but when found usually occurs in association with lactic acidosis and anemia.
- Inflammatory markers
  - C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and TNF-α are nonspecific but can be supportive evidence of an acute inflammatory process and indicative of ongoing cardiac injury.
  - The presence of autoantibodies (e.g., antimyosin) is a negative prognostic finding [32].
  - Endocrine work-up.
  - Thyroid function tests – both profound hyper or hypothyroidism can cause heart failure.
- Arterial blood gas
  - ABGs usually reveal mild hypoxemia in patients who have mild-to-moderate heart failure. Severe heart failure often leads to severe hypoxemia or even hypoxia. Hypocapnia occurs in the early stages of pulmonary edema because of ventilation/perfusion (V/Q) mismatch, progressing to hypercapnia, and respiratory acidosis, related to decreased vital capacity and poor ventilation.

47.11 Diagnostic Studies and Imaging

47.11.1 Chest Radiography

- Cardiomegaly and alveolar edema with pleural effusions and bilateral infiltrates in a butterfly pattern are the classic findings on chest radiography in the setting of heart failure (Fig. 47.1).
- Other signs are haziness of hilar shadows, vascular redistribution, and thickening of interlobular septa (Kerley B lines).

47.11.2 Electrocardiogram (ECG)

- Sinus tachycardia is a common and nearly universal finding in acute and decompensated heart failure. Heart rhythm can be abnormal secondary to cardiac dysfunction or electrolyte abnormalities. However, because an underlying primary arrhythmia (e.g., supraventricular tachycardia) may be the cause of heart failure, the heart rhythm at the time of presentations should be closely scrutinized.
- Conduction abnormalities
  - Heart block can occur as a result of the inciting event (e.g., in association with infectious myocarditis) or in

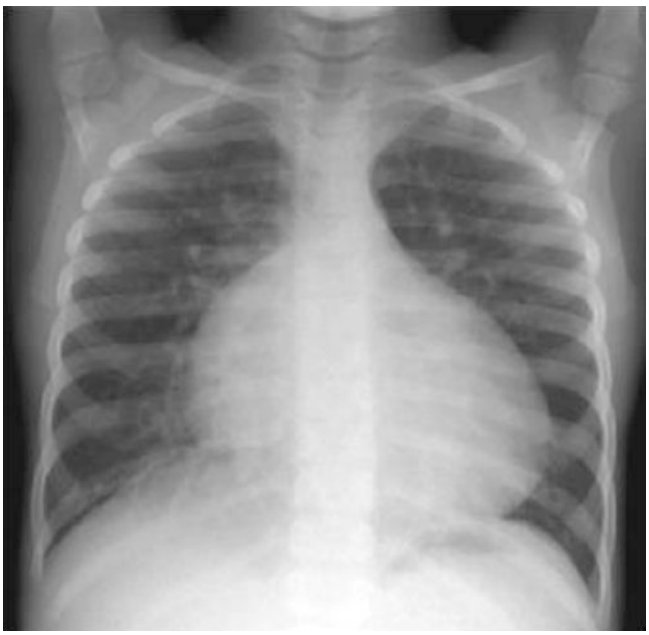

Fig. 47.1 Chest X-ray in cardiac failure: cardiomegaly with increased vascular markings suggestive of pulmonary edema

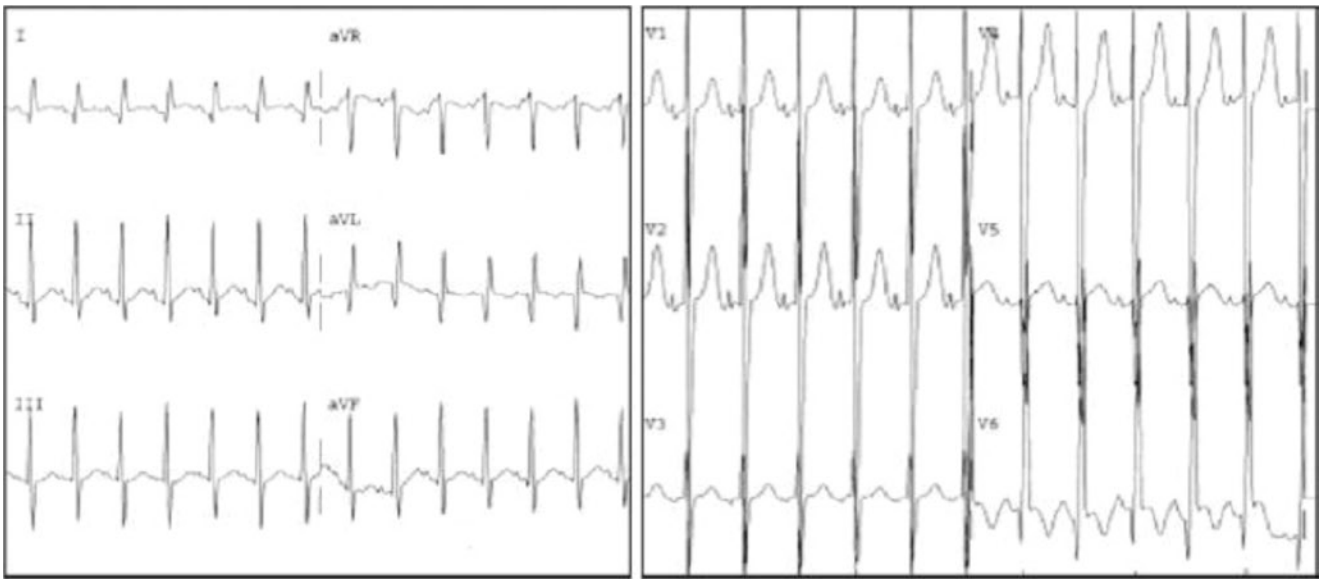

Fig. 47.2 Typical electrocardiogram in anomalous left coronary artery arising from the pulmonary artery (ALCAPA) syndrome: Q waves in I and avL with prominent Q waves in V6

association with medical therapies (e.g., digoxin, verapamil – 1° or higher levels of heart block; amiodarone – prolonged QTc).
  - Congenital complete heart block is associated with eventual development of dilated cardiomyopathy and heart failure. The reported incidence of heart failure in this patient population has been variable and ranges from 6% to 23% [33–35].

- Prolonged QTc and abnormal QT dispersion are commonly associated with cardiomyopathies due to repolarization abnormalities and both have been noted to be markers for poor outcome [36, 37].
- Chamber enlargement/hypertrophy
  - Left atrial enlargement and LV hypertrophy is sensitive for chronic LV dysfunction. In the setting of acute LV dysfunction, with the exception of sinus tachycardia, the ECG may be normal.
  - In acute myocarditis, the classic ECG findings are low QRS voltages with T wave flattening or inversion.
- Prominent Q waves and ST segment abnormalities suggest myocardial ischemia (e.g., anomalous coronary artery, Fig. 47.2).

47.11.3 Echocardiography

Transthoracic echocardiography can thoroughly assess both systolic and diastolic ventricular function. The presence and extent of valvular heart disease, structural congenital heart disease, LV wall thickness, chamber sizes, pericardial disease, regional wall motion abnormalities, proximal coronary artery distribution, and size can all be accurately determined in most children with echocardiography (Fig. 47.3). Shortening fraction (SF) by M-mode and ejection fraction (EF) by M-mode or Simpson's biplane can be obtained (Fig. 47.4). Mitral inflow Doppler, pulmonary venous Doppler, and tissue Doppler techniques can be used to assess left ventricular diastolic function.

Transesophageal echocardiography (TEE) is seldom necessary in pediatric patients as good-quality conventional transthoracic echocardiography is usually obtained. TEE imaging can be helpful when endocarditis is suspected, especially when there is concern about aortic root involvement.

47.11.4 Cardiac Catheterization

Cardiac catheterization is often a necessary adjunct in the diagnostic approach to a patient with heart failure. Direct hemodynamic data in combination with angiograms clarifying structural anatomy can be essential in diagnosing and in some cases treating structural causes of heart failure. Despite advances in imaging technology, anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) remains an elusive diagnosis by echocardiography in some situations and can be definitively identified in the catheterization laboratory.

In idiopathic causes of cardiomyopathy, a myocardial biopsy can result in a definitive diagnosis. Viral myocarditis, metabolic storage diseases, infiltrative cardiomyopathies, and mitochondrial disorders among others can be diagnosed by biopsy. However, unfortunately nonspecific findings such as myocyte hypertrophy, abnormal nuclei,

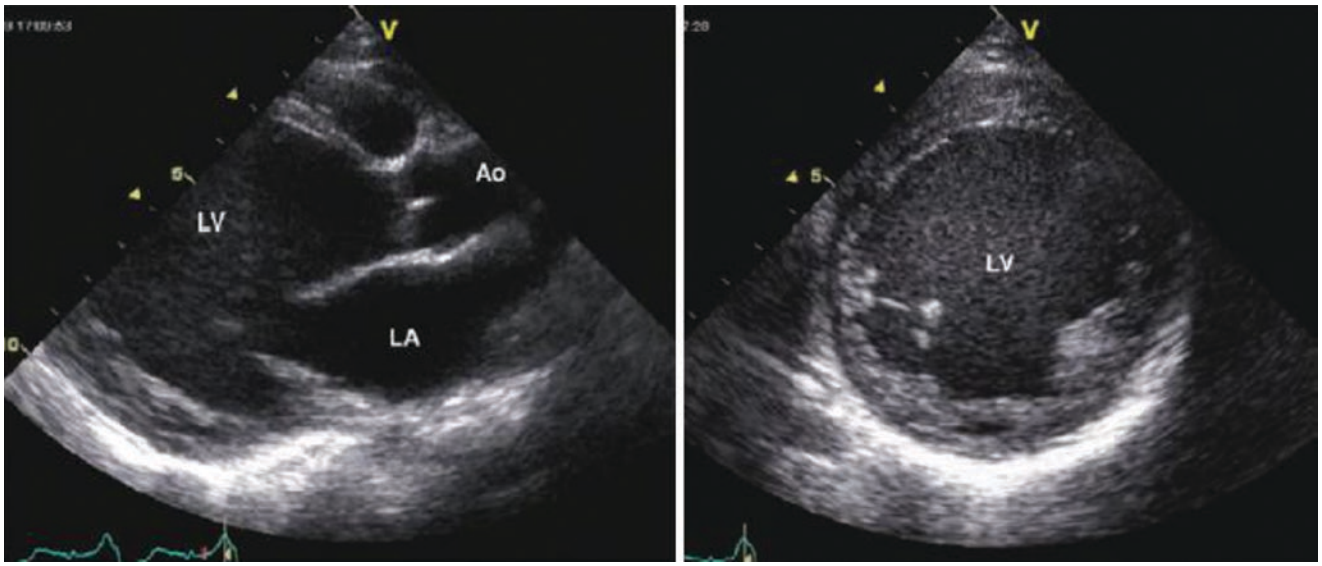

Fig. 47.3 Echocardiogram: parasternal long-axis and short-axis view in a patient with dilated cardiomyopathy showing a very dilated and globular left ventricle

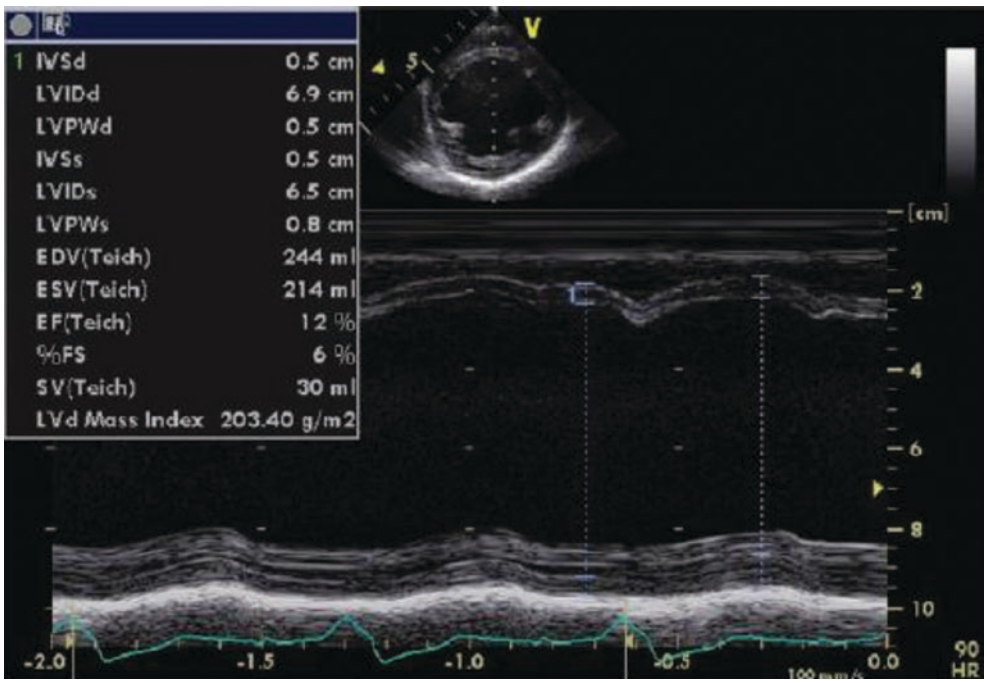

Fig. 47.4 M-mode echocardiography in a patient with dilated cardiomyopathy demonstrating severely depressed left ventricular systolic function (decreased SF and EF)

and fibrosis can also be seen [38]. Endomyocardial biopsies are not without risk. Injury to the tricuspid valve, heart block, arrhythmias, cardiac perforation, and death although rare can occur.

47.11.5 Cardiac Magnetic Resonance Imaging (cMRI)

Although not often necessary in the evaluation of heart failure, cardiac magnetic resonance imaging (cMRI) can be a useful noninvasive adjunct in select cases. Myocardial function including wall motion abnormalities as well as myocardial perfusion and viability can be determined with cMRI [39, 40]. LV subepicardial or intramural edema on T2-weighted cMRI can be suggestive of myocarditis [41]. In addition, cMRI tissue characterization and characterization of scar tissue by late gadolinium enhancement may have prognostic value in adults with dilated cardiomyopathy [42]. Lastly, identification of myocardial noncompaction, arrhythmogenic right ventricular dysplasia, and constrictive pericarditis can be difficult diagnoses to make with echocardiography but can be well-defined by cMRI.

47.12 Monitoring

Of course, the care of all critically ill patients starts with stabilization of the airway and circulation. Once these goals are obtained, further management of the heart failure patient is optimized with the use of invasive hemodynamic monitoring devices:

- Central venous pressure monitoring is necessary to accurately assess fluid status and to evaluate for alterations in the degree of restrictive physiology present. Patients in decompensated heart failure are highly dependent on adequate preload to maintain cardiac output. However, excessive fluid is counterproductive at some point and induction of diuresis may become necessary.
- Swan–Ganz catheters allow measurement of right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and mixed venous oxygen saturation. Use of these catheters is often not realistic in young infants but transducing any central venous line that could be used to trend the filling pressure of the right heart.
- Arterial pressure monitoring is necessary in patients with marked hemodynamic deterioration requiring intravenous support. Continuous arterial pressure readings allow titration of therapy to ensure adequate end-organ perfusion pressure.
- All patients with heart failure should be on constant telemetry in the intensive care unit. Heart rhythm abnormalities and alterations in heart rate must be rapidly assessed and treated.
- In patients who are critically ill and sedated, a Foley catheter can serve as a necessary means of obtaining precise measurements of urine output as a surrogate for renal perfusion.
- Near infrared spectrometry (NIRS) is an emerging technology that may be a useful noninvasive tool for assessing tissue oxygenation and perfusion in the intensive care unit. A study of abdominal site NIRS readings in infants and children requiring an intervention for congenital heart disease demonstrated good correlation with serum lactate and systemic mixed venous saturation [43].

47.13 Medical Treatment

Medical therapy of heart failure (Table 47.4) focuses on three main goals:

Table 47.4 Medical therapy for cardiac failure

Medication	Dosage (iv)	Dosage (po)
Amrinone	Loading 1–4 mg/kg (optional) then 3–15 mcg/kg/min	
Atenolol		1–2 mg/kg q 12–24 h
Captopril		Initial 0.05 mg/kg, then 0.1–2 mg/kg q 8 h
Carvedilol		0.08–0.7 mg/kg q day 12–24 h
Chlorothiazide	5–10 mg/kg q 12 h	10–20 mg/kg q 12 h
Digoxin		Age-dependent dosage: Loading 8–20 μg/kg, then 5–10 μg/kg q day
Dobutamine	5–20 μg/kg/min	
Dopamine	Dopa 3–5 μg/kg/min, beta-1 5–15 μg/kg/min, alpha 15–20 μg/kg/min	
Enalapril		Initial 0.05 mg/kg, then 0.1–0.5 mg/kg q 12 h
Epinephrine	0.01–1 μg/kg/min	
Esmolol	Loading 100–500 μg/kg, then 50–300 μg/kg/min	
Furosemide	0.05–0.4 mg/kg/h, 1–2 mg/kg q 6–24 h	1–2 mg/kg q 6–24 h
Hydrochlorothiazide		1–2 mg/kg q 12–24 h
Labetalol	0.25–4 mg/kg/h, 0.2–1 mg/kg q 6–12 h	1–2 mg/kg q 6–12 h
Levosimendan	Loading 12 μg/kg over 1 h, then 0.1–0.2 μg/kg/min for 24–48 h	
Lisinopril		0.1–0.4 mg/kg q day
Losartan		0.5–1.5 mg/kg q day
Metoprolol	0.1 mg/kg then 1–5 mcg/kg/min	0.1–2 mg/kg q day
Milrinone	Loading 50 μg/kg (optional), then 0.25–0.75 μg/kg/min	
Morphine	0.05–0.4 mg/kg/h, ventilated up to 1.2 mg/kg/h, 0.1–0.2 mg/kg q 1 h	
Nesiritide	Loading 1 μg/kg, then 0.005–0.02 μg/kg/min	
Nitroglycerin	0.5–10 μg/kg/min	
Nitroprusside	0.3–12 μg/kg/min	
Norepinephrine	0.05–0.5 μg/kg/min	
Phenoxybenzamine	Loading 1 mg/kg, then 0.5 mg/kg q 8–12 h	0.2–0.5 mg/kg q 8–12 h
Phenylephrine	Loading 5–10 mcg/kg, then 1–5 mcg/kg/min	
Propranolol		Initial 0.5 mg/kg, then 1–4 mg/kg q 8 h
Spironolactone		1–3 mg/kg q 12–24 h

1. Preload reduction results in decreased pulmonary capillary hydrostatic pressure and reduction of fluid transudation into the pulmonary interstitium and alveoli.
2. Afterload reduction obtained by decreasing systemic vascular resistance results in increased cardiac output and improved end-organ perfusion.
3. Inhibition of both RAAS and vasoconstrictor neurohumoral factors results in vasodilation, thereby increasing cardiac output and reducing myocardial oxygen demand.

47.13.1 Diuretics

- Loop diuretics
  - Diuretic therapy is the cornerstone of heart failure treatment.
  - Loop diuretics inhibit the $Na^+/K^+/2Cl^-$ cotransport system in the loop of Henle. The result is increased excretion of sodium, potassium, chloride, hydrogen, and water. Loop diuretics reduce preload through diuresis and by increasing venous capacitance.
  - Furosemide is the most commonly used, but bumetanide has a higher bioavailability and may be more effective [44].
  - In patients with diastolic heart failure or restrictive physiology who are minimally fluid overloaded, aggressive diuretic use may be associated with hypotension and adverse outcomes, so careful titration based on cardiac output and central venous monitoring is essential.
- Thiazides
  - Thiazides inhibit the Na^+/Cl^- cotransporter in the distal convoluted tubule, resulting in increased sodium and chloride excretion.
  - Hydrochlorothiazide, chlorothiazide, and metolazone are particularly useful in combination with loop diuretics in patients suffering from heart failure.
- Potassium-sparing diuretics
  - The mechanism of action of spironolactone is to block aldosterone effect in the distal tubule and collecting duct. The association of a loop diuretic and spironolactone is useful to maintain serum potassium levels and avoid the need for potassium supplements.
  - The RALES (Randomized Aldactone Evaluation Study) trial in adults demonstrated improved NYHA class and decreased mortality and hospitalization rate in patients with advanced heart failure treated with spironolactone [45]. Whether these findings would translate to the pediatric population is unknown.

47.13.2 Vasodilators

- ACE inhibitors
  - ACE inhibitors block the adverse effects resulting from the chronic activation of the renin–angiotensin system that occurs in heart failure. Prevention of the formation of angiotensin II and its subsequent vasoconstrictive effects and promotion of vasodilation via bradykinin result in reduced afterload and preload and improved stroke volume and cardiac output.
  - Left ventricular remodeling is diminished by ACE inhibitor therapy. Prevention of the formation of angiotensin II results in limitation of myocyte hypertrophy, fibrosis, and myocyte apoptosis that would otherwise occur [46].
  - Captopril rather than enalapril is preferred in neonates because of the delayed capacity of neonates to biotransform enalapril to enalaprilat [47].
  - Studies consistently demonstrate that ACE inhibitors prolong survival and reduce morbidity in adult heart failure [48, 49]. The use of ACE inhibitors in pediatric dilated cardiomyopathy does not have as strong of a body of evidence and has not resulted in improved long-term transplant-free survival [50, 51].
  - In children with a left-to-right shunt, ACE inhibitors reduce the Q_p:Q_s by decreasing systemic vascular resistance but are less effective in those with elevated pulmonary pressures [52, 53]. However, use of ACE inhibitors in infants with single-ventricle physiology does not improve ventricular function or prevent development of heart failure, again demonstrating the challenges of identifying effective treatments in the heterogeneous pediatric cardiac disease population [54].
- Angiotensin receptor blockers (ARBs)
  - ARBs inhibit angiotensin II and are especially useful in patients with heart failure who are otherwise intolerant to ACE inhibitors [55]. Few data are available in children so far.
- Sodium nitroprusside
  - Results in simultaneous preload and afterload reduction with a greater effect on afterload reduction through direct smooth muscle relaxation.
  - Potency and rapidity of onset make it an ideal medication in critical situations and dose should be titrated based on reduction in filling pressures and improvement in symptoms. Because it may induce precipitous falls in blood pressure, intra-arterial blood pressure monitoring is often recommended.

  - Byproducts of nitroprusside include nitric oxide and cyanide. Prolonged use and use in those with hepatic dysfunction should be avoided due to increased risk of thiocyanate toxicity.

- Nitroglycerin

  - Intravenous nitroglycerin provides rapid and titratable preload reduction by increasing venous capacitance. Its arterial vasodilatory effects result in afterload reduction as well. It is widely used in the adult population for patients with ischemic heart disease given its coronary vasodilatory properties, and more sporadically used in pediatrics.
  - Nitroglycerin may be useful in children who have had coronary reimplantation as a result of the arterial switch operation or ALCAPA repair, as it provides afterload reduction while decreasing myocardial oxygen consumption and providing coronary vasodilation and decreasing transmural tension. Nitroglycerin may reverse the coronary vasoconstrictive effects of endothelin-1 postbypass in children undergoing cardiac surgery [56].

- α-Adrenergic blockers

  - Phenoxybenzamine, phentolamine, and nicergoline are potent vasodilators that have been used for the treatment of severe left ventricular failure. Although not widely used for heart failure, these drugs decrease peripheral vascular resistance, resulting in an increase in cardiac output and stroke volume.
  - Combined use of phenoxybenzamine and dopamine has been shown to be beneficial in children with low cardiac output syndrome who are difficult to wean from cardiopulmonary bypass, by preventing the α-adrenergic action of dopamine and encouraging its β-adrenergic action [57].

47.13.3 Intravenous Inotropes

Inotropic support must be used judiciously and with caution in the setting of patients with heart failure. Although increased inotropy results in improved cardiac output and blood pressure, it comes at the expense of increased myocardial oxygen consumption and demand. The failing myocardium has a limited reserve, and complete hemodynamic collapse can occur as a result of high-dose inotropic support in this setting. Additionally, tolerance to catecholamine-based inotropes can develop rapidly through downregulation of adrenoreceptors. For this reason, early and elective use of mechanical circulatory support should be considered in all patients with severe myocardial dysfunction that is refractory to medical therapy including low-dose inotropic support. Mechanical support is covered in detail elsewhere and will not be discussed in this chapter.

- Dopamine

  - Effects are dose dependent. As with other inotropic agents, moderate and high dosages are arrhythmogenic and may be counterproductive as a result of increased myocardial oxygen demand.
  - Low dosages (0.5–3 μg/kg/min) cause stimulation of dopaminergic receptors within the renal and splanchnic vascular beds, causing vasodilation and increased diuresis.
  - Moderate dosages (3–10 μg/kg/min) cause stimulation of β-receptors in the myocardium, resulting in increased cardiac contractility (inotropy), blood pressure, and heart rate.
  - High dosages (10–20 μg/kg/min) cause stimulation of α-receptors, resulting in peripheral and pulmonary vasoconstriction and therefore increased SVR and PVR.

- Dobutamine

  - A β_1-receptor agonist, with some β_2-receptor and minimal α-receptor activity.
  - Intravenous dobutamine induces significant positive inotropic effects with mild chronotropic effects. It also induces mild peripheral vasodilation, decreasing SVR and PVR.
  - The combined effect of increased inotropy with decreased afterload results in a significant increase in cardiac output.

- Epinephrine

  - A β_1-, β_2-, and α-receptor agonist that primarily exerts β effects at low doses (0.01–0.02 μg/kg/min) with α and β effects at higher doses. Vasodilation via β_2-receptor effect is seen in low doses, while at higher doses, positive inotropic effects, tachycardia, and mild increased blood pressure secondary to vasoconstriction result.

- Norepinephrine

  - An α- and β_1-receptor agonist, resulting in vasoconstriction and significant increases in afterload with subsequent increase in myocardial oxygen demand and reduced cardiac output.

- Isoproterenol
  - β_1- and β_2-receptor agonist induces increased inotropy and increased heart rate but is potentially arrhythmogenic.

47.13.4 Phosphodiesterase Inhibitors

Phosphodiesterases (PDEs) are enzymes that hydrolyze the second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), with PDE1 and PDE3 being the major cAMP-hydrolyzing PDE families in human cardiomyocytes [58, 59]. PDE5 selectively hydrolyzes cGMP, which is a second messenger in nitric oxide signaling and regulates a wide variety of cellular function, including hypertrophy and remodeling of the ventricular myocardium.

- Milrinone and amrinone
  - Milrinone and amrinone are PDE3 inhibitors thought to increase intracellular cAMP, resulting in protein kinase A-mediated phospholamban phosphorylation and a subsequent increase in inotropy secondary to increased sarcoplasmic reticulum calcium uptake.
  - The hemodynamic effects of PDE3 inhibition include (1) a positive inotropic effect, (2) peripheral vasodilation (via activation of protein kinase G), and (3) improved myocardial relaxation (lusitropy).
  - Despite numerous studies documenting beneficial, short-term hemodynamic effects of PDE3 inhibition, chronic use of PDE3 inhibition in adults with severe heart failure has not shown improvements in major clinical outcomes [60, 61], with an increase in cardiovascular mortality [62] likely secondary to an increase in ventricular arrhythmias [63, 64]. Milrinone has been demonstrated to be useful in children with low cardiac output syndrome following cardiac surgery [65, 66] and is often used as a bridge to heart transplant or recovery in children with heart failure. Milrinone improves symptoms and decreases signs of heart failure on examination in children [67, 68], and clinical experience suggests that arrhythmias and sudden death are extremely rare in children treated with milrinone, suggesting that its use is safe on a chronic basis [67].
- Sildenafil, tadalafil, and udenafil
  - Sildenafil, tadalafil, and udenafil are selective PDE5 inhibitors which act to increase intracellular cGMP levels.
  - PDE5 inhibitors are routinely used to promote pulmonary vascular smooth muscle relaxation in patients with pulmonary arterial hypertension, and use of PDE5 inhibitors has been extrapolated to patients with right heart failure and failing Fontan palliation [69, 70]. Direct myocardial effects of PDE5 inhibitors are currently being evaluated.

47.13.5 Oral Heart Failure Agents

- β-Adrenergic blocking agents (metoprolol, carvedilol)
  - Ratio of β_1:β_2 receptors in the nonfailing myocardium is approximately 3:1. In adult heart failure, there is downregulation of β_1 receptors resulting in a ratio of 1:1. Notably, myocardium from children with heart failure demonstrate downregulation of both β1 and β2 receptors [20]. This difference in β-adrenergic receptor adaptation has implications for effectiveness of β-blocker therapy, with different agents having varying β-receptor selectivity [25].
  - The putative beneficial effect of β-blockade is mediated primarily through inhibition of sympathetic system activation that occurs in heart failure but also reversal of adverse remodeling and upregulation of myocardial β-receptors.
  - β-Blockers improve symptoms, exercise tolerance, cardiac hemodynamics, LV ejection fraction, decrease mortality, and decrease myocardial oxygen consumption in adults with heart failure [71, 72]. β-Blockers are recommended for use in adults with stable heart failure resulting from left ventricular dysfunction. Data in children is less clear: in a multicenter, randomized placebo controlled trial of the nonselective β-blocker carvedilol, there was no improvement in clinical outcomes in children with symptomatic heart failure treated with carvedilol versus placebo [73]. Notably, the results of this trial are difficult to interpret due to a relatively small sample size, the heterogeneous etiologies of heart failure, and the high rate of spontaneous improvements. Nevertheless, these results are markedly different than the overwhelmingly beneficial effects of β-blocker therapy in adults with heart failure.
  - In children with left-to-right shunts and overcirculation, β-blocker therapy improves feeding, weight gain, and symptoms [74].
  - When initiating therapy, β-blockers should be started at a very low dosage in euvolemic patients and gradually increased to maximum therapeutic dosage with close monitoring according to heart rate and blood pressure [75].

- Digoxin
  - Acts by inhibiting the Na^+/K^+–ATPase transport pump and inhibits sodium and potassium transport across cell membranes. This increases the velocity and shortening of cardiac muscle, resulting in a shift upward and to the left of the ventricular function (Frank–Starling) curve. The positive inotropic effect is due to an increase in the availability of cytosolic calcium during systole, thus increasing the velocity and extent of myocardial sarcomere shortening [76, 77].
  - Routine use of digoxin for pediatric heart failure is controversial. Adult studies demonstrate no mortality benefit but improved symptoms and decreased hospitalizations [78].
  - Digoxin toxicity can affect the gastrointestinal (nausea, vomiting), neurologic (headache, visual disturbances), and cardiac (heart block and arrhythmias) systems. Particular attention should be paid when digoxin is used in association with loop diuretics, as hypokalemia enhances digoxin intoxication.
- Nesiritide
  - A recombinant B-type natriuretic peptide.
  - While early studies demonstrated some encouraging evidence that nesiritide could relieve symptoms in adults with acute heart failure, more recent studies are less encouraging [79].
  - There are very few pediatric data to support the use of nesiritide in children. In children with primary heart failure or low cardiac output after heart surgery, nesiritide has been associated with improved diuresis in a small, uncontrolled study [80].
- Levosimendan
  - A calcium-sensitizing agent with inodilator properties.
  - In a retrospective study of 19 children with low cardiac output postcardiopulmonary bypass, levosimendan demonstrates trends toward improved hemodynamics with heart rate reduction, increase in mean arterial blood pressure, improvement of systolic and diastolic function, reduction in lactate, and reduced conventional inotropic requirement [81].
  - In another single-center retrospective study of 15 children, levosimendan did not increase myocardial oxygen consumption and resulted in improvement in myocardial performance in children with end-stage or acute heart failure who are dependent on intravenous inotropic support [82]. Levosimendan is not approved in the United States, and further investigations specific to the pediatric population are needed prior to any recommendations for its use [83].

47.13.6 Anticoagulation

Intracardiac thrombus and embolic events are a complication of heart failure in children. The protective effect of anticoagulation to prevent thromboembolic events is unclear with ongoing studies aimed at determining optimal therapy [84]. Risk factors to consider include severe left ventricular dysfunction and dilation, history of thromboembolism, and atrial fibrillation.

47.14 Nutrition

Growth failure is common in infants and children with significant heart failure due to increased metabolic demands. Infants suffering from heart failure require a higher caloric intake, about 140–160 kcal/kg of body weight, to ensure adequate weight gain [85]. In order to avoid volume overload, the concentration of the formula is increased (20–24 kcal/30 ml) providing no osmotic diarrhea occurs.

If the child is too sick to eat by mouth, gavage feeding should be instituted. In infants with severe heart failure or ductus arteriosus-dependent circulation, enteric feeding should be carefully monitored as mesenteric ischemia can lead to necrotizing enterocolitis. In this situation, parenteral nutrition is an alternative.

47.15 Outcomes

The outcome of pediatric heart failure depends on the underlying diagnosis and the availability of appropriate medical and surgical treatment. Dilated cardiomyopathy is the most common form of heart muscle disease in children. The survival rate for this disease in children is highly variable, but larger registry-based studies suggest a 40% incidence of death or heart transplantation within 2 years of the diagnosis [86]. Myocarditis has generally had a better prognosis than idiopathic dilated cardiomyopathy even if mechanical circulatory support is necessary. Fifty to eighty percent of patients with viral myocarditis have been reported to have complete resolution of their cardiomyopathy within 2 years of their diagnosis [87].

Children with failed palliation of congenital heart defects present another group of patients that require management for heart failure. Systemic right ventricular failure, single

ventricle failure, or postcardiopulmonary bypass failure all present unique management challenges in the cardiac intensive care unit. New modalities of therapy have improved outcomes and survival in pediatric patients with heart failure. Mechanical circulatory support and heart transplantation are viable options in patients with end-stage heart disease or complex cardiac defects. These subjects are discussed in detail elsewhere in this text and therefore will not be addressed here but nevertheless are important and vital adjuncts when medical therapy fails.

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Chapter 48
Shock in the Cardiac Patient

Carly Scahill and Robert Bishop

Abstract Shock is defined as an imbalance between oxygen delivery (DO2) and oxygen consumption (VO2). Oxygen demand greater than oxygen delivery leads to a severe decrease in tissue oxygenation, nutrient delivery, and eventually cell death. Shock can damage all tissues and quickly progress to multiorgan failure. This is why early identification and treatment of shock is critical to prevent irreversible cell death. This chapter provides an overview of the diagnosis and management of this complex entity.

48.1 Definition of Shock

Shock is defined as an imbalance between oxygen delivery (DO2) and oxygen consumption (VO2). Oxygen demand greater than oxygen delivery leads to a severe decrease in tissue oxygenation, nutrient delivery, and eventually cell death. Shock can damage all tissues and quickly progress to multiorgan failure. This is why early identification and treatment of shock is critical to prevent irreversible cell death.

48.2 Pathophysiology

The initial consequence of the imbalance between DO2 and VO2 is that cells can no longer sustain aerobic metabolism, and compensatory mechanisms must be activated in order to prevent cellular necrosis. In order to understand the pathophysiology of shock one must first understand what elements control DO2.

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48.2.1 Oxygen Delivery (DO2)

Oxygen delivery is the product of cardiac output (CO) and arterial oxygen content (CaO2). CaO2 is determined by hemoglobin concentration, arterial oxygen saturation, and the partial pressure of oxygen in arterial blood.

$$\mathrm{CaO2} = \left(\mathrm{Hgb} \times \mathrm{SaO2} \times 1.36\right) + \left(\mathrm{paO2} \times 0.0031\right)$$

- Where 1.36 mL is the amount of oxygen bound to 1 gram of Hgb and 0.0031 represents the amount of oxygen dissolved in plasma.

Cardiac output is the product of heart rate (HR) and stroke volume (SV). Where stroke volume is dependent on preload, afterload, and contractility

$$\mathrm{CO} = \mathrm{HR} \times \mathrm{SV}$$

48.2.1.1 Preload

Preload is the amount of blood that returns back to the heart. It is synonymous with the end-diastolic volume in the ventricles. The amount of preload is influenced by the difference between mean systemic pressure and right atrial pressure. Intravascular volume and vascular capacitance determine mean systemic pressure. Ventricular compliance and intrathoracic pressure determine right atrial pressure. Therefore, preload is dependent on intravascular volume, vascular capacitance, ventricular compliance, and intrathoracic pressure. According to the principles of Frank-Starling, as preload increase cardiac output increases. This is due to not only the increase in volume but also an increase in the force of contraction as a result of the length-tension relationship.

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48.2.1.2 Afterload

Afterload is the sum of resistances against which the ventricle must pump in order to eject blood to the systemic circulation. It can be thought of as the tension or wall stress on the individual ventricular muscle fibers. Factors effecting afterload include systemic vascular resistance, arterial stiffness, and aortic valve stenosis. Additionally, ventricular volume and ventricular thickness impact afterload. According to the law of Laplace, the tension on the muscle fibers in the ventricle, and hence afterload, is directly proportional to the pressure within in the ventricle multiplied by the radius of the ventricle, or the volume in the ventricle, divided by the ventricular wall thickness. Therefore, the greater the ventricular volume, the higher the afterload. Whereas the thicker the ventricular wall, the less tension experienced by each sarcomere unit. An increase in afterload leads to a decrease in cardiac output. This is partially due to the force–velocity relationship. The greater the afterload, the slower the velocity of cardiac muscle fiber shortening. Fiber shortening time is limited so if shortening velocity is decreased than volume ejected from the ventricle is decreased. With ventricular dysfunction, cardiac output is even more susceptible to changes in afterload.

48.2.1.3 Contractility

Contractility is the intrinsic capacity of the myocytes to contract and generate force. It is affected by multiple mechanisms. The sympathetic nervous system, parasympathetic nervous system, and circulating catecholamines play a large role in inotropy. Preload, via the Frank- Starling mechanism, influences contractility. As sarcomere length increases, with increasing preload, contractile force increases. Heart rate influences contractility via the Bowditch effect. An increase in heart rate causes an accumulation of intracellular calcium which is then available for release during the next contraction producing an increase in contractile force. A sudden increase in afterload brings about an increase in contractility. This is called the Anrep effect. The intrinsic increase in inotropy with an acute increase in afterload is an autoregulation mechanism to partially compensate for the increase in ventricular end systolic volume and decrease in stroke volume with an increase in afterload. Contractility can also be affected by exogenous inotropic agents, pharmacologic cardiac depressants, cardiomyopathy, ischemia, and arrhythmias. Most of the above mechanisms ultimately lead to an increase in inotropy through calcium. This is either through increasing release of calcium from the sarcoplasmic reticulum, increasing calcium influx during the action potential or an increase in troponin C sensitivity for calcium (Fig. 48.1).

48.2.2 Decrease in Oxygen Delivery

Circulatory function depends on complex interactions between the heart, central and peripheral circulation, and the neurohormonal axis. All of these components constantly change in order to adapt to tissue oxygen demands. The outcome of these interactions is an adequate tissue perfusion and oxygen delivery. When oxygen delivery decreases, the body utilizes autoregulatory mechanisms to facilitate the balance between oxygen delivery and oxygen demand.

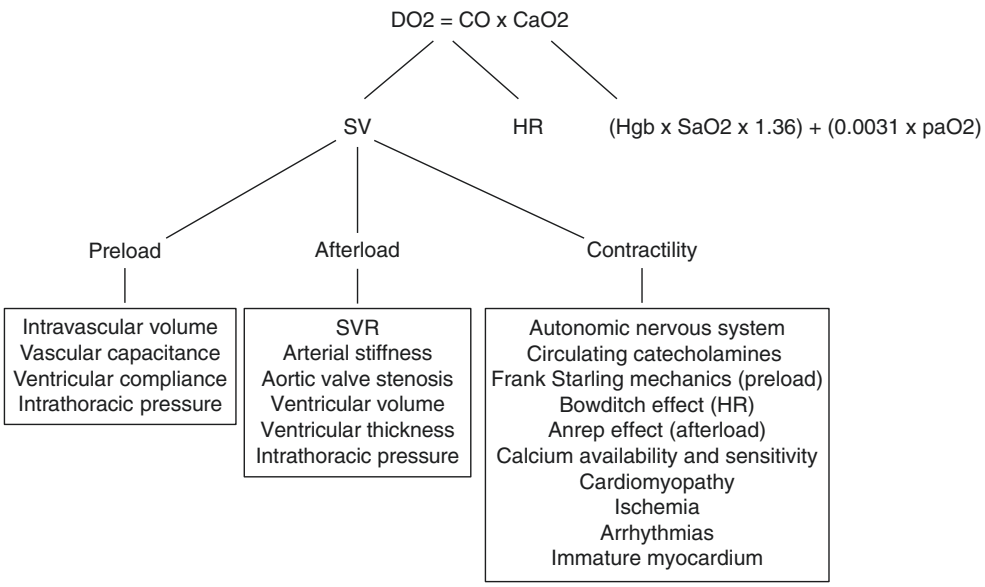
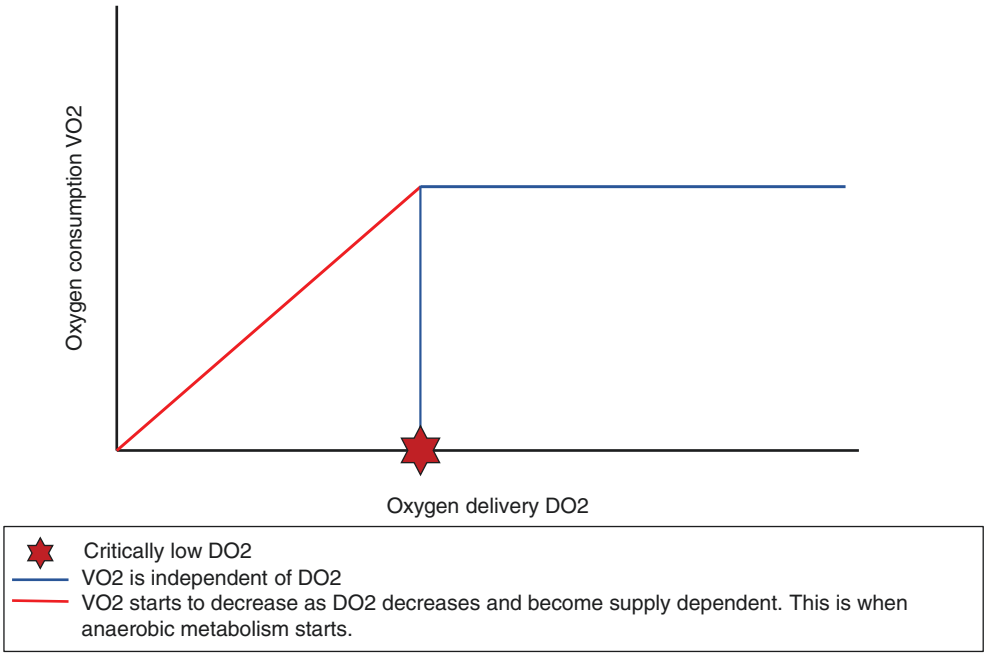


Fig. 48.1 Oxygen delivery

Fig. 48.2 Critically low DO_2



When CaO_2 is reduced, there is a compensatory increase in CO. If the compensatory increase in CO does not fully make up for the decrease in CaO_2 then oxygen extraction increases. Oxygen extraction continues to increase until a critically low DO_2 is reached. If the DO_2 is low enough, then the increase in oxygen extraction will not be enough to meet oxygen demands. It is at this point that VO_2 begins to fall and anaerobic metabolism starts (Fig. 48.2). This is the start of the state of shock; when the critical DO_2 and oxygen extraction is reached. The critical DO_2 can change and is directly related to oxygen demand; however, the critical oxygen extraction does not change.

When CO decreases, the body has compensatory mechanisms to attempt to preserve oxygen delivery to vital organs. The vascular resistance of the less vital organs, such as the dermis and mesentery, increases allowing cardiac output to be reallocated to more vital organs such as the brain and heart. Additionally, each organ is capable of extracting a greater amount of oxygen. When perfusion to an organ decreases, previously closed capillaries are opened. This opening of additional capillaries increases the capillary surface area and hence increases the area for gas exchange.

48.2.3 Factors that Influence Oxygen Delivery and Oxygen Demand

As stated above, there are many factors that can influence CO and SVR. These include ventricular systolic and diastolic function, arrhythmias, release of local vasodilators (e.g., adenosine), release of endothelial vasodilators or vasoconstrictors (e.g., EDRF-NO and EDCF), smooth muscle activity, autonomic nervous system balance, baroreceptors and central vasomotor control, catecholamine stress response, renin-angiotensin-aldosterone system, vasopressin levels, and level of endogenous vasodilators.

Adequate transport of oxygen and elimination of metabolic waste is also reliant on adequate ventilation, adequate oxygen transport by normal hemoglobin, and adequate oxygen extraction and consumption. For example, hemoglobin's ability to transport oxygen may be altered by high levels of methemoglobin. Additionally, adequate oxygen extraction may be altered by carbon monoxide or shifts in the hemoglobin oxygen dissociation curve.

48.2.4 Hemoglobin Oxygen Dissociation Curve

Oxygen saturation is the percentage of hemoglobin (Hgb) that is bound to oxygen. The amount of O_2 bound to Hgb is related to the partial pressure of oxygen for which the Hgb is exposed. Hgb in the lungs is exposed to a high partial pressure of O_2 so O_2 binds readily to Hgb. However, as blood leaves the lungs and circulates to other body tissue and organs, the partial pressure of O_2 is low, so O_2 is released from Hgb into the tissue. The hemoglobin oxygen dissociation curve illustrates Hgb's affinity for oxygen at any given partial pressure of O_2 (Fig. 48.3).

Certain conditions will shift the hemoglobin oxygen dissociation curve right or left. Physiologic states where tissues

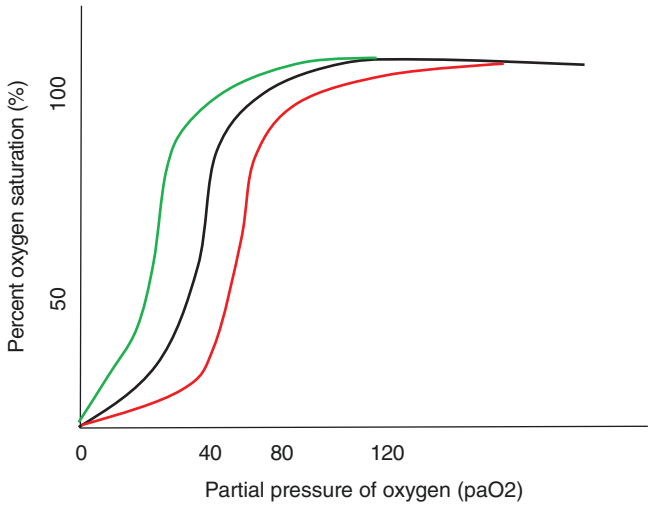


Fig. 48.3 The hemoglobin oxygen dissociation curve

need more O_2 shift the curve to the right and represent a lower affinity of O_2 to be bound to Hgb. These include the following:

- Decrease in pH
- Increase in pCO_2
- Increase in 2,3 DPG
- Increase in temperature
- Increase in H+

Conditions which shift the curve to the left represent a high affinity of O_2 for Hgb. These include:

- Increase in pH
- Decrease in pCO2
- Decrease in 2,3 DPG
- Decrease in temperature
- Decrease in H+
- Methemoglobin
- Fetal hemoglobin

48.2.5 Effects of Cardiopulmonary Interactions on Oxygen Delivery and Demand

Mechanical ventilation aids in the balance between oxygen delivery and oxygen demand by decreasing oxygen demand. Ordinarily, the diaphragm muscle does not require a large portion of the total cardiac output and generally utilizes less than 5% of the overall VO2. In a state of shock, respiratory effort increases to compensate for the metabolic acidosis. With the increase in respiratory effort, the diaphragm may utilize up to 50% of the overall VO2, redistributing a large portion of the CO to the respiratory muscles at the sacrifice of other vital organs. Mechanical ventilation reduces the respiratory effort, and the limited CO can be used by other organs.

Ventilation, both spontaneous and mechanical, impacts cardiac output by altering preload and afterload. Right heart preload is determined by the pressure gradient between mean systemic pressure and right atrial pressure. The right atrial pressure is affected by intrathoracic pressure. During spontaneous inspiration, negative intrathoracic pressure is generated. This leads to an increase in right atrial transmural pressure, the atrium distends, right atrial pressure decreases, and preload increases. Additionally, with inspiration, the diaphragm moves down, increasing intra-abdominal pressure. The increase in intra-abdominal pressure causes an increase in pressure in the intra-abdominal vessels. The increased pressure gradient between the inferior vena cava and the right atrium leads to an increase in venous return. On the other hand, mechanical ventilation generates positive intrathoracic pressure. This leads to a decrease in right atrial transmural pressure, an increase in right atrial pressure, and a decrease in venous return.

Ventilation alters left heart preload though its effects on right ventricular preload, afterload and ventricular interdependence. During spontaneous inspiration, right-sided venous return increases, and hence, right ventricular filling increases. With increased right ventricular volume, the RV septal wall imposes on the LV cavity decreasing LV compliance and decreasing left-sided venous return. If ventilation strategies increase RV afterload (described below), then not only does this decrease pulmonary venous return, but the increased RV afterload increases RV diastolic pressure which, similar to above, alters the RV septal wall. The septum bows into the LV, decreasing LV compliance and left-sided venous return. This is exacerbated by the fact that decreased LV volume reduces the LV systolic pressure, reducing the LV systolic contribution on RV ejection and leading to a continued increase in RV volume.

Ventilation effects RV afterload by altering pulmonary vasoconstriction and vasodilation. Respiratory acidosis and alveolar hypoxia lead to vasoconstriction and thus an increase in RV afterload. Additionally, pulmonary vascular resistance is elevated when lung volume is below or above functional residual capacity. LV afterload is decreased with positive pressure ventilation. This can be explained by the Laplace law. Mechanical ventilation generates positive intrathoracic pressure. This positive intrathoracic pressure causes a decrease in intrathoracic aortic transmural pressure. This results in decreased compliance, decreased volume, and increased pressure relative to the extrathoracic arterial vessels. This creates a driving pressure from the intrathoracic aorta to the extrathoracic arterial vessels and hence a decrease in afterload. With LV systolic dysfunction,

the effects of positive intrathoracic pressure on LV afterload usually outweigh the decrease in RV preload, whereas during diastolic dysfunction, the changes in preload can significantly alter cardiac output.

48.2.6 Factors Unique to the Neonatal Patient

Neonatal myocardium is not fully developed. There is cellular and structural disorganization. Compared to mature myocardium, there is also a higher proportion of noncontractile elements to contractile tissue. This all leads to a heart that generates less contractile force and is less compliant. While neonatal myocardium does respond to increases in volume, the increase in cardiac output seen with increasing ventricular volume is much less than that of mature myocardium. Additionally, the ability of neonatal myocardium to increase contractility in response to inotropic agents is reduced compared to older patients. Neonates have a limited ability to increase cardiac output by increasing stroke volume and are very depended on increases in heart rate to augment cardiac output. The neonatal heart also has immature t-tubules and sarcoplasmic reticulum making myocyte contraction highly dependent on extracellular calcium.

48.3 The Five Different Types of Shock

Diagnosis of shock involves the clinical recognition of signs and symptoms. These may be nonspecific and appear late in presentation making the identification of shock difficult. This is particularly true in small infants and patients whose circulatory failure is partially compensated. Below are the five different types of shock that can occur (Table 48.1). It is important to recognize that different types of shock may coexist in the same patient. It is also crucial to keep in mind that a cardiac patient in shock is not necessarily in cardiogenic shock.

48.3.1 Hypovolemic Shock

Hypovolemic shock is secondary to a lack of intravascular volume. This is the most common cause of shock in pediatrics. Rapid reduction in intravascular volume causes an abrupt decrease in preload and therefore stroke volume and cardiac output. When hypovolemic shock is caused by hemorrhage, in addition to the decrease in cardiac output, CaO2 is also decreased, and hemoglobin transport is affected. Patients who have significant capillary leak, such as those subjected to the inflammatory effects of cardiopulmonary bypass, can be relatively hypovolemic. Despite appearing total body fluid positive, their intravascular space may be substantially depleted.

48.3.2 Cardiogenic Shock

Cardiogenic shock is a state of inadequate tissue oxygen delivery due to a primary cardiac dysfunction or failure. This can occur with anything that causes cardiac dysfunction such as cardiac infarct or ischemia, cardiomyopathy, significant valve regurgitation, arrhythmias, and ductal-dependent congenital heart disease with ductal constriction. This can also be seen postoperatively and manifest as low cardiac output syndrome.

48.3.3 Obstructive (Extracardiac) Shock

Obstructive shock is due to obstructions that produce either a massive increase in afterload or a decrease in preload. An increase in afterload may occur with anatomic anomalies, such as left-sided obstructive lesions like coarctation of the aorta or interrupted aortic arch. It can also be due to functional anomalies such as systemic hypertension or pulmonary hypertension. A decrease in preload is due to situations that affect cardiac filling like cardiac tamponade, tension pneumothorax, or abdominal compartment syndrome.

Table 48.1 Types of shock

Hypovolemic	Cardiogenic	Obstructive	Distributive	Dissociative
Inadequate volume	Ventricular dysfunction	Tamponade	Sepsis	Severe anemia
Hemorrhage	Infarct/Ischemia	Constrictive pericarditis	Toxic	Methemoglobin
Dehydration	Dilated cardiomyopathy	Tension pneumothorax	Anaphylactic	Carbon monoxide toxicity
	myocarditis	Severe systemic hypertension	Neurogenic	Anything that decreases capacity to deliver O2
	Valve regurgitation	Pulmonary hypertension	Inflammatory	
	Arrhythmia	Abdominal compartment syndrome	Vascular bed anomaly	
	Low cardiac output syndrome	Anatomic anomalies		
	Ductal-dependent congenital heart disease with ductal constriction			

48.3.4 Distributive (Vasoplegic) Shock

Distributive shock is due to a severely decreased vascular tone. These patients may have normal or even hyperdynamic cardiac function, but the decrease in vascular tone causes a relative hypovolemia. Preload is significantly decreased because of the increased vascular capacitance. This can be caused by conditions such as sepsis, anaphylaxis, systemic inflammatory disorders and spinal cord injuries. Despite the relative hypovolemia, these patients often do not adequately respond to volume administration alone.

48.3.5 Dissociative Shock

Dissociative shock is due to an abnormality in oxygen transport or oxygen extraction. This can be caused by severe anemia, methemoglobinemia, and carbon monoxide intoxication.

48.4 Diagnosis

48.4.1 Clinical History

A good clinical history is helpful in differentiating what type of shock a patient is in. A history of increased volume losses, such as diarrhea, vomiting, bleeding, or trauma, may suggest the diagnosis of hypovolemic shock. A patient who presents with fever or a history of being immunocompromised may point toward septic shock. If a neonate presents with a history of tachypnea, poor growth, and feeding difficulties, this might indicate cardiogenic shock.

48.4.2 Clinical Examination

A good clinical exam is just as paramount as a good history. Signs of shock are wide ranging and may not always be specific. They can include things such as hypothermia, hyperthermia, alterations in the heart rate, altered mental status, lethargy, peripheral vasodilation or vasoconstriction, hypotension, murmur, or hepatomegaly.

48.4.3 Warm Shock Verses Cold Shock

Based on clinical examination, this condition is divided into warm shock and cold shock. Differentiating between these two stages of shock can help guide treatment. As shock progresses, the microcirculation tends to promote perfusion of target organs by inducing peripheral vasoconstriction. This helps to maintain blood flow to vital organs in states of low cardiac output. Additionally, the body's compensatory response to a decrease in stroke volume and contractility is to increase systemic vascular resistance. It is important to keep in mind that perfusion pressure is equal to mean arterial pressure minus central venous pressure. There are however some exceptions to this situation. Patients in septic, anaphylactic, or inflammatory shock may initially present with significant vasoplegia.

48.4.3.1 Cold Shock

Cold shock represents a state of vasoconstriction. This occurs generally during the early stages of shock. Due to the compensatory mechanism of increased SVR, these patients can have normal blood pressure. Clinically, they present with decreased or weak pulses, cool mottled skin, delayed capillary refill (>3 seconds), narrow pulse pressure, and a relatively increased diastolic blood pressure.

48.4.3.2 Warm Shock

Warm shock represents a state of vasodilation. Clinically, these patients present with bounding pulses, flushed ruddy skin, and flash cap refill (<1 second) and are often hypotensive.

48.4.4 Blood Pressure

As stated above, not all patients in shock are hypotensive. Blood pressure may be within the adequate range for the patient's age if they are in early shock when compensatory mechanisms are still able to compensate. Cardiac output is proportional to perfusion pressure and inversely proportional to systemic vascular resistance. While, as stated above, vital organs autoregulate to maintain local perfusion in states of generalized low flow, there is a critically low perfusion pressure in which autoregulation can no longer compensate. As a general rule, the following formula can be used to guide goal mean arterial pressure

$$\begin{aligned}\text{Threshold perfusion pressure} &= (\text{MAP} - \text{CVP}) \\ &= 55 + (\text{age} \times 1.5)\end{aligned}$$

48.4.5 Heart Rate

Tachycardia is a common sign of shock. This is particularly true in neonates whose main compensatory mechanism to increase cardiac output is increasing heart rate. In some circumstances, this physiologic response may be blunted by autonomic or pharmacologic influence, but in general, patients in shock tend to be tachycardic whether they are in warm or cold shock. Heart rate < 90 b/min or > 160 b/min in critically ill infants and < 70 b/min or > 150 b/min in critically ill children is associated with greater mortality. Refer to the most recent Pediatric Advanced Life Support Guidelines for normal vital signs by age.

48.4.6 Additional Clinical Exam Findings

In addition to blood pressure, heart rate and neurologic status, examining skin perfusion and color can be valuable. Skin perfusion will aid in the differentiation between cold and warm shock. Other nonspecific markers that may be affected during states of shock are abnormalities in temperature including not only hyperthermia and hypothermia but also an increase in central to peripheral temperature gradient. A normal central to peripheral temperature gradient is <3 degrees Celsius. Urine output may also decrease during states of shock. Normal urine output is >1 ml/kg/hr.

48.4.7 Diagnostic and Monitoring Tests and Devices

While a good history and clinical exam are of utmost importance, they do not stand alone in the diagnosis and monitoring of shock. In fact, *Ranjit* et al. reported in an observational study that up to 66% of children deemed to be in cold shock by seasoned physicians were actually noted to be vasodilated by invasive monitoring. Below are test and devices that are beneficial in both diagnosis of shock and monitoring for response to treatment.

48.4.7.1 Blood Gases (Arterial and Venous)

Arterial blood gas can be used to monitor acid–base status. Usually, patients in shock have metabolic acidosis. In addition, blood gases can be used to monitor the arterial to venous carbon dioxide gradient, arterial to venous oxygen gradient, arterial to alveolar oxygen gradient, and abnormalities in ventilation.

48.4.7.2 Serum Lactate

Patients in shock will eventually develop hyperlactatemia or lactic acidosis. Once a critically low DO2 is reached and oxygen extraction has been maximized, anaerobic glycolysis starts. Lactate is a byproduct of anaerobic metabolism and therefore is an indication of inadequate oxygen delivery and tissue hypoxia. A normal lactate level is <2 mmol/L. Elevated lactate levels have been shown to be associated with increased morbidity and mortality. Trending lactate level is of importance, especially when monitoring for physiologic improvement to treatment. It is important to keep in mind however that lactate concentrations may increase due to mechanism other than inadequate oxygen delivery and anaerobic metabolism. Lactate can accumulate due to lack of elimination, usually as a result of liver dysfunction. Lactate can also be elevated in the setting of type B hyperlactatemia such as inflammation induced enhanced glycolysis, catecholamine excess, or hyperglycemic ketoacidosis.

48.4.7.3 Oxygen Extraction Ratio

The oxygen extraction ratio is oxygen consumption divided by oxygen delivery.

$$\mathrm{OER} = \mathrm{VO2} / \mathrm{DO2}$$

As highlighted in the pathophysiology section, oxygen delivery is equal to cardiac output multiplied by oxygen content.

$$\mathrm{DO2} = \mathrm{CO}\left(\mathrm{CaO2}\right)$$

According to the Fick equation, cardiac output equals oxygen consumption divided by the arteriovenous oxygen content difference.

$$\mathrm{CO} = \mathrm{VO2} / \left(\mathrm{CaO2} - \mathrm{CvO2}\right)$$

By rearranging this equation, then

$$\mathrm{VO2} = \mathrm{CO}\left(\mathrm{CaO2} - \mathrm{CvO2}\right)$$
$$\text{Since}\,\mathrm{OER} = \mathrm{VO2} / \mathrm{DO2}$$
$$\mathrm{OER} = \mathrm{CO}\left(\mathrm{CaO2} - \mathrm{CvO2}\right) / \mathrm{CO}\left(\mathrm{CaO2}\right)$$

canceling everything out and ignoring dissolved oxygen, the following equation that can be easily calculated in a clinical setting:

$$\mathrm{OER} = \left(\mathrm{SaO2} - \mathrm{SvO2}\right) / \mathrm{SaO2}$$

A normal OER is 25%. OER is considered elevated between 30 and 50%, impending shock between 50 and 60% and shock if >60%.

48.4.7.4 SvO2 or Mixed Venous Saturation

As stated herein, when O2 delivery decreases, O2 extraction increases. This is why SvO2 (or mixed venous saturation) can be used as a sign of inadequate oxygen delivery. If O2 extraction increases, then SvO2 will decrease. One must compare arterial saturation to venous saturation to interpret these results. A normal arteriovenous O2 gradient is <25%. A low SvO2 represents a state of high O2 extraction in order to compensate for low O2 delivery. De Oliveira et al. demonstrated in a randomized controlled trial of pediatric patients with septic shock that treatment directed at maintaining a SvO2 > 70% rather than treatment directed at blood pressure and capillary refill alone decreased mortality from 39% to 12% with a number needed to treat of only 3.6. In order to obtain a SvO2 value, the patient must have a central venous catheter (CVP). Correct interpretation requires a valid blood sample free from intracardiac mixing or streaming of blood. In a heart with no intracardiac shunting, the most accurate mixed venous saturation is sampled from the main pulmonary artery. Multiple studies have shown that a SvcO2, drawn off a CVP line at the superior vena cava/right atrial junction, is not significantly different from a sample drawn from the main pulmonary artery. A SvcO2 also has the added benefit of being a good reflection of mixed venous saturation in patients with intracardiac shunting as it is sampled just prior to entering the heart. One must be careful with interpreting a mixed venous saturation that comes directly from the right atrium as there can be falsely low values from streaming of deoxygenated blood from the coronary sinus or falsely elevated values from a left to right shunt at the atrial septum. It is important to be aware that in some situations, there can be a normal or high SvO2 even during states of shock. This can occur due to impairment of oxygen extraction from inappropriate distribution of flow in the microcirculation and capillary shunting during distributive or vasoplegic shock or from mitochondrial damage. In this situation, other markers of adequate tissue oxygen delivery need to be utilized.

48.4.7.5 Venous to Arterial Carbon Dioxide Tension (pvCO2–paCO2)

According to the Fick equation VCO2 or CO_2 production is equal to cardiac output multiplied by the arteriovenous CO_2 content difference: VCO2 = CO(CvCO2–CaCO2).

The relationship between pCO2 and CO_2 content is curvilinear but much more linear than the oxygen dissociation curve, so pvCO2 and paCO2 can be substituted for CvCO2 and CaCO2. Therefore, VCO2 = CO(pvCO2–paCO2) where (pvCO2–paCO2) is the venous to arterial CO_2 tension. Rearranging the equation (pvCO2–paCO2) = VCO2/CO. Thus, venous to arterial CO_2 tension (or v-a CO_2 tension) is proportional to CO_2 production and inversely proportional to cardiac output. A normal v-a CO_2 tension is between 2 and 6 mmHg. During states of shock and tissue hypoxia, there is an increased production of H+ ions. These H+ ions will be buffered by bicarbonate which in turn will produce CO_2 and H20. The increased production of CO_2 will cause an increase in v-a CO_2 tension unless cardiac output increases proportionally. The increased cardiac output will lead to increased CO_2 clearance. Therefore, v-a CO_2 tension is a better marker of cardiac output rather than tissue hypoxia. In states of low cardiac output, even if CO_2 production is not increased, the v-a CO_2 tension will increase. This is due to lack of CO_2 clearance and buildup in tissues and venous blood. Vallee et al. showed that even in patients with normal SvO2, those with lactate >2 mmol/L had a v-a CO_2 tension >6 mmHg. Ospina et al. reported, in a population of septic shock patients, that those with persistently high v-a CO_2 tension (defined as >6 mmHg) had an increased risk of mortality (relative risk 2.33, $p = 0.01$). When v-a CO_2 tension is elevated, even in the setting of a normal or elevated SvO2, one should consider impaired perfusion and focus treatment on improving cardiac output. On the other hand, if v-a CO_2 tension is normal (< 6 mmHg) and tissue hypoxia is present, treatment focused on increasing cardiac output may not be the best first-line remedy.

48.4.7.6 Central Venous Pressure Monitoring (CVP)

CVP monitoring can be used as a marker of intravascular volume and hence preload. However, it is important to remember that changes in intrathoracic pressure can alter CVP measurements. Additionally, anything that causes right-sided obstructive disease or right ventricular diastolic dysfunction can present with an elevated CVP even in the setting of volume depletion. If little change in CVP is seen after a fluid bolus is given, this indicates that the venous capacitance system is underfilled. This patient may benefit from additional fluid administration. In contrast, if CVP increases after a fluid bolus at the expense of a decrease in perfusion pressure (MAP-CVP), this indicates that too much fluid has been given.

48.4.7.7 Chest X-Ray

Chest X-ray may be useful in assessing the cardiac silhouette for cardiomegaly, lung fields for pulmonary edema, infection or other respiratory anomalies.

48.4.7.8 Electrocardiogram

An EKG is very nonspecific but may be useful to rule out arrhythmias or conductive disorders as the source of shock. You may also see low voltage in the setting of myocarditis.

48.4.7.9 Bacterial Cultures and Serum Inflammatory Markers

Blood, urine, respiratory, and cerebral spinal fluid cultures can all be considered when evaluating for the source of septic shock. Additionally, complete blood count with differential (CBCd), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and procalcitonin (PCT) levels can all aid in the diagnosis and treatment of septic shock.

48.4.7.10 Echocardiography

Echocardiography is important in the diagnosis of cardiogenic shock and ductal-dependent congenital heart disease. Regardless of the etiology of shock having an understanding of cardiac function will help guide medical therapy and efficacy of treatment.

48.4.7.11 Cardiac Catheterization, Cardiac CT Angiography, and Cardiac MRI

If invasive monitoring, labs, and echocardiography do not provide a clear etiology for the patients shock, then the above test may be helpful. For example, MRI may be useful in the diagnosis of myocarditis, CT angiography may be useful in the diagnosis of extracardiac obstructive lesions, and cardiac catheterization may be useful in the diagnosis of pulmonary hypertension.

48.4.7.12 Near-Infrared Spectroscopy (NIRS)

NIRS is a noninvasive, harmless way to monitor regional tissue oxygenation. The optical properties of Hgb change when bound to O2. The dominant absorbers of the near-infrared electromagnetic spectrum are oxygenated Hgb, deoxygenated Hgb, and H_2O. This allows light to penetrate several centimeters through tissue, including the skull, before it is detected. The spectra of oxygenated and deoxygenated Hgb are different enough that spectroscopy can detect separate concentrations of each molecule. This technology provides us information about regional oxygen saturations. It is often used to monitor brain, renal, and mesenteric oxygen saturations. Since factors such as myoglobin, skin pigmentation, and peripheral edema can influence results, it is most helpful to follow the trend in NIRS rather than a specific number.

48.4.7.13 Continuous Cardiac Output Devices

Swan–Ganz catheters measure right-sided heart pressures and pulmonary capillary wedge pressure. It can be used to measure continuous SvO2 and estimate cardiac index through thermodilution techniques. With the principles of Fick, these parameters can be used to estimate systemic vascular resistance and pulmonary vascular resistance. PiCCO, through pulse contour analysis and thermodilution, can estimate cardiac index, stroke volume, systemic vascular resistance, and ventricular end-diastolic volume. Flo-Trac displays continuous cardiac output and SvO2 by sampling multiple pressure points along the arterial pressure curve.

48.5 Management of Shock

Management of shock in the pediatric patient shares common aspects regardless of the etiology and must be initiated immediately. No workup or imaging studies should delay medical measures to stabilize the patient. The first goal in management of shock is to preserve life. The second goal is to preserve multiorgan function.

There are three lines of management:

1. Resuscitation following the "A-B-C" principles (nowadays seen rather as "C-A-B," following the order of priorities where circulation is by far the most important)
2. Multiorgan support
3. Specific therapy directed by etiology and clinical presentation

48.5.1 Airway/Breathing

Patency of a patient's airway, adequate oxygenation, and adequate gas exchange must be ensured. If the patient has respiratory distress, clinicians should consider intubation and mechanical ventilation sooner rather than later. Recall from the physiology section above, mechanical ventilation reduces respiratory effort and the VO2 utilized by the respiratory muscles, allowing the limited CO to be used by other organs. It is important however to keep in mind that induction of

anesthesia or sedation in patients with limited cardiac output is not without risk. Rapid sequence intubation drugs, strategy and rescue therapy should be carefully thought out prior to induction and based on patient's presentation. For example, etomidate should be avoided if there is concern for infection or adrenocortical dysfunction.

48.5.2 Circulation/Vascular Access

The most important step should be to ensure that the effective circulating volume is optimized. In order for this to occur, the patient must first have appropriate vascular access. Patients who stay relatively stable may be managed with peripheral lines at the beginning while monitoring for rapid improvement. Patients who present critically ill, or in whom peripheral access is difficult to obtain, should have an indwelling central line inserted as soon as possible. If this is not able to be accomplished in a timely fashion, intraosseous lines are a good palliation until further stabilization allows for the insertion of central venous lines. An arterial line should also be strongly considered. This will allow for continuous blood pressure monitoring and the ability to obtain serial blood gases.

48.5.3 Circulation/Administration of Volume Expanders

Patients who receive aggressive and early fluid resuscitation have the best chance of surviving severe septic or hypovolemic shock. The type of fluid to give should be based on each individual patient. Types of fluid include blood, fresh frozen plasma, platelets, isotonic crystalloid, or colloid solution. The American College of Critical Care Medicine, in the most recent septic shock guidelines, recommends administration of up to 60 ml/kg of fluid in 20 ml/kg bolus in as little as 10-minutes. It is important to assess for hepatomegaly, rales or crackles after each bolus. One needs to be very cautious with volume resuscitation in patients with cardiogenic shock. Volume administration, particularly at fast infusion rates, can result in worsening decompensation in this patient population. Since the type of shock is not always known immediately at presentation, this highlights the importance of physical exam and monitoring for response to treatment. If a patient does not improve or worsens in spite of adequate and aggressive volume administration they should have a cardiovascular workup to evaluate cardiac function. In fluid refractory shock, additional pharmacologic treatment must be initiated.

48.5.4 Circulation/Inotropic Agents, Vasodilators, or Vasopressors

The choice of drugs to use depends on the suspected etiology of shock. All inotropic and vasocoactive agents should be carefully used, taking into account their potential for adverse effects, including increased myocardial oxygen consumption and arrhythmias.

48.6 Pharmacologic Treatment of Shock

48.6.1 Adrenergic Receptors

In order to understand the mechanism of action of the inotropic/vasoactive drugs one must first understand the function of the different types of adrenergic receptors.

Alpha 1: Receptors are located on vascular smooth muscle including skin, pulmonary, and coronary circulation. Activation of alpha 1 leads to vasoconstriction.

Beta 1: Receptors are located on the myocardium and activation leads to increased contractility. Receptors are also located on the sinus node leading to increase in heart rate and the AV node leading to increase in conduction velocity.

Beta 2: Receptors are located on vascular smooth muscle, mesenteric, splanchnic, skeletal muscle, and bronchial smooth muscle. Activation causes vasodilation.

Dopamine 1: Receptors are located on renal vasculature and coronary circulation. Activation leads to vasodilation.

Dopamine 2: Receptors are located on mesenteric and splanchnic vasculature, and activation causes vasodilation.

48.6.2 Drugs

48.6.2.1 Dopamine

Dopamine works on the dopaminergic, beta 1 and alpha 1 receptors. At low doses, between 2 and 5 mcg/kg/minute, it mostly works on the dopamine receptors promoting renal, splanchnic, and coronary perfusion. However, the use of "renal dose" dopamine to improve renal function remains unproven. At moderate doses, between 5 and 10 mcg/kg/minute, it largely has beta 1 effects improving myocardial contractility, cardiac output, and enhancing conduction. At higher doses between 10 and 20 mcg/kg/minute, it primarily works on alpha 1 receptors inducing peripheral vasoconstriction. Dopamine remains the recommended first choice for

fluid refractory septic shock in neonates. In preterm infants, dopamine has been shown to be more effective than dobutamine, colloid fluid, or hydrocortisone alone at increasing mean arterial blood pressure. However, dopamine has recently come into question as the first-line treatment for shock in the non-neonatal population. A double-blinded randomized controlled trial evaluated dopamine versus epinephrine as a first-line vasoactive drug in pediatric patients with septic shock. This study concluded that dopamine was associated with increased mortality and hospital-acquired infection compared to epinephrine. As a result, in infants and children, it is recommended to use dopamine as a first-line agent in septic shock only if epinephrine or norepinephrine is not available. One theory to explain the worse outcomes is that dopamine may increase myocardial oxygen consumption out of portion to the increase in cardiac output altering the balance between oxygen consumption and oxygen delivery.

48.6.2.2 Dobutamine

Dobutamine is a primary beta-1 agonist that also offers the advantage of a beta-2-mediated vasodilatory effect in patients requiring peripheral vasodilation. In some circumstances, this drug is an appropriate choice for cardiogenic shock; however, it has fallen out of favor with the innovation of milrinone (discussed below). Therapeutic doses for dobutamine vary between 5 and 20 mcg/kg/minute.

48.6.2.3 Epinephrine

Epinephrine works on the beta 1, beta 2, and alpha 1 receptors. At doses between 0.002 and 0.008 mcg/kg/minute, it predominately works on beta 1 and beta 2 receptors increasing contractility and heart rate and promoting vasodilation, particularly in the skin and skeletal musculature. At higher doses 0.01–0.3 mcg/kg/minute, there is more alpha 1 effects producing vasoconstriction. When cardiac function is significantly depressed, regardless of the etiology, an epinephrine infusion should be promptly started. Additionally, epinephrine is recommended as the first-line agent in infants and children with fluid refractory, cold septic shock. With use of epinephrine, especially at high dose, it is important to be aware of potential side effects. Epinephrine will increase myocardial oxygen consumption, and ventricular arrhythmias may be triggered. Epinephrine can also cause hyperglycemia by increasing gluconeogenesis and hindering insulin activity. In addition to hyperglycemia, the increase in gluconeogenesis can stimulate the Cori cycle and subsequently increase serum lactate levels regardless of adequate tissue perfusion.

48.6.2.4 Norepinephrine

Norepinephrine works on alpha 1 and beta 1 receptors inducing vasoconstriction, increased contractility, and increased heart rate. Norepinephrine should be considered with fluid refractory distributive shock when a patient presents with clinical findings of warm shock. Therapeutic doses for norepinephrine vary between 0.05 and 2 mcg/kg/minute. Arrhythmias and peripheral ischemia are known side effects of norepinephrine.

48.6.2.5 Milrinone

Milrinone is a phosphodiesterase type III inhibitor. It is beneficial for patients with cardiogenic shock because it improves myocardial contractility while decreasing systemic vascular resistance, providing some degree of non-selective pulmonary vasodilation and increasing diastolic relaxation (lusitropy). The functionality of milrinone is independent of the adrenergic receptors. Milrinone blocks the breakdown of cAMP leading to an increase in intracellular cAMP which ultimately causes an increase in intracellular calcium. Since milrione does not depend on adrenergic receptors, it is effective even in states of adrenergic receptor desensitization, such as can occur with long-standing heart failure. The standard dosing is 0.25–0.75 mcg/kg/minute. For patients with primary cardiac anomalies, congenital or acquired, milrinone is the first-line inotrope. In postoperative pediatric cardiac patients, the use of milrinone has been shown to reduce the risk of low cardiac output syndrome. In children, milrinone may be loaded with a dose of 50 mcg/kg over a period of 10–15 minutes followed by a continuous maintenance dose of 0.25–0.75 mcg/kg/min. The dose must be adjusted to creatinine clearance in the case of renal impairment.

48.6.2.6 Levosimendan

Levosimendan is a newer inodilator with potent positive inotropic and systemic vasodilator activity. There are reports of having a favorable effect in reducing pulmonary vascular resistance and endothelin-1 levels and improving RV function. It acts as a calcium sensitizer by binding troponin C that exposes actin and myosin elements allowing for a more efficient contraction. In addition, it opens ATP-sensitive K-channels in vascular smooth muscles causing systemic and coronary artery vasodilation. Lastly, it opens mitochondrial ATP-sensitive K-channels in cardiomyocytes causing a cardioprotective effect. To date, it appears to have minimal

side effects and does not appear to be arrhythmogenic. One study looking at levosimendan versus milrinone, in neonates after open-heart surgery, showed no difference in cardiac output between the two groups. Additionally, there was a low arrhythmia incidence, and no hypotension necessitating discontinuation of levosimendan**.** Dosing for levosimendan in pediatric patients involves a loading dose of 12 mcg/kg over 1 hour, followed by a continuous infusion of 0.1–0.2 mcg/kg/minute for 24 hours. Levosimendan can also be administered over 48 hours without a loading dose, especially in children on other vasodilator drugs. Milrinone should be stopped during levosimendan infusion, to avoid excessive vasodilatation and hypotension.

48.6.2.7 Vasopressors

Patients with vasoplegic shock require the use of peripheral vasoconstrictors. As stated above, this can be accomplished with high-dose dopamine, high-dose epinephrine, and norepinephrine. Vasopressin induces peripheral vasoconstriction through a mechanism independent of the adrenergic receptors. It is therefore useful in patients with alpha-adrenergic receptor down regulation, which can occur with septic shock. Additionally, unlike catecholamines, vasopressin increases systemic vascular resistance without the additional beta-adrenergic stimulation and increase in myocardial oxygen demand. The dosing of vasopressin is between 0.0001–0.005 units/kg/minute. Phenylephrine is another selective peripheral vasoconstrictor. It works on the alpha 1 receptors only. Typical dosing is between 0.5 and 5 mcg/kg/minute. Vasopressors should be titrated to achieve a normal perfusion pressure. Increasing systemic vascular resistance too much can compromise cardiac output. Vasopressors may need to be used in association with inotropic agents if the cardiac function is affected.

48.6.2.8 Calcium

Calcium therapy (5–20 mg/kg/hour using 10% calcium chloride) may be useful when treating shock in patients with documented hypocalcemia. It may also be helpful in patients having required blood transfusion, and also for treating shock caused by arrhythmias precipitated by hyperkalemia, hypermagnesemia, or calcium blocker intoxication. Calcium administration is also very useful for the neonatal population. Some reports in literature have raised concerns with regard to rapid and supra-therapeutic levels of calcium and potential myocardial toxicity.

48.6.2.9 Antibiotics and Steroids

Antibiotics should be given immediately in all patients with possible septic shock. The use of corticosteroids although controversial should still be considered, particularly in patients with purpura fulminant, suspicion of Waterhouse–Friderichsen syndrome, patients who have previously received steroids, neonates, those who received etomidate for intubation induction or those with catecholamine refractory shock. Administration of hydrocortisone at 50–100 mg/m^2/day may be beneficial and lifesaving. A cortisol level may be drawn prior to the administration of the first dose, in order to decide the need to pursue steroid administration. If basal levels are less than 20 mcg/dl or a change of less than 9 mcg/dl after ACTH stimulation then relative adrenal insufficiency should be considered.

48.6.2.10 Thyroid Replacement

Serum thyroid hormone concentrations have been shown to decline transiently during critical illness and after surgical procedures. Tri-iodothyronine may be used in patients with refractory hypotension following cardiac surgery. A double-blinded randomized controlled study investigating tri-iodothyronine versus placebo in children after cardiac surgery demonstrated improved myocardial function in patients with low cardiac output syndrome. While there has been some benefit seen with this patient population, it is still unclear whether tri-iodothyronine is advantageous with other forms of shock. Tri-iodothyronine may be given at a dose of 0.1–0.4 mcg/kg/dose (up to a maximum of 20 mcg) IV every 8–12 hours.

48.6.2.11 Sodium Bicarbonate

The use of sodium bicarbonate in the treatment of shock is controversial. Patients with depressed myocardial function who develop severe acidosis may not optimally respond to catecholamines. However, studies in patients with cardiac arrest have not demonstrated improved survival rates associated with the use of bicarbonate. The use of bicarbonate has also not been shown to improve the ability to defibrillate or to enhance oxygen debt. Treatment with bicarbonate may theoretically worsen intracellular acidosis while correcting serum levels. This is due to the fact that bicarbonate combines with acid (H^+) in serum resulting in the production of carbon dioxide and water (Henderson–Hasselbach equation). Then, it readily enters

the cells and triggers the opposite reaction increasing intracellular acidosis. Treatment with bicarbonate may induce a paradoxical cerebral acidosis (for the same reason as above). Therefore, patients in shock who develop severe acidosis should be corrected with a judicious use of inotropic drugs, volume resuscitation, and optimal ventilation. Nevertheless, with patients in refractory shock, who do not respond to catecholamines, or whenever there is an ongoing bicarbonate loss, careful use of bicarbonate may be indicated.

There are two ways to estimate the amount of bicarbonate to administer:

1. Administer 0.5–2 mEq/kg/dose IV infused over 2 minutes.
2. Calculate the bicarbonate deficit based on an arterial blood gas and the formula below.

$$\text{Bicarbonate Deficit}(\text{mEq}) = 0.4 \times \text{weight}(\text{kg}) \times (24 - \text{patient's bicarb level})$$

Half of the estimated amount of bicarbonate may be administered over 20 minutes and the other half over 4 hours, if a new arterial blood gas reveals the persistent need.

48.6.2.12 Prostaglandin E_1 (PGE_1)

Neonates who present in shock of unknown etiology or with cardiac murmurs, cyanosis, asymmetrical peripheral pulses, absent femoral pulses, or any other signs suggesting obstructive left cardiac malformations, must be immediately started on a continuous infusion of PGE_1 between 0.05 and 0.1 μg/kg/minute. This may be a lifesaving measure as it reestablishes patency of the ductus arteriosus. Once the ductus arteriosus is reopened, the dose of PGE_1 can be decreased. The most common side effects of PGE_1 include apnea, hypopnea, and fever.

48.7 Additional Therapies

Some patients with specific etiologies of shock, or shock refractory to medical therapy, require more additional management other than the above medical management. Below is a list of additional therapies that sometimes need to be utilized in the treatment of shock:

- Treatment of pulmonary arterial hypertension
- Treatment of arrhythmias
- Surgery to create of an intracardiac "pop-off"
- Surgery to correct any residual cardiac lesions
- Sternal opening post-cardiac surgery
- Total exanguino-transfusion or plasmapheresis
- Anti-endotoxins
- Continuous veno-venous hemodiafiltration (CVVHD)
- Hypothermia
- Atrioventricular and interventricular resynchronization
- Extracorporeal life support (ECLS)

48.8 Conclusion

Shock occurs when there is an imbalance between oxygen delivery and oxygen consumption. The goal of therapy is to reestablish the balance between DO2 and VO2 whether through increasing oxygen delivery or decreasing oxygen consumption. Understanding the different types of shock and the different ways shock will clinically present can aid in early diagnosis and tailoring treatment modalities. In addition to history and clinical exam, it is important to understand the invasive and noninvasive test and devices that can be used to help diagnosis and monitor efficacy of treatment. The earlier shock is recognized and successfully treated, the higher the chance of avoiding morbidities and mortality.

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Chapter 49
Mechanical Circulatory Support in Pediatric Cardiac Surgery

Peter D. Wearden, Ana Maria Manrique, and Kent Kelly

Abstract Extracorporeal membrane oxygenation (ECMO) or extracorporeal life support (ECLS) is the implementation of the cardiopulmonary bypass machine for prolonged periods of time to sustain systemic perfusion and gas exchange. The support is preferred for patients with potentially treatable pulmonary or cardiac disease. Currently, it is the most common method of mechanical circulatory support for pediatric patients. The development and improvement of this technology has allowed ECMO to progress from a salvage therapy to a commonly used treatment allowing time for cardiopulmonary recovery. Many centers have continually available rapidly deployed ECMO teams for the rapid resuscitation of patients. Some of the advantages of ECMO include rapid setup, providing both respiratory and cardiac support, reliable support with known outcomes, and a now vast clinical experience.

Extracorporeal membrane oxygenation (ECMO) or extracorporeal life support (ECLS) is the implementation of the cardiopulmonary bypass machine for prolonged periods of time to sustain systemic perfusion and gas exchange. The support is preferred for patients with potentially treatable pulmonary or cardiac disease. Currently, it is the most common method of mechanical circulatory support for pediatric patients. The development and improvement of this technology has allowed ECMO to progress from a salvage therapy to a commonly used treatment allowing time for cardiopulmonary recovery. Many centers have continually available rapidly deployed ECMO teams for the rapid resuscitation of patients. Some of the advantages of ECMO include rapid setup, providing both respiratory and cardiac support, reliable support with known outcomes, and a now vast clinical experience.

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49.1 Background

In 1977, Bartlett et al. published the first larger series of neonates undergoing ECMO for respiratory failure with a survival rate of 55%. Prior to this, an NIH-sponsored adult study had demonstrated poor outcomes, and ECMO had been largely abandoned. At the time of Bartlett's paper, cardiac disease was viewed as a contraindication for mechanical support. Incidentally, some patients had been placed on ECMO prior to a cardiac diagnosis being made and these cases were reported as being successful. In 1987, Kanter et al. reported a case series of 13 patients carrying a cardiac diagnosis with a 48% of survival. Today, the yearly number of cardiac cases supported with ECMO has increased from 30 in 1986 to 682 in 2007.

Other important events in the development of ECLS include:

- 1960–1968, Lande AJ, Bramson ML, Pierce EC, Kolobow T: Development of membrane oxygenator
- 1972, Hill et al.: first successful use of prolonged extracorporeal support
- 1973, Soeter et al.: first reported use of ECMO in a child with Tetralogy of Fallot after surgery for an extended period of time
- 1976, Bartlett RH et al.: first successful clinical application for neonatal respiratory failure
- 1986, ECMO progresses from a clinical research project to a standard of care for neonatal respiratory failure after Bartlett's larger publication [1, 2]

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49.1.1 The Development of the Extracorporeal Life Support Organization (ELSO)

In 1989, a group of centers began to pool their data regarding the number of cases, etiology of cardiopulmonary failure, complications, and survival by center with regard to the utilization of ECMO. This group was increased as continually more centers began to adapt this technology. In 1989, cardiac indications for ECMO were only 7% of the total of pediatric ECMO cases. This number has rapidly increased as has the survival of these patients. In July 2007, a 61% survival for pediatric cardiac ECMO was reported and a 58% survival for neonatal cardiac cases [3].

49.2 Circuits and Equipment

The typical ECMO system is composed of the following:

1. Pump
2. Oxygenator
3. Heat exchanger
4. Cannulae

In the typical veno-arterial ECMO (VA) system, the deoxygenated blood is removed from the patient through a venous cannula, and as it moves through the circuit, it passes through the bladder, the saturation probe (which continuously monitors the SVO_2), and the access ports (where blood sampling is drawn and medications are given). Blood next passes through the pump. The blood is then pumped through the oxygenator and then the heat exchanger. Finally, the blood is returned to the patient through an arterial line and cannula (Fig. 49.1).

From this basic model, there are many different configurations according to center preferences.

49.2.1 Pump

There are two types of pumps commonly utilized: roller pumps and centrifugal pumps.

The *Roller Pump* generates a continuous blood flow by compressing the tubing within a "raceway." The *Centrifugal pump* forces blood flow via a spinning rotor, which is magnetically coupled to a motor. The drainage of blood from the patient depends in part upon gravity, the hydrostatic pressure as determined by the difference in the height of the right atrium of the patient and the level of the pump, and by any negative suction created by the pump itself. Pump output can be recorded as liters of flow per minute or revolutions per minute (rpm).

There are several other differences between roller and centrifugal pumps. Despite certain advantages of the cen-

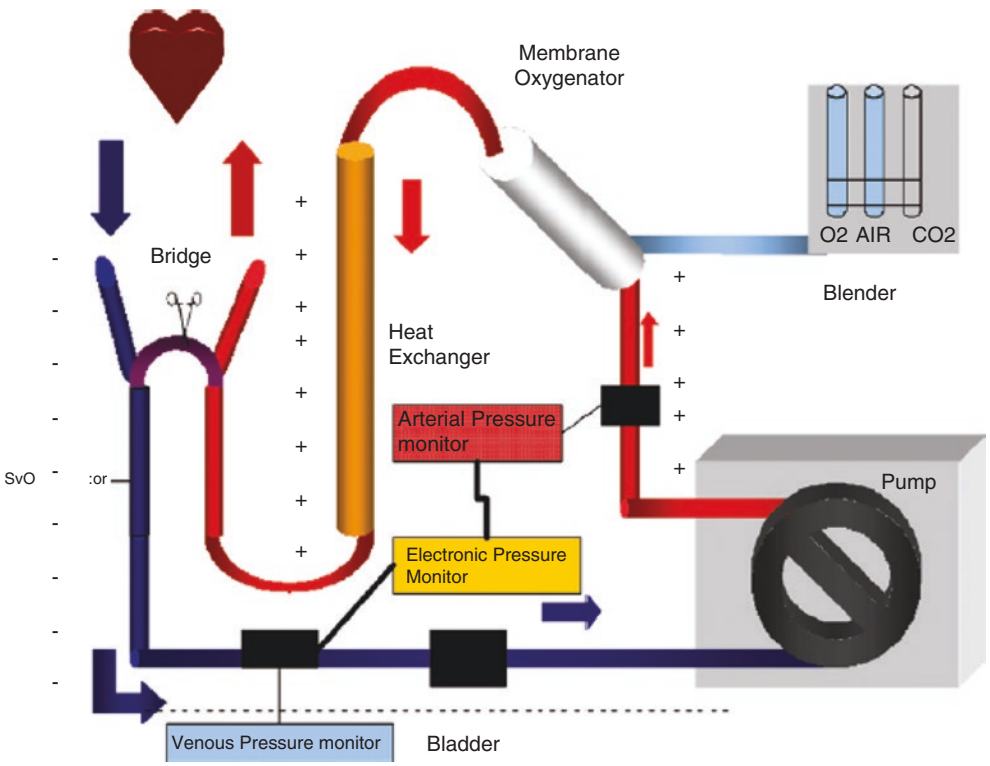

Fig. 49.1 ECMO Circuit. −− Negative pressure; ++ Positive pressure

Table 49.1 Differences between roller and centrifugal Pumps

	Roller pumps	Centrifugal pumps
Blood flow	Sequential tubing compression	Spinning rotor
Venous drainage	Gravity dependent	Dependent on suction generated by rotor
Pressure control	Continuous servo-regulation	Electromagnetically
Preload dependent	++	+++
Afterload dependent	+	+++
Excessive negative pressure	+++	++
Tubing wear-rupture	+++	+
Hemolysis	+++	++
Hemolyisis with low or high flow	++	+++
Length of functional life	+++	+
Embolization of air or particles from the tubing	+++	+
Platelet activation	+++	+
Complement and cytokine levels	+++	+

trifugal pumps, their use has become limited (in combination with silicone membrane oxygenators) because of the increased compliance and higher resistance, thus leading to increased hemolysis [4] (Table 49.1).

49.2.2 Oxygenator

The first attempt to use a pump oxygenator was made in 1951 by Clarance Dennis. At this point in time, the most commonly used oxygenator was the bubble oxygenator. This type of oxygenator was used from the mid-1950s and until the late 1970s. The issues related to this type of oxygenator, particularly with foaming and massive air embolism, encouraged the development of membrane oxygenators. In membrane oxygenators, as opposed to the bubble type, there is no direct interface between gas and blood. Gas exchange instead occurs across the surface of a membrane. There are two types of membrane oxygenators widely available: microporous and nonporous membranes. These oxygenators permitted indirect contact with oxygen minimizing the risk of air embolism and do not need a gas removal and defoaming system. Several materials have been used to develop these membranes including cellulose, polyethylene, silicone, and most recently polymethylpentene. In 1972, Y. Nose developed the first polymeric hollow fiber oxygenator device which increased the surface area over which gas exchange could occur. The currently preferred membrane has a flat reinforced rubber membrane envelope wound in a spiral fashion around a polycarbonate spool. The unit is encased by a tight fitting silicone rubber sleeve. The gas compartment is formed by the inside of the envelope. Blood flows on the outside of this envelope. The gas flows through a countercurrent system across the membrane. Additionally, this system confers low flow resistance and low priming volumes.

Gas exchange is facilitated by a countercurrent system, in which the delivered gas from the circuit is regulated to the blood flow of the patient. The difference in the partial pressure of the gases between one side and the other of the membrane, the countercurrent flow, and the ongoing consumption of the O_2 and CO_2 production will determine the rate of gas exchange.

The diffusion of CO_2 through the membrane is particularly effective. CO_2 transfer rate is 6 times greater in the silicone membrane than O_2 exchange; thus, the rate of CO_2 transfer provides a sensitive measure of the loss of functioning membrane surface area. CO_2 is controlled by the rate (sweep) of the ventilating gas delivered to the membrane. Due to this great effectiveness of CO_2 exchange, $paCO_2$ may decrease below normal levels, requiring the addition of CO_2 to the gas mixture to prevent the suppression of the respiratory center and alterations in pH.

The coefficient of diffusion of oxygen is significantly lower than that for CO_2 and is dependent on the transit time of the oxygenated hemoglobin through the membrane. The oxygen blood saturation is restricted in each oxygenator because of their limited flow rate. There are different size and surface area oxygenators used for a given patient's body surface area.

Oxygenators may experience several mechanical complications. These include a propensity for plasma leakage, structural defects, extravasation, or accumulation of fluid and blood products and thromboses. These issues may be exacerbated by certain conditions, particularly the use of parenteral lipid nutrition.

49.2.2.1 Bladder

The bladder is the inlet portion of the circuit and provides a buffer of volume for the normal fluctuations of venous return and also serves as a location for air trapping on the venous side of the circuit. The bladder provides access to blood flowing through the circuit, whereby pharmacologic agents, blood products, and fluid may be administered.

The pump stops when the level drops below a programmed level. Blood from the cannula drains into the bladder passively. The function of this bladder is to prevent negative pressure from pulling the vessel wall into the cannula and reducing the risk of damage to the vena cava. The bladder is connected to a servo regulator mechanism, which reduces or stops pump flow in the event of venous return decrease to

unsafe levels. Some centers, in order to reduce the artificial surface contacting the blood, have replaced bladders with negative pressure sensing mechanisms.

49.2.3 Heater Exchanger

The heater maintains and regulates the corporal temperature from 25 to 40 °C. The device is equipped with a water reservoir and a pump. This is a polycarbonate cylinder with stainless steel tubes inside for blood passage. Hot water circulates into the cylinder transferring heat to the stainless steel tubes, which are filled with flowing blood.

During the time that blood flow through the circuit is cooling, the heat exchanger warms the blood to body temperature before it returns to the patient. It also serves as an air trap. Heat loss is avoided with the distal placement of the heat exchanger in the circuit. The post-heat-exchanger blood temperature is monitored and the water temperature is adjusted accordingly.

Failure of this system occurs 1–2% and is due to leakage.

49.2.4 Cannulae

Cannulae are available in various shapes and sizes depending upon patient size and the site of cannulation. There are recommended guidelines regarding the appropriate size cannula based upon desired flow rates and pressure drops, the site of placement (neck vs. groin vs. chest), flow direction (venous vs. arterial), and patient weight.

Selection of the appropriate cannula size will decrease hemolysis and will increase the system efficiency. Oversized cannula will obstruct flow especially in neonates when it is placed in the aortic position and increase rates of thrombosis.

49.2.4.1 Tubing

Tubing is an important component in the system particularly with regard to the systemic inflammatory response and anticoagulation. Several materials have been developed since 1930. The most commonly used material is polyvinyl chloride (PVC). This material has the disadvantage of releasing di-2-ethylexylphthalate (DEHP), which has been associated with decreased fertility in animal studies; however, there are not conclusive studies of detrimental effects in neonates exposed to this material during ECMO runs. The leaching is further promoted by the action of the roller over the tube wall. This part of the tubing, or "raceway section," is often made of thicker tubing which gives more durability and resistance to the rupture.

More recently, heparin-bonded tubing has been introduced, with which anticoagulation with heparin may be avoided for a limited period of time. This tubing is coated with a bioactive surface of covalent forces which bind heparin to the tubing. There are several experimental and clinical studies demonstrating a decrease in the release of inflammatory reactants and platelet consumption utilizing this tubing. Currently, there are not conclusive data regarding mortality. Carmeda Bioactive Surface (CBAS; Carmeda Stockholm, Sweden) is the most common heparin-coated circuit used [5, 6].

49.2.4.2 Bridge

The venous circuit may be connected to the arterial circuit through a short segment of tubing. This segment allows continuous blood flow through the system while the patient is temporally disconnected from the ECMO support; such as, during a trial of weaning. During this process, the cannula are usually "flushed" or opened every 10–20 min to decrease risk of segmental blood stasis in the segment closed to blood flow. Generally, bridges are placed only at the time of weaning.

49.2.4.3 Equipment System

The ECMO console includes three components (Fig. 49.2):

1. Console or base
2. The pump module
3. System control panel

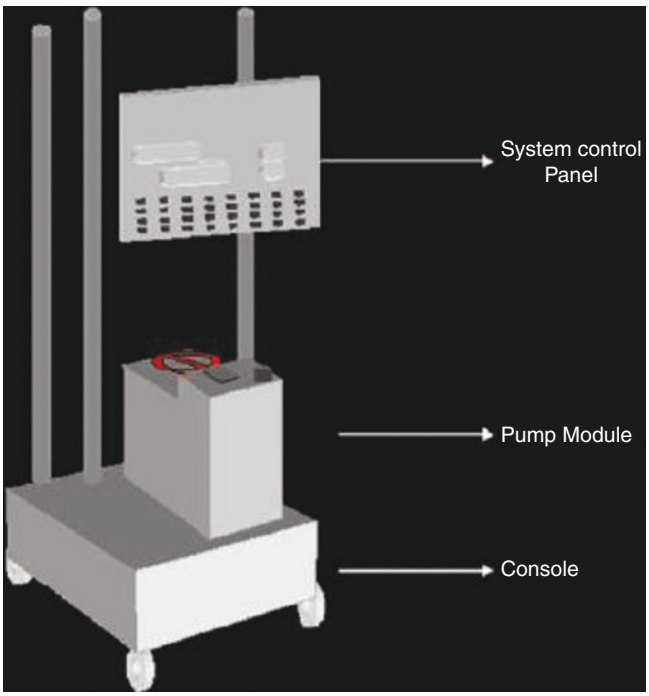

Fig. 49.2 ECMO pump system

Monitoring and Alarm System There are two safety systems required; air detectors and pressure alarms.

There are several alarm systems throughout the circuit: Pressure of the returning flow is monitored before it reaches the bladder. This servo-regulated system in the roller pump permits a decrease or halt to pump flow when the volume in the bladder, or venous cannula, is under a critical pre-estimated level. The venous alarm will be activated whenever there is decreased blood return to the pump as may happen in the case of displacement, obstruction, or kinking of the venous cannula, decrease in the blood volume, pneumothorax, pneumopericardium, hemothorax, or hemopericardium. The next set of pressure transducers is usually placed before and after the oxygenator and may alert the operator to thrombosis or failure of the membrane; those conditions increase the pressure and can cause rupture of the circuit.

Air trapping can occur in the bladder, the oxygenator, and the heat exchanger. Additionally, there is a bubble detector and trapping mechanism just before the circuit returns to the patient. All these systems permit the aspiration of the bubbles through the ports placed near each component.

49.2.4.4 The Gas Delivery System

It is composed of three basic components:

1. O_2 flowmeter
2. CO_2 flowmeter
3. Air/oxygen blender

49.2.4.5 Types of ECMO

1. Veno-arterial ECMO (VA)

Blood is drained from the right atrium to the pump and returned to the patient through an arterial cannula (aorta, carotid artery, or femoral artery). This is the mode which provides both cardiac and pulmonary support.

2. Veno-venous ECMO (VV)

The catheter is a double lumen one placed in the right atrium which can remove and infuse blood flow at the same time. This system requires normal cardiac function and provides only respiratory support. Its function is dependent upon minimal "recirculation" of blood.

49.3 Indications for ECMO Support

Selection of appropriate patients for ECMO support is challenging, continually evolving, and institution dependent. There are several criteria which have been developed to help in this decision-making process. However, these criteria have been based on indicators of tissue perfusion and they are not applicable for all the cases.

There are several pediatric cardiac clinical scenarios in which ECMO is most frequently used:

1. Acute heart failure (AHF) in patients with congenital heart disease (CHD) and acute decompensation
2. AHF after pediatric cardiac surgery (ventricular dysfunction and failure to wean from cardiopulmonary bypass) or low cardiac output syndrome (LCOS)
3. Severe pulmonary hypertension with CHD
4. Cardiomyopathy with acute heart decompensation as a bridge to recovery or transplantation
5. During cardiopulmonary reanimation or cardiogenic shock

Current publications from some centers have used it routinely in hypoplastic left heart syndrome repair (Stage I) for 24–48 h and some use it as a "prophylactic" tool in patients with a high risk of developing postoperative myocardial dysfunction [7].

ECMO support is used for both short and long term, depending upon the indications and the state of recovery. Despite improved outcomes in cardiac ECMO, the outcomes remain inferior when compared to ECMO for respiratory indications. In this regard, careful selection of the patients is the main point to improve survival.

49.3.1 Acute Heart Failure (AHF)

Pediatric patients with AHF have a high incidence of cardiac recovery with mechanical assistance. The causes of acute heart failure can be postsurgical, or not related with cardiac surgery.

Postoperative AHF may occur in patients with previous normal myocardial function induced by prolonged cardiopulmonary bypass, complex surgery, cardiotomy, and inadequate myocardial protection. Moreover, patients with previous cardiac dysfunction have an increased tendency to develop AHF after exposure to CPB.

There are two reasons to consider ECMO after surgery:

1. LCOS that usually occurs after surgery and has an etiology which is multifactorial.
2. Difficulty in weaning from CPB.

Currently, there is a tendency to initiate ECMO in the early postoperative period to maintain adequate perfusion, minimize ongoing myocardial insult, and enhance myocardial recovery.

The initiation of ECMO in these patients creates a favorable environment for myocardial recovery. Studies have supported improved outcomes with the prompt implementation of ECMO after surgery is performed [8].

Considering AHF in a non-postoperative setting such as acute myocarditis and end-stage cardiomyopathy, ECMO is an important tool as a bridge to heart transplant or recovery. Higher mortality in this group of patients may be related to the length of time on ECMO before finding a suitable organ donor. The inevitable consequences of a prolonged ECMO run including multiorgan failure remain the limiting factor for survival [9].

Appropriate selection of patients with reversible ventricular dysfunction and avoidance of end-organ failure are the essential goals of therapy. Infants with a severe coagulopathy that cannot be corrected or patients with major bleeding complications should generally not be considered for ECMO.

The contraindications to ECMO are constantly reassessed according to each center's experience. However, there are certainly some conditions where the use of ECMO is not generally beneficial. Those include patients with incurable malignancy, extreme prematurity, and poor neurological prognosis [10, 11].

49.4 Pre-ECMO Evaluation

Several factors impact survival; these include younger age, low weight, severity of diagnosis, renal dysfunction, sepsis, and multiorgan failure. All of these should be carefully evaluated prior to surgery and an optimized management strategy will improve the outcomes.

Prior to initiating ECMO, a prepared team of surgeons, intensivists, cardiologists, perfusionists, and nurses with assigned roles should be informed, a coordinator will check and maintain the circuit, medications, and presence of the entire staff. It is recommended that each institution develop guidelines according to its experience and resources.

49.5 Timing

The decision to initiate ECMO in a patient after cardiac surgery follows the instinctive judgment of the surgical team; however, early institution of mechanical support has been related with better outcomes.

AHF produces a critical mismatch between tissue oxygen demand and delivery, for both systemic circulation and the myocardium. Medical management of myocardial dysfunction with inotropic support produces tachycardia, increased afterload, and myocardial wall tension increasing oxygen demand and consumption. These stresses increase cardiac injury and compromise the myocardial recovery. The early institution of ECMO allows for a rapid improvement in myocardial perfusion and maximizes oxygen delivery and cardiac output. Organ injury is the major contribution to morbidity and mortality in patients with cardiac dysfunction. As such, prompt optimization of systemic perfusion with mechanical support will avoid the multiorganic failure cascade.

Early mechanical circulatory support should be considered as a tool to address severe heart failure after surgery rather than as a "rescue" therapy. The early use of ECMO in that setting improves clinical outcomes and increases hospital survival [12].

49.6 Initiation of ECMO

49.6.1 Cannulation

Procedures for cannulation require preparation of the necessary equipment and medications including muscle relaxant, sedatives, heparin, and the medications required to the prime pump.

Options for veno-arterial cannulation include:

1. Transthoracic: Right atrium – ascending aorta
2. Peripheral:
   (a) Internal jugular vein – common carotid artery (right side)
   (b) Femoral vein – femoral artery

The selection of the cannulation site should be based on the specific conditions of the patient such as age, weight, accessibility, and indication. Transthoracic cannulation is usually indicated in the postoperative setting during emergent situations such as cardiac arrest or into the operating room.

In neonates and infants, not in the immediate postoperative period, cannulation of the neck is preferred. Larger children and adults will require femoral cannulation in order to achieve adequate drainage. Disadvantages of the cannulation of the neck include the need of reconstruction or sacrifice of the vessels once the ECMO support is discontinued. Generally, only the right neck is utilized.

In transthoracic cannulation, the aortic cannula should be placed above Sino-tubular junction. Adequate position of the cannula in all cannulations is confirmed by chest X-ray. The tip of the arterial cannula in neck cannulation should be just above the arch of the aorta at the base of the innominate artery, the venous cannula should be in the right atrium and with the patient's neck hyperextended, and proper position will be just slightly above the right hemidiaphragm. In the femoral cannulation, the arterial cannula should be advanced through the descending aorta.

The potential for left ventricular distension should be recognized. Increasing the flow through the pump will decrease

the pulmonary flow and the venous return to the left heart when the pressure of the left atrium is high. An atrial septostomy, or separate left ventricular vent may be necessary to vent the left atrium. This procedure is especially necessary in patients with severe ventricular dysfunction. The decompression of the left ventricle is extremely important to decrease the risk of myocardial ischemia. Septostomy and venting is also useful to avoid pulmonary edema.

49.7 Operation of the System

Resistance The flow through the system follows the Poiseulle's Law; the resistance through the circuit is determined by the length and diameter of the tubing and by the viscosity of the fluids.

$$R = 8nl/\pi r^4 \ \text{dyne} - \text{s}/\text{cm}^2 \ (R = \text{resistance})$$

With a longer tube the resistance is greater; resistance decreases with a larger radius. The highest resistance of the circuit is at the level of arterial cannula. Also the resistance is given by the difference between the pressures at the inlet and the outlet port. It is expressed as mmHg/LPM.

The highest point of pressure (200–350 mmHg) is between the pump head and the membrane. The usual pressures in the circuit are between 80 and 250 mmHg. Pressures over 300 mmHg will cause hemolysis and could rupture the circuit. The difference in pressure between the inlet and outlet of the circuit is close to 100–150 mmHg.

Causes of higher pressures post-membrane include: kinked tubing, clots, cannula which are tied too tightly, flow too great for the particular size of the cannula, malpositioning against the wall of the aorta or dissection of the aortic arch.

Blood Flow This depends on length and radius of the tubing, but in this case, the amount of flow also depends on the diameter of the venous catheter. Large catheters maximize flow and improve oxygenation.

The "ideal" flow through the circuit should be laminar to avoid shear of the blood and clot formation which occurs at the angles and connections.

The level of pressure controls the direction of the flow. Negative pressures are necessary from the outflow catheter (venous catheter) up to the pump head. High flow makes these pressures more negative.

The flow produced by the pump is non-pulsatile.

Venous saturation is continually monitored and may decrease from the acceptable range due to anemia, blood loss, and a decrease in pump flow or an increase in oxygen consumption.

Gas Transfer Oxygen transfer is related to the FIO_2 of the ventilating gas, hemoglobin level, bypass flow, and the oxyhemoglobin saturation.

Carbon dioxide transfer is related to the CO_2 level in the inlet blood, the rate of flow of oxygenator ventilating gas, and the CO_2 level in the oxygenator ventilating gas.

Pressure in the blood compartment should be greater than pressure in the gas compartment to avoid over-pressurization and the passage of gas into the blood resulting in air embolism.

Oxygen Delivery The oxygen delivery will be determined by the oxygen content (HbO_2 + O_2 dissolved) and the blood flow. An increase in flow, Hb blender O_2, and a decrease of any right to left shunt increases the oxygenation. An adequate cannula size to maximize the venous blood drainage and the maintenance of a high hematocrit will help to provide adequate oxygen delivery.

Carbon Dioxide pCO_2 40–45 Torr provides adequate respiratory drive for the brain. This can be achieved by intraining CO_2 to the ventilating gas of the membrane. CO_2 levels may also be maintained by increasing or decreasing the total sweep flow. Approximately, 0.8 m^2 of the membrane surface will transfer 70 cc/min/m^2 of O_2.

49.8 Management

49.8.1 Monitoring

End-organ perfusion:

1. SVO_2
2. Lactate
3. Thromboelastogram
4. NIRS
5. Oxygen saturation

Arterial blood gases (ABG) should be performed at least daily on the patient and compared with machine gases. Discrepancies may be related to the failure of the membrane.

Flow Rate Indicators of systemic perfusion will determine the adequacy of ECMO flow. Those include urinary output, body temperature, capillary refill, SVO_2, and lactate. There are recommendations for flow rate according body surface area. Flows may be achieved at 120–150 cc/kg/min. Neonates may needflow up to 200 cc/kg/min, where as in adults 80 cc/kg/min are adequate flow rates.

The blood flow rate is used according to the surface of the membrane, from 2.5 L/min until 13.5 L/min.

Patients with large PDA's or systemic-pulmonary shunts may require higher flow rates to maintain effective oxygen delivery.

49.8.2 Regulation of pO_2 and pCO_2

The concentration and flow of the gases will determine the gas exchange. The gas exchange occurs down a concentration gradient. The ventilatory gas flow is called "sweep flow." The gas flow through the membrane is regulated by O_2 and CO_2 flow meters and an oxygen blender. The flow of the gas in the membrane is limited to ensure that the pressure of the gas is lower than the pressure of the blood. The FIO_2 can be manipulated by mixing O_2 with air. A larger membrane should be used to increase pO_2 when the FIO_2 is maximal (100%). The exchange of CO_2 is much more efficient than O_2. To remove CO_2 from the system, the gas flow should be increased. The percentage of CO_2 gas in the total gas flow should be below 5%.

The total gas flow should be maintained above 1 L/min to blow off the water vapor formed during the passage of cool gas over the warm blood.

To decrease the patient pCO_2 level:

1. Increase the O_2 flow.
2. Decrease the CO_2 flow.
3. Increase the level of ventilation by the respirator.

To increase the patient pCO_2 level:

1. Decrease the O_2 flow.
2. Increase the CO_2 flow.
3. Decrease the level of ventilation from the respirator.

To increase the patient's pO2:

1. Increase the rate of flow.
2. Increase oxygenator FiO_2.
3. Increase the FIO_2 in patient ventilator settings.

To decrease the patient's pO_2:

1. Decrease the rate of flow.
2. Decrease the oxygenator FIO_2.
3. Decrease the FIO_2 on the ventilator.

49.8.3 Anticoagulation

The flow of the blood through the ECMO circuit produces profound effects on hemostasis. Platelets decrease in number and function due to the continuous microthrombi formation. In addition, activated platelets undergo a morphologic change and express GPIIb/IIIa receptors, increasing platelet binding with fibrinogen. The artificial material of the circuit interacts with proteins of the membrane surface and coagulation factors activating the coagulation cascade. This effect can be decreased by the administration of albumin to the circuit.

Heparin will block the clot formation by its binding and activation of antithrombin III. Antithrombin III inactivates thrombin, factors Xa, IX, XI, and XIII. Regular measurement of activated clotting time (ACT) is necessary to achieve equilibrium between the thrombus formation and bleeding. Heparin should be initiated with a beginning dose of 30–150 Units/kg before cannulation to reach an ACT approximately 200 s to assure adequate systemic anticoagulation.

After initiation of ECMO, a continuous infusion of heparin of 25–50 Units/kg generally will achieve an ACT in the desired range of 180–200 s. If the ACT falls below 160 s or drops rapidly, an additional bolus dose of heparin (10–20 Units/kg) may be necessary. If the ACT is greater than 300 s, the heparin infusion should be continued at a lower rate.

Heparin requirements will change according to transfusions as well as renal and liver function.

During ECMO, patients frequently require packed red cell transfusions to ensure adequate oxygenation. Additionally, FFP and cryoprecipitate are required when fibrinogen levels decrease below 100 mg/dl. Platelet count should be maintained over 100,000 with normal platelet function.

Antifibrinolytics are used to decrease fibrinogen consumption. Continuous infusions of aminocaproic acid, tranexamic acid, and aprotinin have been shown to decrease the incidence of hemorrhage.

Other reported alternatives for anticoagulation include *Argatroban* and *Nafamostat mesilate*. They have in addition an antifibrinolytic effect. They can also be used to inhibit platelet aggregation induced by adenosine diphosphate (ADP), platelet activating factor, and arachidonic acid.

Heparin-coated circuits have been developed with the goal of reducing heparin requirements. With the help of covalent or ionic forces, they are able to maintain locally the heparin within the internal surface of the circuit.

49.8.4 Fluids and Electrolytes

The non-pulsatile flow from the pump produces alterations in the metabolism of the renin and increases its production resulting in altered electrolyte balance. During ECMO, the requirements for potassium are often higher while requirements for sodium may be decreased. Loss of fluid through the oxygenator can be about 2 $cc/m^2/h$.

Electrolytes: should be maintained at normal levels.

An adequate replacement would be:

- Na^+ = 0–2 mEq/kg/day.
- K^+ = 4–6 mEq/kg/day.
- Ca^{2+} = 30–50 mg/kg/day.

Daily fluids should range from 80 to 150 ml/kg/day of $D_{10}W$ to $D_{20}W$ depending on the age and other factors such as sepsis, cerebral ischemia, etc. Electrolytes should be monitored every 8 h. The production of renin will produce a decrease in the urinary output that can be resolved with the addition of diuretics (Furosemide 1–2 mg/kg).

Blood glucose should be monitored every 4 h.

Hyperalimentation is usually maintained.

49.8.5 Pulmonary Function

Mechanical ventilation decreases atelectasis and reduces afterload and pulmonary resistance during the support period and should be maintained. Ventilation should be maintained with parameters that avoid barotrauma, pneumothorax, or collapse. Pulmonary care with periodic bagging, suctioning, and tracheal lavage should be performed. Ventilator parameters should be increased progressively during ECMO weaning.

49.8.6 Hemofiltration–Renal

During the first 24–48 h, ECMO patients may experience a decrease in urine output. Hemodialysis may be needed during ECMO and can be performed via a direct connection to the ECMO circuit.

A hemofilter is connected to a port on the arterial side of the ECMO circuit and the outlet to a venous side. It is used to remove fluid from the patient during transfusions, fluid replacement, or when urine output decreases. The micropores of the hemofilter are not bigger than 5 μm and this permits constant blood flow through the hollow fibers. The system will pull out water and mineral solutes and heparin while red blood cells are retained.

49.8.7 Shunt

Due to the lower pulmonary resistance, almost all infants develop a left to right or systemic to pulmonary shunt through a patent PDA during the first 2–3 days of ECMO; this can be suspected because of a persistent low paO_2, pulmonary edema, and low urine output in the face of high ECMO flows. These patients require a careful fluid management and consideration of surgical reduction of the degree of shunting (i.e., shunt ligahon).

49.8.8 Nutrition

Early initiation of nutrition will improve recovery in these patients. Enteral nutrition has some advantages in maintaining the gut membrane integrity and the immunologic system. The risk of enterocolitis in neonates due to a decrease in splanchnic perfusion has not been demonstrated during ECMO. Parenteral nutrition increases the risk of obstruction of the membrane due to the fat emulsion (the lipid component should be administered in a different central venous line and not to the circuit if at all possible).

49.8.9 Medications and Blood Products

RBC's, albumin, IV infusion medications, antibiotics, and other medications are usually administrated through the venous line. Hyperalimentation, heparin drips, and continuous infusion drips are usually administrated through the arterial side after the oxygenator. Platelets, cryoprecipitates, antihypertensive agents, sedation drugs, and emergency medications should be given in the arterial line after the oxygenator and before the heat exchanger.

The volume of distribution of most medications is altered during ECMO due to changes in the total body water in addition to renal and hepatic metabolic changes, making the pharmacokinetics of most drugs unpredictable. Also, some medications may bind to the circuit material decreasing their bioavailability.

49.9 Systemic Response to ECMO

When evaluating the systemic response to ECMO, one should consider that there are some differences between CPB and ECMO with regard to the inflammatory response:

1. Longer duration of ECMO compared with CPB.
2. Protamine administration after CPB to reverse anticoagulation.
3. Hypothermia.
4. Presence of a cardiotomy reservoir with including cardiotomy suction and an air blood interface.
5. Ischemia and reperfusion injury during and after aortic cross-clamp.
6. Cardiorespiratory support is usually partial during ECMO support; the heart maintains the pulsatile flow preserving organ function and preventing vasoconstriction.

The activation of the inflammatory cascade is due to the exposure of the patient's circulating blood to the surface of the circuit. Inflammation triggered by ECMO can lead to organ dysfunction and derangement of the hemostatic and fibrinolytic cascades.

The neutrophils are the final effectors of cell and tissue damage. Their activation maintains and amplifies the inflammatory cascade. Clinically, the peak value of leukocytosis during ECMO is usually (36 h after initiation) and is correlated with worsening of the pulmonary dysfunction. Plasmapheresis and leukocyte filtration are techniques used to decrease the number of activated cells in the plasma. There are not conclusive studies, but these modalities are frequently used.

Activation of the immunologic system has been demonstrated by:

1. An increase of the complexes of factor XIIa-C1 esterase inhibitor
2. A decrease of kallikrein inhibitory capacity
3. An increase of thrombin – antithrombin formation
4. The generation of fibrinogen degradation products

The system activates platelets causing morphologic changes and the release of their granule content. This platelet activation produces a complex interaction with cytokines, leucocytes, complement system, and other systemic inflammatory mediators.

Medications used during ECMO are often given to decrease the inflammatory response and to modulate the platelet activation.

Use of steroids has been correlated with a reduction of pro-inflammatory cytokines and an enhanced level of anti-inflammatory IL-10; in the clinical setting, its use has been correlated with shorter ECMO support duration and mechanical ventilation days. The improvement of the pulmonary microcirculation may play a major role in the beneficial effect of the steroids during ECMO.

49.10 Weaning

The decision to wean ECMO should depend on the condition of the patient, the correction of the underlying anatomical or physiologic defect, the neurological prognosis, and the family dynamics. Despite its generally limited time frame some publications have reported ECMO support for up to 6 weeks, the neurological outcomes and quality of life remain unclear. Poor survival has generally been described after 3 weeks of support in different studies [13].

Biochemical and clinical indicators of improvement include: during a decrease pump flow, adequate blood pressure is maintained with a recovery of the cardiac function by echocardiography.

Several attempts at weaning ECMO may cause reperfusion injury and can be detrimental. Thus, it is reasonable to have several positive indicators before attempting a trial. It is also important to balance this with the knowledge that patients having a shorter duration of support will have a greater chance of survival [14, 15].

49.11 Complications

Complications of ECMO include mechanical, hemorrhagic, neurologic, renal, cardiovascular, pulmonary, infectious, and metabolic.

The most common complication, excluding the requirement of inotropic support, in the neonatal group is bleeding, and it is also the main cause of death. Organ injury is the major contribution to morbidity, especially neurologic injury, which is the most common reason to discontinue ECMO [16].

Stroke, disseminated intravascular coagulation (DIC), and renal dysfunction or multiorgan dysfunction has been identified as the major complications causing death in ECMO after pediatric cardiac surgery.

The highest reported mechanical complication includes clots in the system.

Renal insufficiency requiring hemofiltration is also one of the most common causes and is associated with high mortality.

Complications of cannulation include misplacement of the cannulae which may cause occlusion, injury, and damage to the aortic wall or valve leaflets.

The major complications of ECMO have been related to cerebral edema and intracranial hemorrhage. Patients should be followed closely to detect any presence of seizure. Intracranial hemorrhage may be examined for with head ultrasounds. An intracranial hemorrhage greater than grade II generally requires adjustments in heparin doses and close follow-up and potential discontinuation of support.

49.11.1 Failure of Circuit

Membrane failure can be evidenced by an increase in the CO_2 content and a decrease of the O_2. The failure is caused by membrane defects and exposure of the membrane to high outflow pressures or clots.

Consideration should be given to changing the circuit or its components when there is a clot in the circuit (post-membrane) or when there is a concern of the possibility of rupture.

Power failure: The pump should be hand-cranked manually until the power returns.

Air: If the air is distal to the oxygenator connection, ECMO flow should be stopped immediately. When the air is in the venous line it can be trapped in a bridge, bladder, or the oxygenator and removed.

49.12 Current Outcomes

The large surface area that ECMO circuit requires enhances the inflammatory response, with activation and consumption of the coagulation factors increased hemolysis, thrombosis, and multiorgan dysfunction. New systems of circulatory support without oxygenators permits prolonged periods of support and currently are seeing increasing acceptance and better outcomes [17]. The greatest challenges of ECMO support are related to: anticoagulation, neurological outcome, duration of support, recovery, trauma to blood elements and mechanical issues (Table 49.2).

Cardiac arrest, bleeding, renal failure, and prolonged intubation prior to ECMO have been identified as risk factors for death [16].

A multivariate analysis from Morris et al. [18] revealed that age less than 1 month and male gender significantly affected hospital survival in patients who required ECMO after cardiac surgery. They did not find any significant independent predictors in the nonsurgical ECMO group. Furthermore, they did not find that failure of separation from the cardiopulmonary bypass machine or cardiac physiology alterations (single ventricle) were correlated significantly with hospital survival.

Table 49.2 Current ECMO outcomes for cardiac support

Author, year of publication, city,	Years of study, number of patients	ECMO indication	Hospital survival	Cause of death	Neurological injury after survival
Alsoufi et al. 2007 [21] (Toronto–Saudi Arabia)	2000–2005 80 patients	ECMO in refractory cardiac arrest	37%	Ischemic brain injury	11%
Fisher et al. ELSO registry 2007 [22] (Toronto–Michigan)	1987–2005 151 patients	For primary graft dysfunction after lung transplantation	42%	Multiple organ failure (12%)	12%
Delmo Walter EM et al. 2007 (Berlin)	1987–2005 110 patients	Perioperative circulatory failure	57%	Multiple organ failure	
Sachweh et al. 2007 [13] (Aechen)	1996–2007 24 patients	Failure to wean from cardiopulmonary bypass	50%	Multiple organ failure	4%
Pizarro C et al. 2006 [17] (Wilgmington)	2004–2005 44 patients	For postoperative rescue of high-risk patients following cardiac repair:	50%	Multiple organ failure	10%
Thourani V et al. 2006 [23] Athlanta	27 patients	(VA-ECMO) in pediatric cardiac support	59%		
Ravishankar C et al. 2006 [7] Philadelphia–Pittsburgh	1998–2005 382 patients	After stage I reconstruction	38%		
Hoskote A et al. 2006 [24] Toronto	1997–2003 25 patients	After staged palliation of a functional single ventricle	44%	Multiorgan failure	
Chow NK 2006 [24] Tapei	1987–2004 204 patients	For perioperative cardiac allograft failure	52%		
Allan C et al. 2006 [25] Boston	1996–2004 22 patients	Emergent use of ECMO during pediatric cardiac catheterization	82%		48%
Balsaim G et al. 2006 [15] Jeddah	2000–2004 26	After pediatric cardiac surgery	46%	Stroke, DIC	
Chaturvedi RR et al. [18] 2004	81 patients	Postcardiotomy cardiac failure	Initiated in ICU: 29% Initiated in OR: 64%		
Mehta U et al. 2000 [24]	8 patients	Cardiomyopathy, myocarditis, or arrhythmia	End-stage dilated cardiomyopathy: 80% Acute myocarditis: 33%		
Morris MC et al. 2004 [18]	1997–2004 137 patients	Pediatric cardiac ICU	39%		
Del Nido P et al. 1992 [26]		After sudden cardiac arrest in the postoperative period	55%		

The duration of ECMO has been shown to affect survival. While some have shown that most patients who survive recover contractile function within 48–72 h. The time interval from CPR to rescue R-ECMO has been noted as a limiting factor in the effectiveness of any rescue during acute cardiac and pulmonary failure. At the Children's Hospital of Pittsburgh, survival was 100% in patients with CPR times less than 15 min, whereas survival was 55% in those who underwent CPR for more than 42 min.

49.13 Pediatric Ventricular Assist Devices

With the advent of improved technology, circulatory support without an oxygenator is available for the pediatric population. The experience published by different institutions around the world is growing. Some studies have demonstrated improvements in survival, especially when the indication is for long-term bridge in pre-transplant patients [16, 19].

Advantages:

1. Relatively easy implantation
2. Fast set-up time
3. Low priming volume
4. Low level of anticoagulation
5. Less trauma and risk of infection
6. More mobility of the patient
7. Do not require ICU
8. Decreased requirement of anticoagulation
9. Longer term support
10. Pulsatile flow
11. Small size

The indication for circulatory support with a Ventricular Assist Devices (VAD) system is oriented to the patient disease process [19, 20].

Types and availability of VADs used in the pediatric population include:

1. *Paracorporeal*:
   (a) *Pneumatic pulsatile*
      (i) Abiomed BVS 5000 (Abiomed Inc., Delaware, MA)
      (ii) Berlin Heart EXCOR (Berlin Heart AG, Germany)
      (iii) MEDOS HIA (MEDOS, Germany)
      (iv) Heartmate I (Thoratec, Plasanton, CA)
      (v) Toyobo (Japan)
      (vi) Novacor (Baxter, Irvine CA)
2. *Intracorporeal or implantable*
   (a) *Continuous axialor centrifugal flow*:
      (i) MicroMed DeBakey (Micromed Technologies)
      (ii) Jarvik 2000 (Jarvik, NY)
      (iii) The INCOR VAD Berlin Heart (Germany)
      (iv) Thoratec Heartmate II Duraheart (Temuro, Japan)

49.13.1 Devices Underdevelopment

1. Pediatric Ventricular Assist Device (Penn State)
2. Pediatric Jarvik 2000 (Jarvik Heart Inc. NY)
3. PediaFlow VAD (Pittsburgh)
4. PediPump (Cleveland Clinic)
5. Levitronix centrifugal Pump (Pittsburgh)
6. Pediatric Cardiopulmonary Assist System (Ension)
7. Pediatric pVAD (Cardiac Assist, Inc. Pittsburgh)
8. Toddler VAD (Pittsburgh)

49.13.1.1 Anticoagulation

Anticoagulation management for VADs reflects the postsurgical nature of VAD implantation and focuses more heavily on platelet inhibition. Unfractionated heparin should be started 24–48 h after implantation if the platelets count is higher than 20,000/μL and there is no clinical bleeding.

49.13.1.2 Unfractionated Heparin Therapy (IV)

Initial dose is 10 Units/kg/h (15 Units/Kg/h < 12 months of age), after 6 h if the patient is not bleeding, increase infusion to 20 Units/kg/h (28 Units/kg/h < 12 months of age). PTT and antifactor X_a should be obtained 6 h after the increased dose. Therapeutic range for PTT of 1.5–2.5 times (patient baseline) and antifactor X_a of 0.35–0.5 U/ml, then use PTT to follow therapy.

Thromboelastograms should be obtained in the early postoperative period and every 24 h during the first week.

Heparin should be increased if R < 8.0 and decreased if R < 15.

In addition, renal and hepatic functions require monitoring.

49.13.1.3 Platelet Inhibition Therapy

Initiate dipyridamole 4 mg/kg/day (max dose 10 mg/kg/day) after 48 h if there is not bleeding, patient is hemo-

dynamically stable, and platelet function in the TEG is normal (MA >56 mm, G > 6 and < 10, arachidonic acid inhibition is <70%), and the platelet count is >40,000.

Aspirin may be started (1 mg/kg/day) at day 4 postimplantation when the MA > 72 mm and G > 8.

Fresh frozen plasma (10–15 ml/kg) or platelets (1 unit/5 kg body weight) might be administered in case of decrease in clot factors or platelet dysfunction.

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Chapter 50
Heart Transplantation

Matthew D. Zinn, Steven A. Webber, Victor O. Morell, and Mahesh S. Sharma

Abstract Heart transplantation in children has steadily expanded since the first operation was performed in 1967. It remains the last therapeutic option for patients with end-stage heart failure from congenital heart disease and cardiomyopathy. Patients must undergo a comprehensive evaluation prior to transplant to fully understand the risk and benefits of the procedure. Waitlist mortality currently sits at about 10%, which has decreased dramatically with the advent of the ventricular assist device. Survival has increased as well, with roughly 50% surviving to 15 years posttransplant. While it can significantly prolong one's life, serious complications are common, including graft rejection and multisystem disease secondary to necessary postoperative management and immunosuppression. This chapter provides the reader with an in-depth, state-of-the-art review of pediatric heart transplantation, with focus on management in the intensive care unit.

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50.1 Introduction

The field of cardiac transplantation was born 50 years ago in 1967 when Dr. Christiaan Barnard performed the first successful human heart transplant in Cape Town, South Africa. Dr. Adrian Kantrowitz performed the first pediatric heart transplant 3 days later in an infant in New York, NY, USA. While Dr. Kantrowitz did not pursue a career as a transplant surgeon, he and his team forever changed the field of cardiology by developing the left ventricular assist device (VAD) and intra-aortic balloon pump. The last half century has brought countless advances in medical technology, improved understanding of the immunology surrounding solid-organ transplantation, creation of immunosuppression capable of extending the life of the graft with reduced adverse drug effects, and higher awareness of organ donation. As of 2016, 120 pediatric heart transplant centers were reporting data to The International Society of Heart and Lung Transplantation (ISHLT) registry [1]. The number of transplants has risen steadily from 414 in the year 2000 to 684 in 2015 [1]. There has also been a steady increase in survival over the past several decades. The first year is the most crucial for all patients. Those surviving the first year after transplant have a median survival of over 15 years regardless of the age at transplant. The care provided in the cardiac intensive care unit in the first few days to weeks after transplant has a profound impact on not only survival to hospital discharge but long-term survival of the transplanted organ and patient. This chapter will provide an up-to-date overview of pediatric heart transplantation with a focus on management in the intensive care unit.

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50.2 Indications for HT

Heart transplantation is the final common endpoint for children with refractory heart failure. Clinicians have maximized medical therapy with beta-blockers, angiotensin-converting enzyme inhibitors (ACE-i), aldosterone antagonists, antiarrhythmics, and diuretics. Ambulatory inotropes can no longer stave off incessant symptoms of heart failure. Many require prolonged mechanical circulatory support. Thankfully, advances in medical management and mechanical circulatory support technology have made heart transplantation a realistic option for an increasing number of patients. Congenital heart disease (CHD) remains the most common initial diagnosis in infants requiring heart transplantation. Fifty-five percent of infants transplanted from 2009 to 2016 had CHD, while 37% had cardiomyopathy [1]. The ratio of congenital heart disease to cardiomyopathy gradually reverses with age. Cardiomyopathy was the primary diagnosis in 54% of adolescents, while only 23% had CHD.

Common contraindications include active infections (bacterial, fungal, hepatitis B/C, human immunodeficiency virus), pulmonary vascular resistance (PVR) > 6 Woods units × m^2 (WU × m^2) that is unresponsive to vasodilator therapy [2], transpulmonary gradient (TPG) > 15 mmHg [2], inadequate intraparenchymal pulmonary vascular bed, diffuse pulmonary vein stenosis, recent or current treatment of malignancy with inadequate follow-up to ensure likely cure, genetic conditions or multisystem disease that will not improve after heart transplantation, prior nonadherence with medical therapy, and inadequate social support. Classification of absolute and relative contraindications can vary by center. The final decision of transplant candidacy is made by a multidisciplinary team including transplant cardiology, cardiac surgery, cardiac intensive care, nursing, social work, and transplant psychology.

50.3 Transplant Evaluation

Evaluation for heart transplantation is a complex and time-consuming process. While the data obtained is similar, the duration and location of the evaluation can vary by transplant indication and age. Inpatient evaluations can be completed in a few days due to ease of obtaining the necessary testing, which is often seen in critically ill patients. The outpatient evaluation is commonly spread out over an entire week for stable heart failure and cardiomyopathy patients. Infants are more commonly evaluated while inpatient, whereas children and adolescents often receive an outpatient evaluation. The evaluation is always inpatient after implantation of a VAD, except in cases where myocardial recovery is possible and the VAD is considered temporary.

Table 50.1 Evaluation of candidates for heart transplantation

History and physical examination
Required consultations:
Pediatric transplant cardiologist, congenital cardiovascular surgeon, cardiac anesthesiology, infectious disease specialist, physical medicine and rehabilitation, transplant psychologist, transplant nurse coordinator, social work, child life, nutrition, pharmacy, hospital financial consultant
Additional consultations (as required):
Pulmonology, hepatology, genetics, neurology, oncology, nephrology, supportive/palliative care
Cardiac/anatomical diagnostic studies
Chest radiograph, electrocardiogram, echocardiogram, cardiac catheterization, 4-extremity vascular ultrasound, abdominal ultrasound
In selected patients: Exercise test, ventilation-perfusion scan, chest CT or MRI, pulmonary function tests
Blood type (ABO), anti-HLA antibody screen, complete blood count and white cell differential, platelet count, coagulation screen, blood urea nitrogen, serum creatinine, glucose, calcium, magnesium, liver function tests, lipid profile, brain natriuretic peptide
Serologic screening for antibodies to the following pathogens: Cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex, human immunodeficiency, varicella, hepatitis A, B, C, D, and measles; antibodies to toxoplasma gondii
PPD placement or QuantiFERON-TB gold
Immunization record and administration of updated immunizations as needed

The transplant evaluation consists of bloodwork, imaging, subspecialty consultations, and education. The current heart transplant evaluation protocol at The Children's Hospital of Pittsburgh is outlined in Table 50.1.

50.3.1 Anatomic Considerations

The first step in the evaluation is clearly defining the anatomy. This step may have been performed long ago, but must be revisited and updated. Heart transplantation requires no complicated intracardiac repairs. Conversely, heart transplantation can be complicated by extracardiac vascular issues and abnormalities. The medical and surgical teams must have a clear understanding of the following: cardiac position in the chest, size and location of the superior and inferior vena cava, presence of an interrupted inferior vena cava, hypoplasia of the branch pulmonary arteries, stenosis of the pulmonary veins, and size and surgical history of the aorta. This information is often obtained via a contrast chest computed tomography (CT) scan or magnetic resonance imaging (MRI). These axial studies are also crucial for determining the location of vascular structures posterior to the sternum which can be injured during the sternotomy and require urgent cardiopulmonary bypass cannulation. Additional imaging studies sent prior to transplant include an abdominal ultrasound to determine the presence and loca-

tion of the abdominal viscera, and a vascular ultrasound of the extremities to evaluate the patency of the central arteries and veins. Access to these vessels is needed post-transplant for rejection monitoring and may be needed pre-transplant for extracorporeal membrane oxygenation (ECMO). A recent echocardiogram, electrocardiogram, and chest radiograph are required. An exercise stress test, 6-minute walk test, lung perfusion scan, and pulmonary function testing should be considered in certain patients.

50.3.2 Hemodynamic Considerations

Cardiac catheterization provides vital hemodynamic data in many evaluations. The results can ultimately determine one's transplant candidacy. Information obtained during heart catheterization provides insight into the health of the pulmonary vascular bed and lung parenchyma. The most important valves obtained are the PVR and TPG. PVR under 6 WU × m^2 is considered acceptable for heart transplantation [2]. PVR between 6 and 9 WU × m^2 may be safe for transplant, with recent studies showing no decrease in survival after transplant [3, 4]. Fixed PVR over 10 WU × m^2 is generally considered a contraindication to heart transplantation alone, and should shift the evaluation toward a combined heart-lung transplant. In addition, pulmonary venous desaturation can indicate parenchymal lung disease or diffuse arteriovenous malformations, which are often contraindications to heart transplant alone. A TPG under 15 mmHg is considered acceptable for heart transplantation [2].

Elevated PVR at baseline is often seen in our patient population. Heart transplant is feasible if the pulmonary vascular bed is reactive to pulmonary vasodilator therapy. Patients commonly wait for transplant on inhaled nitric oxide, oxygen, milrinone, intravenous prostacyclin analogs, and/or ventricular assist devices – all capable of lowering PVR. Hemodynamic data is obtained at regular intervals while waiting to ensure the patient remains a good candidate for heart transplantation.

50.3.3 Laboratory Evaluation

Some of the most important data required for heart transplant evaluation is obtained via bloodwork. Standard tests such as a basic metabolic panel, hepatic function panel, complete blood count, prothrombin time/INR, partial thromboplastin time, fasting lipid profile, and hemoglobin A1c provide information on general health as well as provide a baseline prior to starting immunosuppression.

Further testing provides critical hematologic, infectious, and immunologic data necessary for transplant listing and organ acceptance. Blood group typing must be sent on two separate occasions to determine the recipient blood type. Children under 2 years of age can be considered for an ABO incompatible heart transplant due to their immature immune system and ability to develop accommodation toward an organ from a donor with a different blood type. Isohemagglutinins are sent to determine the presence and titer of recipient blood group antibody. Patients listed for ABO-incompatible transplant are placed on a specific blood transfusion protocol to avoid development of blood group antibody while awaiting transplantation.

Infections can and will complicate any transplant due to the recipient's immunocompromised state. HIV and hepatitis (A, B, and C) status are necessary for listing in UNOS. Epstein-Barr virus (EBV) exposure is important in determining one's risk for developing posttransplant lymphoproliferative disease (PTLD). Exposure to cytomegalovirus (CMV), specifically a mismatch between donor and recipient, requires antiviral prophylaxis with ganciclovir immediate after transplant. New or previous exposure to toxoplasma gondii and herpes simplex virus may lead to a significant de novo or reactivation infection after transplant and require more intense antimicrobial prophylaxis if identified peri-transplant. Antibody titers are also sent against vaccine targets such as varicella and measles. A repeat vaccination series is considered if the patients lacks immunity, depending on estimated time to transplant.

Human leukocyte antigen (HLA) typing and antibody levels are sent to allow for appropriate organ matching and avoidance of potentially detrimental antibodies. The results also help determine the need for desensitization therapy prior to transplant in patients with high, and potentially prohibitive, levels of HLA antibody.

50.3.4 Consults

Subspecialty and ancillary staff consolations are the final aspect of the transplant evaluation. Patients at our institution are required to meet with the transplant cardiologist, transplant nurse coordinator, cardiothoracic surgeon, infectious disease, physical medicine and rehabilitation, social work, psychology, nutrition, child life, and pharmacy prior to listing. Additional consults are placed as needed for patients with chronic or possible disease in other organ systems, such as hepatology, pulmonology, neurology, genetics, and supportive/palliative care. These visits provide each team the ability to evaluate every aspect of the patient and provide detailed education on the risks and benefits of transplantation. It is here where the parents and caregivers can ask questions and obtain the answers needed to truly understand life after pediatric heart transplantation.

50.3.5 Listing

Patients are arranged on the United Network for Organ Sharing (UNOS) pediatric heart transplant list according to the severity of illness and duration on the list. The most critically ill patients are listed status 1A. These patients are admitted to the hospital and require one of the following: continuous mechanical ventilation, use of an intra-aortic balloon pump, prostaglandins for ductal-dependent pulmonary or systemic circulation, or multiple intravenous inotropes or a single high-dose inotrope in a patient with CHD. Presence of a VAD also qualifies for status 1A listing but does not require hospitalization. Status 1B patients require one or more inotropes but do not meet 1A criteria, or are patients less than 1 year old with hypertrophic or restrictive cardiomyopathy at the time of listing. All other patients are listed status 2. The average waitlist time for infants at our institution is 2–4 months, with school age children waiting 4–6 months. Adolescent wait time remains the shortest (often less than 2 months) due to an expanded donor pool including adolescents and small adults.

50.4 Pretransplant Management

Infants, children, and adolescents wait for transplant in a variety of settings. Many can live at home while maintained on oral medications, an ambulatory inotrope, or a VAD. Others require inpatient management for hemodynamically unstable heart failure despite maximal therapy or numerous comorbid conditions. Inotropic agents are always started in the ICU at our center to closely monitor the hemodynamic response.

Inpatient management of the preoperative transplant candidate is multifaceted. Care often encompasses cardiovascular, respiratory, nutritional, and psychological support. Inotropic agents are commonly used to augment cardiac output in children refractory to oral heart failure medications. A single inotropic agent, such as milrinone or dobutamine, is typically acceptable for home use [5]. Dependence on multiple inotropic agents for hemodynamic stability represents deteriorating clinical status and a higher risk of a sudden cardiac event. In fact, a VAD is indicated within days to weeks for those in cardiogenic shock of dependent/declining on inotropes (Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS]/Pediatric Interagency Registry for Mechanically Assisted Circulatory Support [PediMACS] profiles 1–3). Commonly used inotropes in our intensive care unit include epinephrine, dobutamine, and milrinone. Epinephrine is an alpha- and beta-receptor agonist that acts as a positive chronotrope and inotrope at lower does while causing both systemic and pulmonary vasoconstriction at higher doses. The infusion rate and ultimate need of epinephrine must be discussed daily, as it can induce myocardial contraction band necrosis [6] and a proarrhythmic state. Dobutamine is a beta-receptor agonist that acts primarily as a positive inotrope. Vasoconstriction, ventricular arrhythmias, and increased myocardial oxygen consumption may limit use. Milrinone, through phosphodiesterase 3 inhibition, leads to increased inotropy, lusitropy, and vasodilatation. Milrinone's positive effects and low side effects profile have resulted in widespread use for chronic heart failure.

50.4.1 Mechanical Circulatory Support

Mechanical circulatory support is commonly used prior to heart transplantation. These patients require prolonged admission to either the ICU or the general cardiac inpatient unit. Options for support include extracorporeal membrane oxygenation (ECMO) and VADs. ECMO is typically accomplished through peripherally inserted neck cannulas, where deoxygenated blood is removed from the right atrium, oxygenated within the circuit, and returned to the body via the carotid artery. It is a very effective means of cardiopulmonary support, but carries significant risk. Complications of ECMO include stroke, bleeding, arrhythmia, renal failure, infection, and circuit thrombosis [7]. Survival to discharge with ECMO is poor across all indications, with only 40% of infants and 50% of children/adolescents surviving to hospital discharge [Extracorporeal Life Support Organization Registry 2017]. When used as a bridge to transplant, infants and children supported with ECMO carry only a 20% chance of surviving to hospital discharge [8]. This harrowing statistic pushes many programs away from using ECMO and is the reason behind the significant increase in VAD use.

The number of pediatric VADs reported to PediMACS has significantly increased over the past 4 years [9]. Dilated cardiomyopathy is the most common underlying diagnosis and often requires only an LVAD (80%) in patients progressively declining on inotropes at the time of implantation (INTERMACS 2). Younger patients were more likely to receive a paracorporeal pulsatile or continuous-flow device, while older patients received an intracorporeal continuous-flow device. The most frequently used paracorporeal pulsatile device has consistently demonstrated a 29% incidence of embolic stroke in addition to bleeding and infectious complications [10, 11]. Intracorporeal continuous flow devices carry a much lower rate of neurologic complications at 10% [12] and are being used in smaller patients due to a more tolerable side effect profile. Survival to transplant on a VAD is comparable to requiring no mechanical support [9, 13]. One of the more time consuming and difficult aspect of VAD management revolves around anticoagulation. A complete discussion on VAD use in the CICU can be found in Chap. 50.

50.4.2 Additional Considerations

Pulmonary arterial hypertension (PAH) is a common comorbidity in heart failure patients. Left-sided obstructive lesions, elevated left ventricular end diastolic pressure (LVEPD), and left atrial hypertension lead to variable degrees of secondary PAH prior to transplantation. These conditions must be recognized and treated early to improve postoperative outcomes. As previously mentioned, ideal pretransplant hemodynamics include a PVR below 6 WU x m^2 and a transpulmonary gradient below 15 mmHg. Oral sildenafil, intravenous prostacyclins, and inhaled nitric oxide are frequently employed while on the waitlist to maintain adequate intrapulmonary hemodynamics.

Allosensitization is the process by which an individual develops antibodies to foreign cell markers, such as HLA antigens on the surface of nearly all human cells. Common exposures include blood product transfusions (primarily platelets), use of allograft material during prior cardiac surgery, prior organ transplantation, and prior pregnancies [14, 15]. HLA antibodies increase the risk of a positive crossmatch, antibody-mediated rejection, and limit the poor of acceptable donors, thereby potentially increasing waitlist time. This condition may require desensitization, which is targeted therapy to both remove circulating antibodies and decrease antibody production. Therapeutic agents include intravenous immunoglobulin (IVIg), plasmapheresis, rituximab, and several proteasome inhibitors. The treatment and possible side effects are often managed in the ICU, both before and after transplant.

Nutritional and physical rehabilitation are crucial prior to heart transplantation. Many candidates are malnourished and deconditioned from weeks to months of inadequate caloric intake and high metabolic demand associated with heart failure. Furthermore, decreased exercise tolerance and inactivity lead to muscle wasting and deconditioning. Patients with chronic heart failure, especially those admitted to the cardiac ICU, should receive early and frequent physical and occupational therapy to limit pretransplant loss of mobility, muscle strength, and proficiency with activities of daily living.

50.5 Donor Evaluation

Organ donation is a highly regulated process managed by the United Network of Organ Sharing (UNOS). When a donor is identified, a regional organ procurement organization (OPO) will perform a comprehensive evaluation prior to presenting the data to potential recipients. The investigation is similar in many ways to the previously discussed transplant candidate evaluation. Key elements of the donor evaluation include patient demographics (age, gender, weight, height), donor blood typing, past medical history and current medications, mechanism of death, need for cardiopulmonary resuscitation (CPR), current medical support at the donor hospital, HLA typing, infectious status, and current cardiovascular health (vital signs, ventricular function, and heart rhythm).

The first criterion for matching with a potential organ offer is the location of the donor. The goal ischemic time for heart transplantation is less than 4 hours from the time of donor aortic cross clamp to the time cardiac blood flow is restored in the recipient. Ischemic time beyond 4 hours is associated with decreased survival [1]. Donor OR time, air and ground travel time, and recipient implantation time are all factors impacting the organ ischemic time. The second criterion is blood type. Donor organs are only given to potential recipients with a matching blood type. The lone exception to this rule is when infants are listed for an ABO-incompatible transplant. After matching for location and blood type, the donor organ is offered to a unique list of patients based on the weight of the donor and the listing weight range of the recipient.

The next phase of the donor evaluation revolves around the mechanism of death and resuscitative measures. Donors frequently have a history of CPR. An ideal donor has no history of cardiac arrest, but CPR and cardiac arrest do not preclude a person from organ donation. Downtrending cardiac enzymes such as troponin-I and normal systolic ventricular function on echocardiogram (ECHO) are reassuring signs that the heart is recovering after the initial insult and is likely a suitable donor organ. When assessing ventricular function on ECHO, the donor should be on minimal inotropic agents as they can falsely elevate the systolic ejection fraction. Donors requiring high levels of inotropic support are generally avoided unless the recipient is not expected to survive beyond the next few days. Conversely, donors frequently require vasopressors to maintain an adequate blood pressure, such as vasopressin, norepinephrine, and thyroxine. Brain death is the final common pathway, resulting in loss of many neurohormonal and cardiovascular regulatory functions. Vasopressors are necessary to maintain stable cardiovascular function until the time of organ procurement.

Cardiac function is assessed using standard diagnostic modalities. An electrocardiogram (EKG) is obtained to assess the baseline heart rhythm and intervals. Patients with brain death commonly exhibit a prolonged QT interval, which is a product of the current physiologic state and should not be used to decline the offer [16]. Left ventricular systolic function, as measured on ECHO, should be normal (greater than 50–55%) with normal intracardiac anatomy and no significant valvar regurgitation. If necessary, a cardiac catheterization can be performed to evaluate for coronary artery disease in older donors (>35 years old). These donors are typically avoided in pediatrics due to an increased risk for

coronary allograft vasculopathy (CAV) and decreased long-term survival [17, 18].

Aspects of the donor medical history are also important considerations. Patients with incurable metabolic or genetic conditions that impact the heart are not acceptable donors if the condition will impact the health of the potential donor. Although not a common issue in pediatric heart transplantation, donor substance abuse generally makes one unsuitable for heart transplantation due to the impact on coronary artery health. Donor tobacco use has been associated with increased rejection and decreased survival in a rat model [19] and is generally a contraindication to donation. The same can be said for alcohol and recreational drug use when evaluating adult donors for adolescent recipients, although recent data show no increased recipient mortality after receiving a donor with a significant history of alcohol abuse [20].

Finally, recipient gender and donor-recipient gender matching have been shown to impact survival in both the adult and pediatric heart transplant populations. In general, males have demonstrated improved posttransplant survival compared to females [21, 22]. This curious finding is likely related to many factors, including hormonal variances and donor-recipient size matching [21]. Gender-matched males have the best long-term survival, followed by gender-mismatched males, with gender-matched and gender-mismatched females showing similar survival [21, 22]. A more recent study by Kemna and colleagues [23] of 5795 pediatric heart transplants reported increased allograft loss and decreased overall survival in only female gender-mismatched transplant, while the current ISHLT registry report showed no difference in survival based on gender matching [1]. With slight differences in survival and conflicting data, donor-recipient gender matching does not impact our decision making when evaluating a potential donor.

50.6 Surgical Procedures

There are several factors contributing to the complexity of cardiac transplantation in patients with congenital heart disease, including:

1. The high incidence of anatomical abnormalities
   (a) Anomalous systemic and/or pulmonary venous return
   (b) Dextrocardia with or without situs inversus
   (c) Malposition of the great arteries
2. Small size
   (a) Resulting in significant size mismatch between the donor organ and the recipient
3. Previous operations
   (a) Altered anatomy
   (b) Abnormal circulatory physiology (i.e., aortopulmonary collaterals)
   (c) Increase risk of bleeding

Therefore, it is crucial to clearly delineate the patient's cardiac anatomy at the time of transplantation to identify special needs and adequately plan the surgical procedure. This includes coordination with the procurement team to ensure harvesting of appropriate donor tissue to allow for adequate reconstruction and limiting donor ischemic time.

50.6.1 Recipient Cardiectomy

The recipient cardiectomy is performed under cardiopulmonary bypass with bicaval cannulation and an LV vent, at a temperature of 28–32 °C. After aortic clamping, our preference is to transect the SVC and then the IVC, leaving a small cuff of atrium attached to each cava (preserving the length). The aorta and pulmonary arteries are then divided proximally. Finally, the left atrium is transected, leaving a generous cuff of atrium attached to the pulmonary veins. If the biatrial technique is being utilized, then a segment of the right atrium is left connected to the superior and inferior cava.

50.6.2 Implantation

At The Children's Hospital of Pittsburgh, we are utilizing the bicaval technique as our procedure of choice in all patients, irrespective of their age and size (Fig. 50.1). This technique minimizes atrial suture lines and provides more normal atrial geometry. There is a lower incidence of postoperative arrhythmias and thrombus formation when compared to the biatrial technique (Fig. 50.2). It may also be associated with improved atrioventricular valve function and posttransplant survival.

50.6.2.1 Anomalous Systemic Venous Return [24]

When bilateral SVCs are present (without a connecting vein), our preference is to obtain the full length of the donor's SVC and the innominate vein to perform an end-to-end anastomosis between the recipient's left-sided vena cava (LSVC) and the donor's innominate vein. If the LSVC drains into the coronary sinus, then another alternative is to preserve the

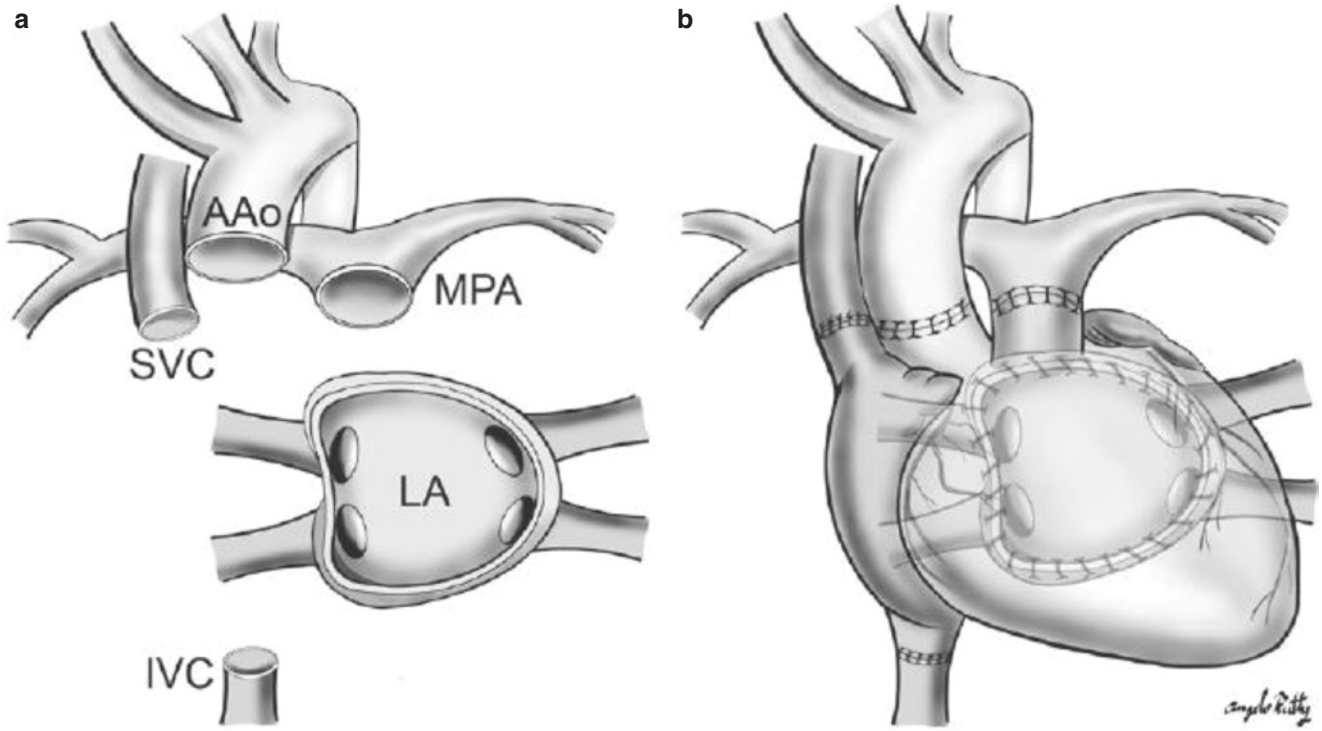

Fig. 50.1 Bicaval technique. (**a**) The recipient cardiectomy has been performed; note the left atrial (LA) cuff and the transected ends of the superior vena cava (SVC), inferior vena cava (IVC), ascending aorta (AAo), and main pulmonary artery (MPA). (**b**) The donor organ has been sutured in place; all anastomoses are performed with a running nonabsorbable suture except for the SVC suture line, where interrupted sutures are used to prevent the development of late stenosis (especially important in neonates and infants)

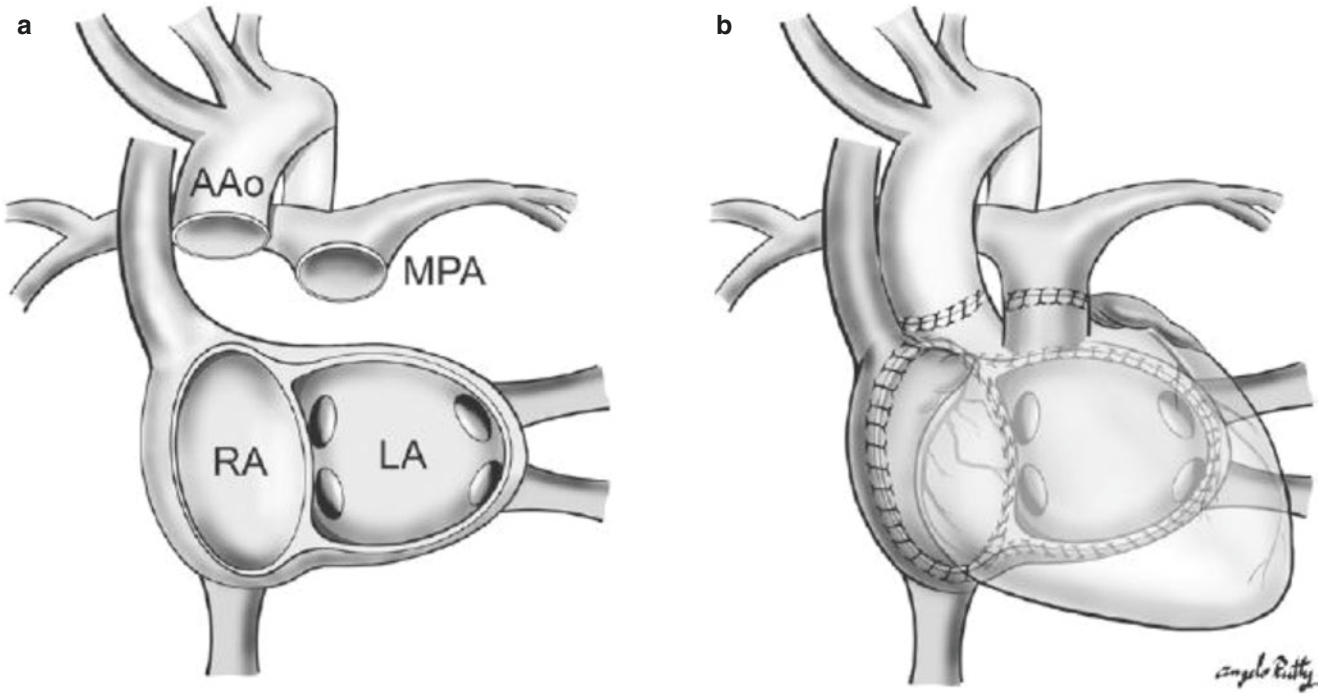

Fig. 50.2 Biatrial technique. (**a**) The recipient cardiectomy has been performed; note the left atrial (LA) and right atrial (RA) cuffs and the transected ends of the ascending aorta (AAo) and main pulmonary artery (MPA). (**b**) The donor organ has been sutured in place; all anastomoses are performed with a running nonabsorbable suture

coronary sinus during the cardiectomy and perform a biatrial cardiac anastomosis, leaving the coronary sinus draining into the right atrium. If a connecting vein is present, the LSVC can be simply ligated.

When an LSVC drains to the roof of the left atrium, an atrial septotomy can be created within the right atrium with creation of an intra-atrial baffle along the roof of the left atrium above the pulmonary veins. Alternatively, this baffle can also be placed inferiorly to join the right atrium at the coronary sinus.

50.6.2.2 Dextrocardia with Situs Solitus

In patients with dextrocardia and normal systemic venous return, the only modification we utilize is the release of the left side of the pericardium in order to allow the apex of the heart to protrude into the left hemithorax.

50.6.2.3 Dextrocardia with Situs Inversus

For these patients, our approach has been to resect the interatrial septum and reroute the SVC and IVC flow to the right side using atrial flaps as tunnels. Cardiac transplantation is then performed using the biatrial technique.

50.6.2.4 Anomalous Pulmonary Venous Return

In patients with total anomalous pulmonary venous return, we first proceed with a standard intracardiac repair, connecting the pulmonary venous confluence to the left atrium, followed by cardiac transplantation.

50.6.2.5 Hypoplastic Left Heart Syndrome

Cardiac transplantation in neonates and infants with hypoplastic left heart syndrome involves one extra step, the reconstruction of the hypoplastic aortic arch. Therefore, during the procurement, it is important to harvest as much of the donor aorta as possible.

50.6.2.6 Hybrid Single-Ventricle Palliation

In addition to cardiac replacement, patients who have undergone a hybrid approach (Fig. 50.3) for stage one palliation will require (1) pulmonary debanding with possible pulmonary artery reconstruction, (2) ductal stent removal, and (3) aortic arch reconstruction [25]. The aortic reconstruction can be performed with end-to-end donor descending thoracic aortic anastomosis (Fig. 50.4) with brachiocephalic "island" vessel reconstruction or arch augmentation using donor aorta.

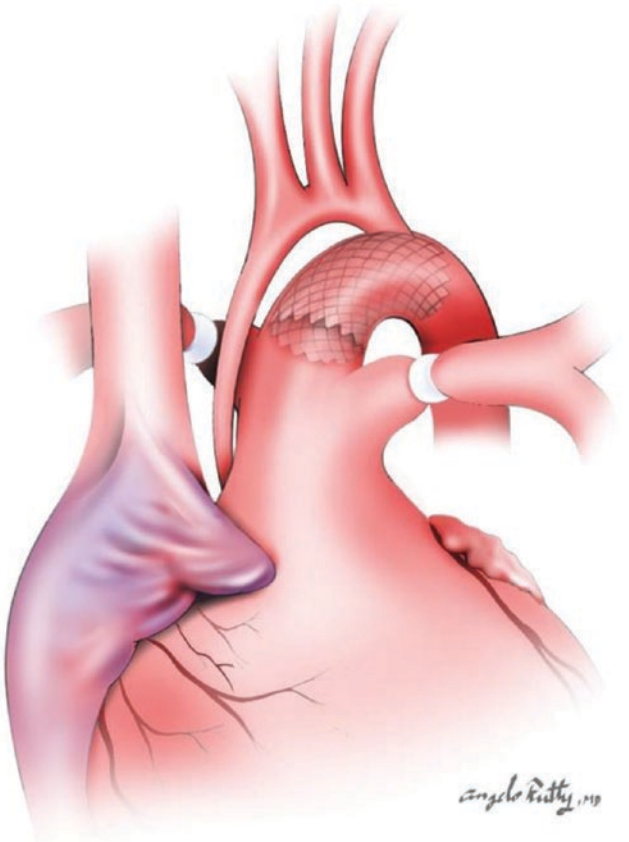

Fig. 50.3 Hypoplastic left heart syndrome with hybrid palliation including bilateral PA banding and ductal stenting

50.7 Postoperative Issues

The first few days after heart transplantation are crucial to the long-term health of both the graft and patient. The donor heart suffers a significant ischemic injury in the time from procurement to reperfusion. Careful planning and efficient surgical technique are necessary to ensure the organ ischemic time is as low as possible, preferably under 4 hours. Nevertheless, there will always be some degree of ventricular dysfunction after transplant due to the unavoidable ischemic injury. Systolic function typically recovers within the first few days after transplant.

50.7.1 Inotropic Agents

Use of inotropic agents in the immediate postoperative period is standard of care. Much like the preoperative period, the

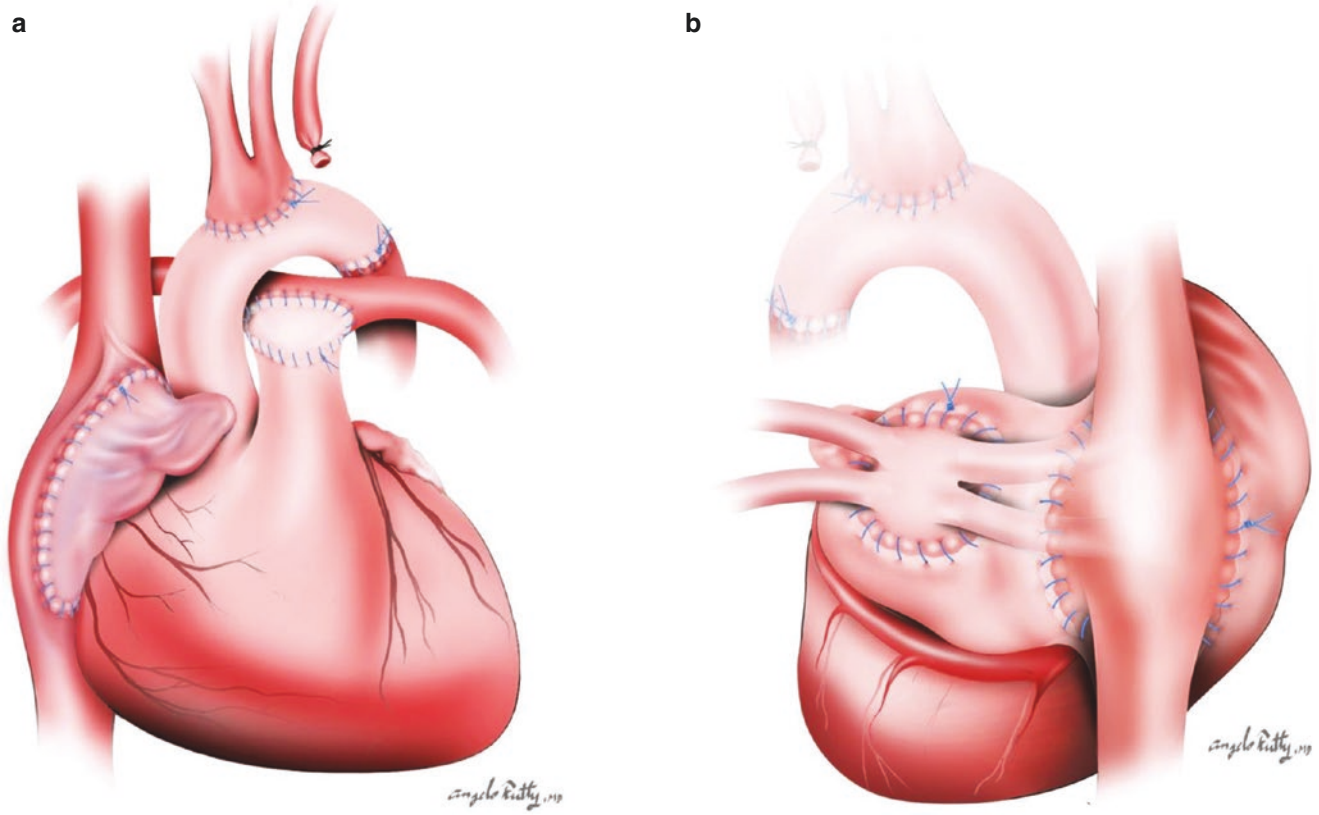

Fig. 50.4 (**a**) Orthotopic heart transplant in HLHS after hybrid showing (1) bi-atrial connection, (2) aortic anastomosis with brachiocephalic "island" with ligated left subclavian artery, and (3) pericardial patch augmentation of the pulmonary artery. (**b**) Completed biatrial connection (posterior view)

specific inotrope used depends of the clinical needs of the patient and the practices of the intensive care unit. Milrinone is used most commonly for its positive inotropic, lusitropic, and vasodilatory properties (especially pulmonary vascular vasodilatation), all while having low anti-arrhythmic potential. Patients return from the OR on epinephrine to maintain adequate blood pressure, in addition to providing inotropic support. Epinephrine is weaned off in the first 1–3 days, while milrinone is weaned more slowly over the first 3–5 days. Milrinone's ability to induce myocardial relaxation is unique and beneficial in the postoperative period since diastolic dysfunction may last for weeks after heart transplantation.

50.7.2 Systemic Hypertension

Attention to blood pressure is crucial to maintain adequate coronary, cerebral, and end-organ perfusion pressure after transplantation. Hypotension is seen commonly in this patient population due to graft dysfunction and vasoplegia. Catecholamine-resistant hypotension and low systemic vascular resistance can lead to end-organ hypoperfusion, even in the setting of normal to high cardiac output. This clinical scenario to thought be to secondary to cytokine upregulation and increased nitric oxide production. Reported risk factors in adults include low preoperative left ventricular ejection fraction, mechanical circulatory support, previous blood transfusions, prolonged cardiopulmonary bypass time, and use of ACE inhibitors. Treatment includes fluid resuscitation, catecholamines (i.e., norepinephrine and epinephrine), and other agents such as vasopressin and methylene blue. Prompt recognition and initiation of therapy will help mitigate morbidity [26–28]. On the other end of spectrum, hypertension is equally common for a multitude of reasons. Oversized donor hearts, intra- and postoperative use of corticosteroids, and pain may all lead to elevated blood pressure. Intravenous calcium channel blockers such as nicardipine and sodium nitroprusside are used to acute treat hypertension. Oral agents such as amlodipine or a beta-blocker may be used as long-term therapies.

50.7.3 Pulmonary Vascular Resistance

Elevated pulmonary vascular resistance must be aggressively managed postoperatively. The right ventricle of the donor heart is presumably accustomed to normal pulmonary vascu-

lar hemodynamics. Placing the heart behind significantly elevated PVR will lead to acute right heart failure. Inhaled nitric oxide (iNO) is started intra-operatively for pulmonary vasodilatation when there is known elevation in PVR. Patients may come to transplant already on oral agents such as sildenafil. Oral agents may be held while on iNO and restarted after extubation and weaning of iNO. Sedation, oxygen, hyperventilation, and milrinone may be used for right heart support and pulmonary vasodilatation. In refractory cases, IV prostacyclins or use of a right-sided VAD may be required.

50.7.4 Cardiac Rate and Rhythm

Arrhythmias also complicate the postoperative period. Sinus node dysfunction may lead to sinus bradycardia. Newly transplanted hearts cannot tolerate low heart rates for age due to their limited ability to increase stroke volume. Ischemic injury to the myocardium reduces compliance and diastolic filling. The heart is dependent on increased heart rates to increase cardiac output when needed. Atrial pacing is often used for transient sinus node dysfunction after transplant. Our unit typically paces infant recipients at 140 beats per minute and teenagers around 100 beats per minute in the immediate postoperative period to ensure adequate cardiac output. Pacing is weaned in the first few days as the sinus node recovers. Isoproterenol, a potent chronotrope and inotrope, is another option. The donor heart can respond to sympathomimetic agents despite its recent denervation. Atrial and ventricular ectopy are common secondary to ischemic injury and electrolyte abnormalities and respond to electrolyte replacement.

50.7.5 Primary Graft Failure

Primary graft failure (PGF) is a severe and potentially fatal complication of transplantation. The definition varies throughout the literature, but commonly cited adult criteria include an LV ejection fraction <40%, significantly elevated intracardiac pressures, use of high-dose inotropic agents, and mechanical circulatory supports [29]. PGF manifests in the first 24 hours after surgery, and not always in the same manner. Some patients cannot wean from cardiopulmonary bypass, necessitating ongoing mechanical circulatory support in the ICU. Other have preserved ventricular function initially, only to develop progressive ventricular dysfunction in the ensuing hours. Inotropic agents and mechanical circulatory support improve cardiac output and allow myocardial rest while the recently transplanted heart recovers from an ischemia-reperfusion injury or an acute immunologic insult [29]. Myocardial recovery, if it is to happen, usually occurs within the first 72 hours. If recovery isn't possible, retransplantation may be an option but has decreased survival when performed within the first year after transplant [30].

50.7.6 Respiratory Support

Need for prolonged mechanical ventilation may occur, especially in critically ill patients and those with significant deconditioning of the respiratory muscles. Anatomically, cardiomegaly may cause bronchomalacia of the left main stem bronchus, resulting in alveolar derecruitment and the need for prolonged intubation for positive airway pressure. Injury to the left phrenic nerve is possible during surgery, leading to a paralyzed left diaphragm and prolonged intubation. This complication is typically tolerated in older children and adolescents, but younger and smaller patients may require diaphragmatic plication to successfully wean of the ventilator.

50.7.7 Immunosuppression

Immunosuppression begins in the operating room with high-dose methylprednisolone (10–20 mg/kg). Daily steroids are no longer the standard of care, with many programs now managing patients on a dual drug regimen. Thymoglobulin is commonly used for induction therapy within 24 hours after transplant. This antihuman thymocyte immunoglobulin is administered over 5 days for a total dose of 7.5 mg/kg, along with a low, tapering dose of methylprednisolone as a premedication. Additional induction options include basiliximab, an interleukin-2 receptor antagonist that inhibits T-cell proliferation, and alemtuzumab, an anti-CD52 T-cell and B-cell monoclonal antibody. Tacrolimus, a calcineurin inhibitor that suppresses T-cell proliferation, is the current primary immunosuppressant. It is ten times more potent and carries a more tolerable side effects profile than its predecessor, cyclosporine. Cyclosporine is still used for patient with tacrolimus intolerance. Tacrolimus is started on the second or third postoperative day with return of normal intestinal function, as well as stable renal function. Secondary immunosuppressants include mycophenolate mofetil, azathioprine, rapamycin, and everolimus. Patients with an uncomplicated postoperative course are typically on two medications within the first week posttransplant. Acute kidney injury, poor intestinal absorption, and serious infections may delay the initiation or titration of posttransplant immunosuppression.

50.7.8 Acute Rejection

Hyperacute rejection is extremely uncommon due to appropriate blood-group matching and avoidance of HLA antigens

against which the donor has existing antibody. Acute graft rejection may be seen early after transplant. There are two classes of rejection – cellular and antibody mediated. During acute cellular rejection (ACR), lymphocytes infiltrate the myocardium causing cell damage, edema, hemorrhage, or necrosis. This process is manifested clinically via tachycardia, decreased systolic graft function on echocardiogram, and low voltages on EKG. Antibody-mediated rejection (AMR) occurs when donor-specific HLA antibody attacks the transplanted heart, resulting in endothelial dysfunction thrombosis and myocyte damage. The gold standard for diagnosing either type of rejection is an endomyocardial biopsy. Histologic and pathologic criteria are used to determine the degree of rejection based on ACR and AMR grading guidelines set forth by the International Society of Heart and Lung Transplantation. The first year after transplant is considered the highest risk for rejection, especially for older children and adolescents. Routine surveillance biopsies are performed every few weeks to months in the first year to monitor for subclinical rejection. ACR is treated with 3–5 days of oral or intravenous steroids, depending on hemodynamic stability. AMR is treated with plasmapheresis, IVIg, rituximab, and proteasome inhibitors.

50.7.9 Renal Function

Renal perfusion can be compromised after transplant secondary to cardiopulmonary bypass, decreased cardiac output, hypotension, and immunosuppression. The effects are usually transient and respond to intravenous diuretics, vasopressors, inotropes, and tight control of immunosuppression levels. Profound acute kidney injury may require hemodialysis. Careful attention must always be paid to the renal function after transplant. Long-term calcineurin inhibitor use leads to decreased glomerular filtration rate, and long-term survivors frequently develop chronic kidney disease that may require dialysis or even renal transplantation. Gastrointestinal complications are common. H2 blockers or proton pump inhibitors are administered postoperatively to prevent gastric ulcers secondary to high-dose steroid use. Therapy may be continued long term for preexisting GERD, which is commonly seen in patients with chronic heart failure. Mycophenolate mofetil (MMF) may cause GI side effects such as abdominal pain, nausea, and diarrhea. Patients who cannot tolerate MMF are switched to an enteric preparation of mycophenolic acid or azathioprine. Neurologic complications are present as well, including stroke and posterior reversible encephalopathy syndrome (PRES). PRES is a transient neurovascular condition that results in headache, hypertension, altered mental status, and seizure [31]. Calcineurin inhibitors such as tacrolimus can induce cerebral vasogenic edema, and symptoms may arise shortly after initiation, especially if there is a rapid rise in drug levels. The condition is reversible through tight blood pressure control and temporary cessation of calcineurin inhibitor therapy.

50.7.10 Infection Prophylaxis

New heart transplant recipients are at high risk for infections secondary to their immunocompromised state. The necessity of all indwelling lines, drains, and catheters is discussed daily on ICU rounds and removed as soon as possible. Long-term indwelling lines are typically replaced during surgery. In our institution, perioperative bacterial prophylaxis is achieved with cefazolin for patients over 1 month of age and cefepime for neonates. The first dose is given prior to chest wall incision and continued for 48 hours. Patients allergic to cefazolin may receive oxacillin, vancomycin, or clindamycin. Cefepime or vancomycin is used with a history of VAD, ECMO, recent sternotomy, open chest, or mediastinal intervention after transplantation. MRSA-positive patient are covered with clindamycin or vancomycin. Ganciclovir and valganciclovir are used for cytomegalovirus (CMV) prophylaxis when there is a recipient-donor mismatch. Acyclovir is used for HSV-positive recipients. We do use prophylactic antiviral therapy for EBV-positive recipients. *Pneumocystis jirovecii* prophylaxis is achieved with trimethoprim-sulfamethoxazole (TMP-SMX) three times weekly. TMP-SMX is given daily when the donor is positive for *Toxoplasma gondii* IgM or IgG. Nystatin is the first choice for most patients for antifungal prophylaxis. High-risk patients are treated with fluconazole or caspofungin. Azole antifungals significantly impair calcineurin-inhibitor metabolism, and it is often necessary to reduce dosing by 75–90% to avoid a toxic drug level.

50.8 Medium- and Long-Term Considerations

Heart transplantation is not a cure for chronic heart failure. In fact, it carries many new and significant complications that are beyond the scope of this chapter. Several of those complications may be managed in the ICU regardless of the time elapsed from transplant.

50.8.1 Allograft Rejection

Rejection of the transplanted heart is a life-long concern. The first year after transplant is the period of greatest risk for

rejection. We have seen a reduction in incidence recently, likely secondary to nearly universal use of tacrolimus over cyclosporine [1]. The percentage of patients with treated rejection in the first year fell from 27% (7/2004–2008) to 15% (2009–6/2016) according to the 2017 annual report of the ISHLT [1]. Older children and adolescents continue to carry the highest risk for early rejection. Patients surviving an episode of treated first year moderate-to-severe acute cellular rejection have a 21-fold risk of developing further episodes of similar rejection, while those without rejection in the first year are at low risk of developing late rejection [32]. Regardless of the reduced incidence, early rejection continues to have a significant impact on mortality. Six percent (6%) of deaths during the first month posttransplant are attributed to acute rejection [1]. The percentage rises to a peak of 16.9% between years 1–3 before falling to 4.9% beyond the tenth year posttransplant.

Rejection must be treated aggressively when suspected. High-dose intravenous methylprednisolone (10–15 mg/kg) is the mainstay of therapy for acute cellular rejection. The treatment course can be 3–5 days depending on the degree of rejection and hemodynamic compromise. Asymptomatic patients lacking hemodynamic compromise may be considered for outpatient therapy with a 3- to 5-day course of oral steroids. Thymoglobulin can be administered for rejection refractory to steroids. Antibody-mediated rejection is treated in several ways. Patients with donor-specific antibodies and equivocal biopsy results can be treated with a monthly dose of IVIg (1 g/kg/dose) for 6 months and a higher intensity rejection surveillance protocol. Treatment must be more aggressive in the presence of clear pathology and graft dysfunction. Plasmapheresis is often used to remove circulating antibodies. Treatment cycles include several successive or intermittent days of pheresis to allow antibody migration out of tissues and into the blood stream for removal. A small number of pharmacologic treatment options exist that target the antibody-producing cell line. Rituximab, a CD20 monoclonal antibody, is used to eliminate immature B cells. Proteasome inhibitors (bortezomib, carfilzomib) target plasma cells, the terminally differentiated B-cell responsible for antibody production. AMR therapies, while effective, carry many potential adverse drug reactions that can seriously impact treatment tolerability.

50.8.2 Coronary Allograft Vasculopathy

Coronary allograft vasculopathy (CAV) is a unique form of atherosclerosis found after heart transplantation. The mechanism of injury is thought to be a combination of an alloimmune response as well as nonimmune factors. The alloimmune nature of the disease is why CAV may also be called chronic allograft rejection. Concentric intimal proliferation of donor smooth muscle cells and recipient mononuclear cell infiltrate result in decreased luminal diameter [33]. Progressive obstruction of proximal coronary arteries and distal pruning of small branches results in decreased myocardial perfusion, diastolic dysfunction from myocardial fibrosis, and ultimately graft failure. This process evolves over months to years. CAV remains the leading cause of death more than 3 years posttransplant, second only to graft failure in the most recent report of the ISHLT registry [1]. Only 43% of pediatric heart transplant recipients are free from CAV at 18 years posttransplant, with greater risk of development seen with increased age at transplant [1]. Adult data has shown a decrease in the prevalence of CAV over time. Increased understanding of the disease process, better recognition and treatment of antibody-mediated rejection, statin use, CMV prophylaxis, and immunosuppressive agents such as mycophenolate mofetil and mammalian target of rapamycin inhibitors (sirolimus) have all contributed to the decreased incidence of CAV over past 30 years [34]. A similar reduction has been seen in pediatrics [1].

CAV is diagnosed by coronary angiography performed during routine surveillance cardiac catheterizations and biopsies. Our center performs coronary angiography 1 year posttransplant and then every other year. The frequency of angiography increases to yearly once CAV is diagnosed, or even more frequently depending on the severity of disease and rate of progression. Statin therapy, daily aspirin, and sirolimus are added to the treatment regimen upon diagnosis. Unfortunately, CAV is often progressive, at times quite rapidly. The only definitive treatment is retransplantation, which itself carries increased mortality compared to primary transplantation [1]. Hospital admissions are common with advanced CAV, frequently to the cardiac ICU for treatment of heart failure and arrhythmias. Patients are at high risk for sudden death and may require ICD placement. Even with successful percutaneous interventions, the risk of death 1 year after intervention is 39% [35]. At this point, the safest plan is inpatient therapy until retransplantation.

50.8.3 Posttransplant Lymphoproliferative Disorder

Posttransplant lymphoproliferative disorder (PTLD) is another feared posttransplant complication. PTLD is mostly EBV-driven [36] and of B-cell lineage. The incidence is roughly 5% by 5 years posttransplant and 10% at 10 years posttransplant [1]. Treatment is frequently by protocol including cyclophosphamide, prednisone, and rituximab.

Immunosuppression is significantly reduced or stopped during chemotherapy, with frequent echocardiograms to monitor for graft dysfunction. The transplant team must then devise a new immunosuppression plan to prevent PTLD recurrence.

50.9 Outcomes

Waitlist mortality and posttransplant survival are two important discussion points in every heart transplant evaluation. Parents and older patients must know the potential complications, both before and after transplant, so they may make an informed decision regarding transplantation. In 2009, Almond and colleagues [37] analyzed waiting list mortality for 3098 pediatric patients using the U.S. Scientific Registry of Transplant Recipients. Waiting list mortality was 17%, with ECMO, ventilator support, CHD, dialysis, status 1A listing, and nonwhite race as independent risk factors for mortality. More recent investigations report a waiting list mortality of 9.6% [38], with race no longer impacting mortality [39]. Status 2 listing carries an extremely low waitlist mortality [40]. Increased use of ventricular assist devices has had a profound impact on waitlist mortality. There has been a 50% reduction in waiting mortality over the first 15 years of this century [41, 42]. Infants under 10 kg continue to carry an elevated risk of mortality [42]. ABO incompatible transplantation in infants is an increasingly used practice which has led to shorter waitlist times [43]. Timing of listing is also important in the pediatric population. Listing an adolescent in the year after their 18th birthday as opposed to the year before leads to an 8.5-month increase in waitlist time, but no increase in waitlist mortality [44].

Overall survival after pediatric heart transplantation is on the rise. Five-year survival has increased from 58% in the 1980s to 81% currently. Infants have the highest long-term survival with a median of 22 years, while adolescents have the lowest median survival at 13 years. Analyzing the entire population, survival after pediatric HT is 84% at 1 year, 79% at 3 years, 74% at 5 years, 62% at 10 years, 52% at 15 years, 43% at 20 years, and 36% at 25 years. All age groups have a median survival of over 15 years if they survive the first year after transplant [1]. The indication for transplant also impacts survival. Transplantation for dilated cardiomyopathy is associated with increased survival compared to CHD in all ages except for recipients aged 6–10 years. Survival remains decreased after retransplantation, especially when necessary in the first year after transplant, and should be avoided within the first 6 months when possible [30]. While nonwhite race remains associated with lower survival [45], female sex no longer carries a survival disadvantage compared to male sex [1].

50.10 Conclusions and Future Directions

Heart transplantation remains the final intervention for end-stage heart failure. We have witnessed significant advancements in care and survival over the past 50 years. Both children and adolescents are surviving longer. The quality of those years has increased as well due to better recognition and management of comorbidities. The invention of the ventricular assist device had a profound impact on transplant medicine. Patients who would have historically waited for months in the hospital can now go home, participate in cardiac rehabilitation, and even attend school. Advancements in adult continuous flow VAD technology will allow the pediatric transplant community to use these devices in progressively smaller patients with a more tolerable side effect profile. Despite recent advances, heart transplantation remains a palliative intervention. Continued survival requires additional transplants later in life. Complications often accumulate in the form of rejection, kidney dysfunction, medication side effects, and time-related deterioration of the transplanted heart. New and more tolerable immunosuppressants would be a welcome addition to our treatment armamentarium. A better understanding of how one's genetic code impacts response to specific medications and risk for rejection will allow us to design targeted treatment plans for each recipient. Finally, the greatest potential advancement lies in regenerative medicine. The transplant world would change dramatically if we were able to grow a heart identical to that of the potential candidate or create an allograft devoid of any identifying HLA or blood group information. While it seems like science fiction now, transplantation without the need for immunosuppression could soon become reality. Until that time, we will continue our pursuit of knowledge so that pediatric heart transplantation may one day provide children with the long and healthy life they all deserve.

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Chapter 51
Arrhythmias in the Intensive Care Unit

Christopher W. Follansbee, Gaurav Arora, and Lee Beerman

Abstract Recognition and management of disorders of cardiac rate and rhythm are key aspects of the care that must be provided to pediatric patients in the intensive care setting. In this chapter, we will discuss the use of the 12-lead ECG, rhythm strip, cardiac bedside monitor, and atrial electrograms in the general approach to the diagnosis of arrhythmias. Management of specific arrhythmias will then be reviewed.

Recognition and management of disorders of cardiac rate and rhythm are key aspects of the care that must be provided to pediatric patients in the intensive care setting. In this chapter, we will discuss the use of the 12-lead ECG, rhythm strip, cardiac bedside monitor, and atrial electrograms in the general approach to the diagnosis of arrhythmias. Management of specific arrhythmias will then be reviewed.

Arrhythmias may present a major threat to hemodynamic stability in a critically ill or postoperative cardiac patient. Cardiac output is compromised by extremes in rate and the loss of AV synchrony which prevents atrial augmentation of atrioventricular filling and output. Numerous factors in the cardiac surgical patient predispose to the development of arrhythmias, including myocardial dysfunction or ischemia, electrolyte abnormalities, hypoxia, a hyperadrenergic state with excess catecholamines (endogenous or therapeutic), recent or old scars in the myocardium, sutures, residual hemodynamic abnormalities following cardiac repair, pain, and anxiety [1, 2].

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51.1 Electrocardiogram

A full description of the 12-lead ECG is beyond the scope or purpose of this chapter, but certain features are important to stress as they may be helpful in identifying arrhythmias [3]. It is essential that any patient undergoing cardiac surgery have a preoperative electrocardiogram available to serve as a baseline. An early postoperative ECG with an associated atrial electrogram is mandatory for early recognition of ischemia, infarction, or new conduction abnormalities.

51.1.1 P Waves

The morphology of the P wave should be assessed to determine whether or not the origin is sinus. Sinus P waves will have a frontal plane axis of 0–90 degrees and should be positive in leads I, II, and AVF. An abnormal P-wave axis would indicate an ectopic focus, participation of the atria in a reentrant arrhythmia, cardiac malposition with dextro- or mesocardia, or heterotaxy syndromes with atrial isomerism or, in the case of transplant recipients, native versus transplanted sinus nodes.

51.1.2 Q Waves

Pediatric patients often have prominent Q waves in the inferior and lateral precordial leads due to the normal initial septal depolarization. As long as these Q waves are less than 0.04 s in duration they may be normal, even with an amplitude up to 7–8 mm. Underlying cardiac conditions, which result in abnormal size or location of Q waves, include congenitally corrected transposition of the great arteries, Wolff–Parkinson–White syndrome, myocardial infarction, and left ventricular hypertrophy, particularly in the setting of hypertrophic cardiomyopathy. New onset Q waves that are wider than 0.04 s may suggest an evolving myocardial infarction.

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51.1.3 QRS Morphology

The QRS complex in a postoperative patient should be compared to the preoperative sinus QRS morphology. If it is the same, the rhythm has to be supraventricular in origin; if it is wider or different from the sinus QRS, it is either ventricular in origin or supraventricular with aberrant conduction. The aberrant conduction may be related to abnormal conduction over the right or left bundle branches, or anterograde conduction over an accessory pathway. The QRS should be evaluated for axis deviation, hypertrophy, abnormal precordial R wave progression, or conduction abnormalities such as a bundle branch block pattern or preexcitation. A *right bundle branch block* (Fig. 51.1a) is frequently seen in patients who had surgical repair for tetralogy of Fallot and, less commonly, AV septal defect or ventricular septal defect. A *left anterior hemiblock* resulting in left axis deviation may be associated with a right bundle branch block in 25% of postoperative patients with tetralogy of Fallot [3]. Left axis deviation is seen preoperatively in certain congenital defects, most notably AV septal defect and tricuspid atresia. A *left bundle branch block* (Fig. 51.1b) pattern may be noted after surgery on the left ventricular outflow tract in patients with discrete or muscular subaortic stenosis. The example of left bundle branch block shown in Fig. 51.1b also shows the usual accompanying left axis deviation.

51.1.4 ST-T Waves

Nonspecific ST-T wave changes are commonly seen in any patient who has had open-heart surgery with the exposure of the epicardial surface to mechanical trauma, blood, fluid, or air. These changes may simple reflect transient pericardial or epimyocardial injury. Worrisome changes possibly indicating myocardial ischemia include focal ST elevations, particularly convex upward, or depressions, either horizontal or down slopping. A higher index of suspicion is required following surgical procedures which result in the manipulation of the coronary arteries such as arterial switch operation, Ross procedure, or aortic valve or root replacement. However, any open-heart procedure involving bypass has some intrinsic risk for air or particulate emboli into the coronary arteries.

51.2 Rhythm Strip

The rhythm strip, particularly one with multiple leads, used in conjunction with the 12-lead ECG is the essential tool utilized for the diagnosis of arrhythmias. The most important aspect of arrhythmia analysis is to identify the P waves, QRS complexes, and note the rate and morphology of each as well as the relationship of the P wave and QRS activity. P-wave morphology is analyzed to determine whether it is sinus or ectopic in origin. The QRS should be defined as narrow (or identical to the QRS noted in baseline sinus rhythm) or wide. A narrow QRS indicates a supraventricular, above the His bundle, origin of the impulse. On the other hand, a wide QRS has a broader differential diagnosis and may be due to a ventricular origin, a supraventricular beat that is conducted aberrantly through one of the bundle branches or anterograde conduction over an accessory pathway. The relationship of P and QRS waves will either be 1:1 association, intermittent association, or complete dissociation between atrial and ventricular activity.

Recognition of P waves presents the biggest challenge because of their relatively low amplitude and they may be "hidden" within the QRS complex or ST-T waves. P-wave detection can be enhanced by the use of the 12-lead ECG, a multilead rhythm strip, and atrial electrograms and by the administration of adenosine. Multiple lead analysis will often allow recognition of a P wave not seen in a standard single lead rhythm strip. An atrial electrogram can be obtained by using intraoperatively placed epicardial wires or by a transesophageal pacing lead (Fig. 51.2). Adenosine is extremely helpful unmasking an atrial tachyarrhythmia obscured by a rapid ventricular response by providing transient AV block (Fig. 51.3).

51.3 Atrial Electrograms

The proper use and understanding of atrial electrograms is extremely valuable in the care of critically ill patients with arrhythmias. Recognition of the relationship between atrial and ventricular activity allows for rapid and accurate diagnosis of almost all disturbances of rhythm and conduction.

Atrial electrograms can be obtained with an esophageal electrode or surgically placed wires, and can be either unipolar or bipolar recordings. Unipolar recordings have smaller atrial deflections, but allow for simultaneous display of surface leads, which is advantageous. Bipolar electrograms, on the other hand, have larger atrial deflections, but do not allow simultaneous display of a pure surface lead, which sometimes makes distinguishing atrial from ventricular activity difficult.

The esophagus sits directly posterior to the left atrium, so a specifically designed esophageal lead may be placed through the nose or mouth into the esophagus to record atrial activity [4]. Alternately, surgically placed atrial wires may be used. If two atrial wires are placed, either unipolar or bipolar electrograms can be recorded [5].

We recommend recording a 3-lead rhythm strip with Leads I, II, and V1. The atrial wire may be connected to

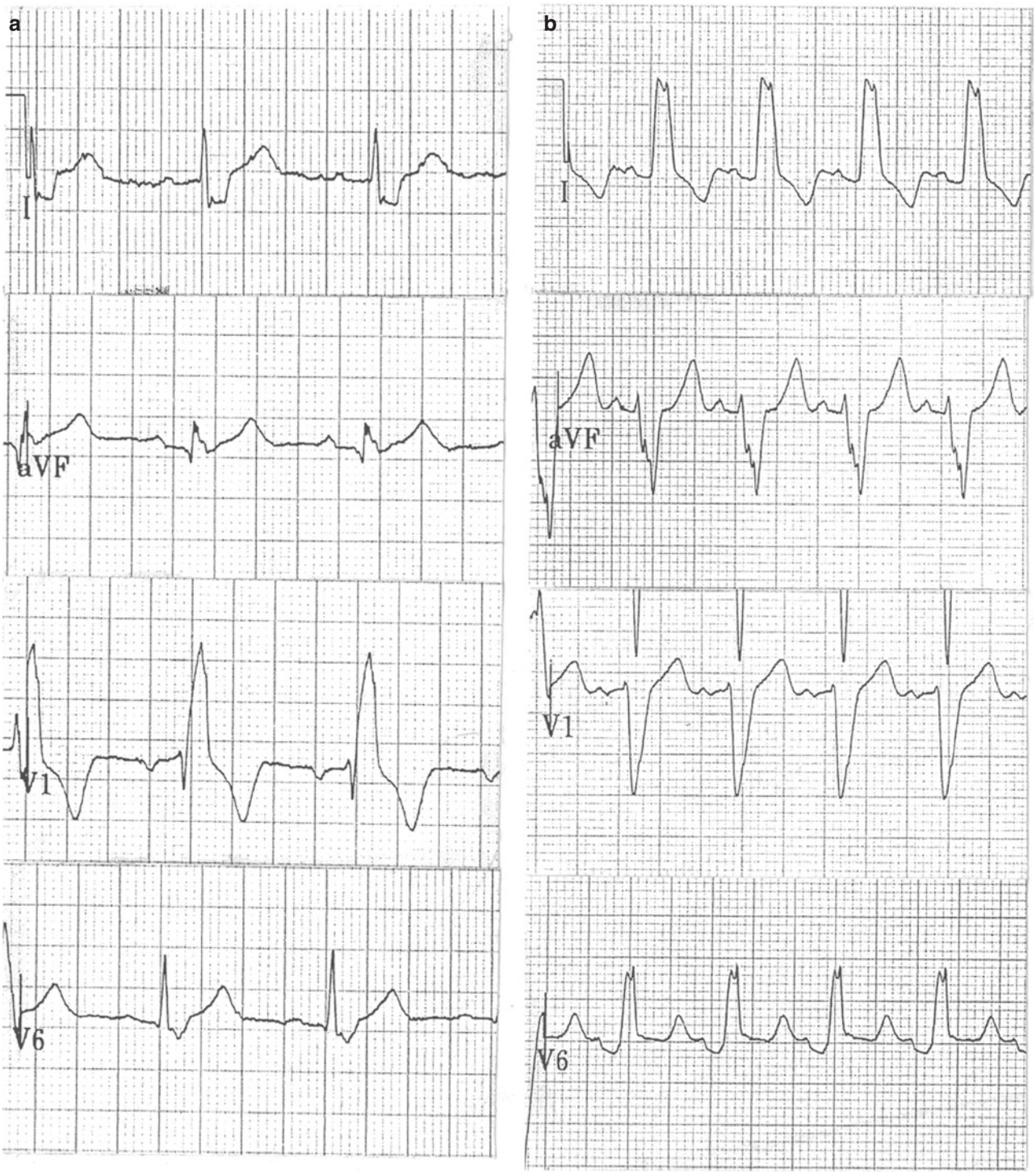

Fig. 51.1 (**a**, **b**) Right and left bundle branch block patterns. (**a**) Right bundle branch block (RBBB) pattern in a patient status postrepair of tetralogy of Fallot. Note the slurred R' in V1 and S wave in V6, (**b**) left bundle branch block pattern in a patient status postsurgical resection of subaortic stenosis. Note the slurred positive RR' wave in I and V6. There is also a left axis deviation manifested by the negative QRS in AVF

either V1 or the left arm lead, which will allow recording a unipolar atrial recording simultaneously with a pure surface Lead II (Fig. 51.4a). A bipolar atrial recording may be obtained by connecting one atrial wire to the right arm lead and the other atrial wire to the left arm ECG lead. Lead I will then record a bipolar atrial electrogram, with leads II and V1 demonstrating unipolar tracings (Fig. 51.4b). As mentioned above, with bipolar electrograms there is no pure

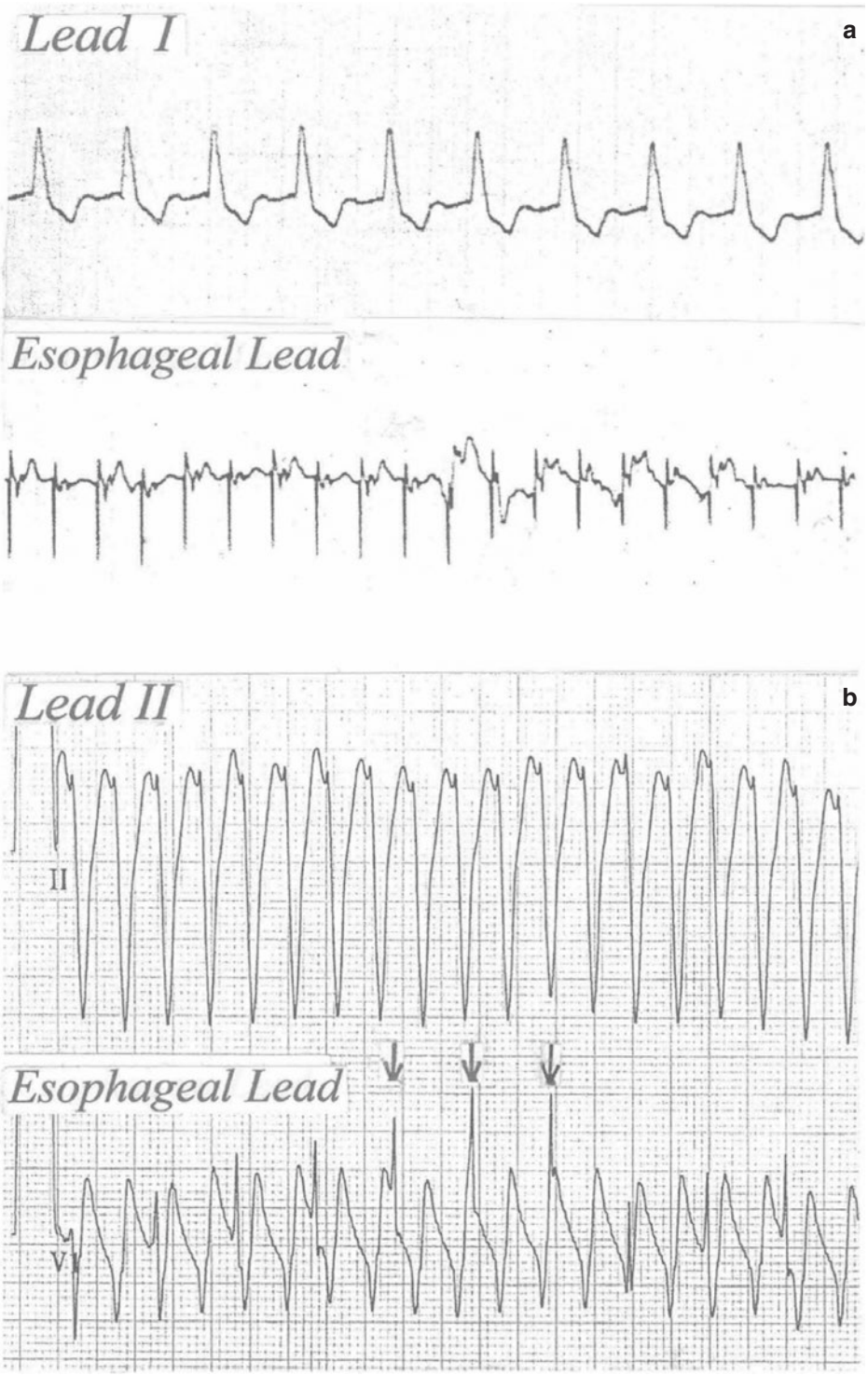

Fig. 51.2 (**a**, **b**) Use of esophageal atrial recording. (**a**) Surface lead I shows a tachycardia without evident P waves; the esophageal lead clearly shows the underlying rhythm is atrial tachycardia with 2:1 AV block, (**b**) surface lead II shows a wide QRS tachycardia without evident P waves; esophageal lead shows atrial activity (*arrows*) with VA dissociation indicative of ventricular tachycardia.

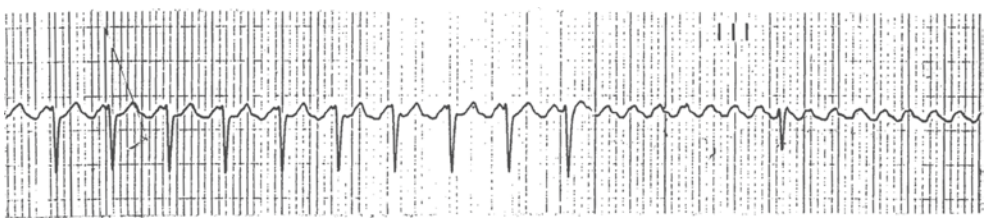

Fig. 51.3 Diagnostic use of adenosine. Adenosine given during a rapid supraventricular rhythm unmasks the underlying atrial flutter not evident before the adenosine induced AV block

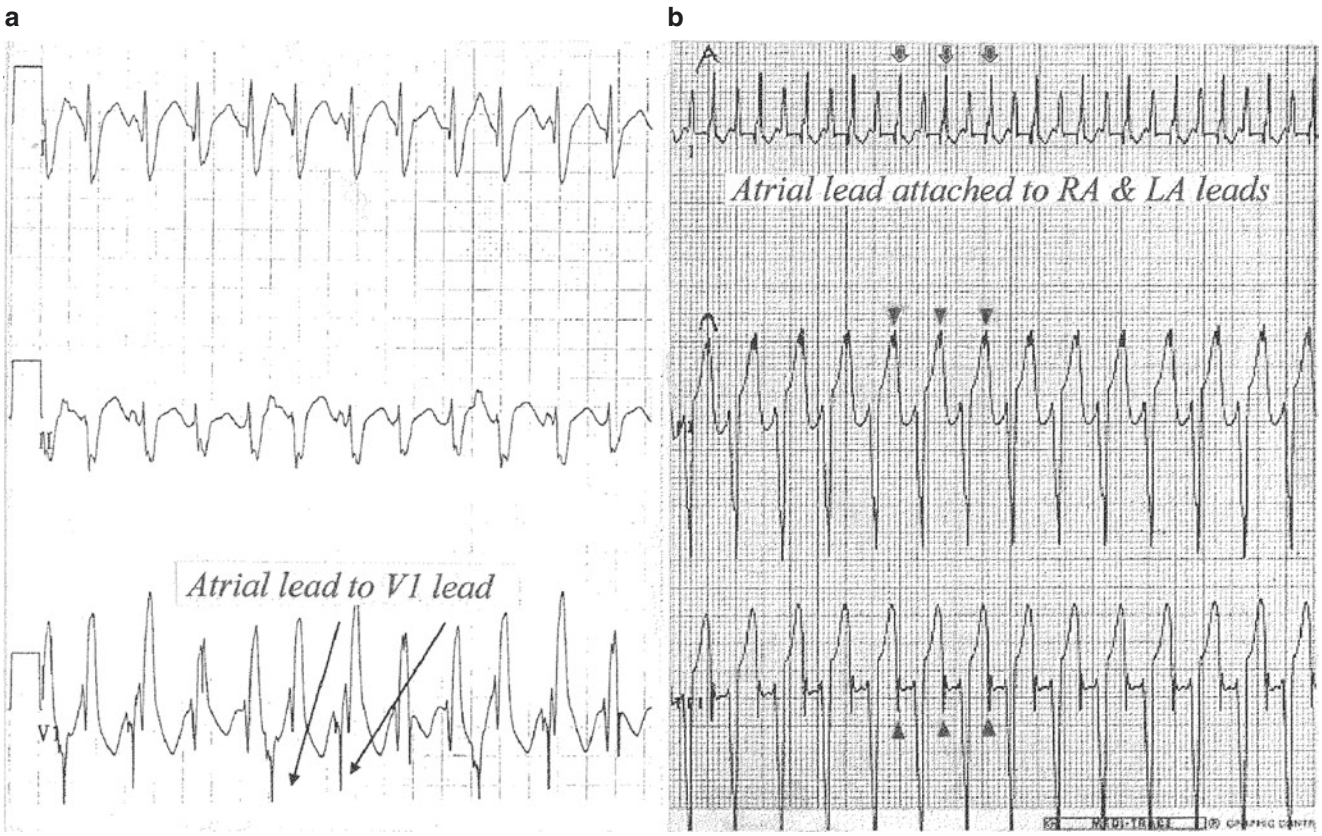

Fig. 51.4 (**a**, **b**) Atrial electrograms. (**a**) Unipolar atrial electrograms are obtained by connecting one atrial lead to V1 ECG cable in a patient with JET. *Arrows* show atrial activity confirming AV dissociation, (**b**) bipolar atrial electrograms are obtained by connecting one atrial lead to the right arm ECG cable and the other atrial lead to the left arm ECG cable. Lead I (*top*) shows bipolar atrial electrograms (*double arrows*) indicating rhythm is likely sinus tachycardia. Leads II and III below show unipolar atrial electrograms (*triangles*)

surface lead displayed. For that reason, we predominantly record unipolar atrial electrograms, or obtain both unipolar and bipolar tracings, in our clinical practice.

51.4 Mechanism of Arrhythmias

Almost all arrhythmias are due to one of two mechanisms, reentry or abnormal automaticity (sometimes referred to as ectopic) [6, 7]. Other mechanisms, such as triggered automaticity, are less common but may play a role in digitalis toxicity-associated arrhythmias or channelopathy-related ventricular arrhythmias. The characteristics of reentry and automatic arrhythmias are noted in Table 51.1. Reentrant arrhythmias typically have a paroxysmal occurrence, sudden onset and offset, and a relatively constant rate. They are effectively treated by overdrive pacing, cardioversion, and respond dramatically to adenosine if the reentrant loop involves the AV node. Conversely, automatic tachycardias tend to be incessant, demonstrate warm up and slow down, and have variable rates related to changes in autonomic tone. They are suppressed, but not terminated by overdrive pacing or cardioversion. Some ectopic foci are adenosine sensitive, but most ectopic rhythms are not directly affected by this drug. Review of the heart rate trend display on the bedside monitor is often valuable in determining the mechanism of an arrhythmia. A reentrant arrhythmia will display a box or rectangular type pattern with an abrupt onset, steady rate, and abrupt offset as opposed to automatic tachycardias that have a more gradual upward and downward heart rate slope (Fig. 51.5).

Table 51.1 Characteristics of arrhythmias

Reentry mechanism
1. Paroxysmal
2. Abrupt onset/offset
3. Constant rate
4. Pacing – induce/terminate
5. Cardioversion – very effective
Automatic mechanism
1. Warm up/cool down
2. Variable rate
3. May be incessant
4. Pacing – not effective
5. Cardioversion – not effective

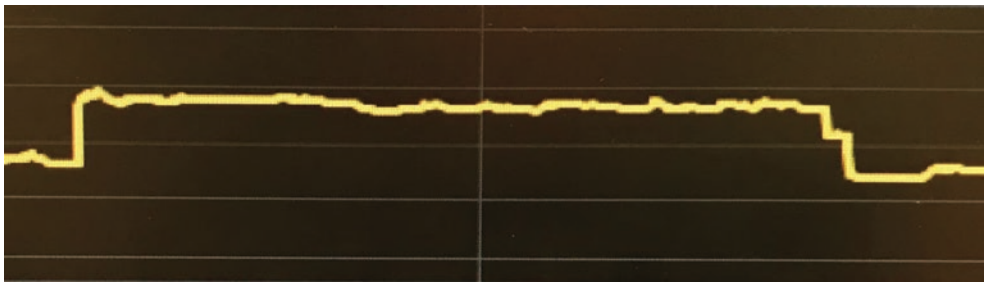

Fig. 51.5 Bedside monitor recording of an episode of reentrant tachycardia. Note the abrupt onset, steady state, and abrupt termination that forms a rectangular pattern

51.5 Classification and Management of Arrhythmias (Table 51.2)

51.5.1 Tachyarrhythmias

51.5.1.1 Supraventricular Arrhythmias

Atrial Arrhythmias

All of the rhythm disturbances in this category depend only on atrial tissue and are independent of AV node conduction.

Premature Atrial Complexes These are relatively common in the newborn and the young infant. They are frequently associated with aberrant conduction and can be differentiated from premature ventricular beats by identifying a preceding P wave (Fig. 51.6a, b). Intermittent pauses may be due to premature contractions that occur so early they are not conducted through the AV node, resulting in an apparent pause. If these nonconducted premature atrial beats occur in a bigeminal fashion, the rhythm can be difficult to distinguish from sinus bradycardia, but the diagnosis should be made by noting P waves on the ST-T wave segment.

Treatment: Premature atrial complexes do not require treatment as long as they do not precipitate runs of sustained tachycardia.

Atrial Ectopic Tachycardia (AET) This arrhythmia may present with incessant tachycardia leading to a cardiomyopathy. It may also occur as a transient postoperative phenomenon within the first several days of surgery. The hallmark of the diagnosis is an abnormal P-wave morphology, unless the ectopic focus arises from the high right atrium near the sinus node. The tachycardia displays a gradual warm up and slow down pattern (Fig. 51.7), and the rate varies with autonomic tone, stress, and exogenous catecholamines. A form of AET with multiple P-wave morphologies and short nonsustained bursts of tachycardia is called chaotic atrial rhythm or multifocal atrial tachycardia. This arrhythmia is most commonly seen in the newborn period or first few months of life.

Table 51.2 Classification of arrhythmias

Tachyarrhythmias
1. Supraventricular
(a) Atrial (independent of AV node)
(i) Premature atrial complexes
(ii) Atrial ectopic tachycardia
(iii) Atrial muscle reentry: classic atrial flutter, atrial fibrillation, intra-atrial muscle reentry
(b) Junctional (involving AV nodal tissue)
(i) Paroxysmal supraventricular tachycardia
(ii) Junctional ectopic tachycardia
2. Ventricular
(a) Ventricular ectopics
(b) Ventricular tachycardia
(c) Ventricular flutter and fibrillation
Bradyarrhythmias
1. Sinus node dysfunction
2. AV block

Treatment: AET is often difficult to treat as it responds only transiently to overdrive pacing and cardioversion. In the immediate postoperative period, it usually requires antiarrhythmic therapy with intravenous amiodarone or procainamide. Temporizing measures with AV nodal blocking agents (i.e., digoxin, beta blockers, or calcium channel blockers) may slow the ventricular rate to a level that is better tolerated from a hemodynamic standpoint. Dexmedetomidine can be used as an adjunctive agent for rate control with additional sedation and hemodynamic benefits. Intravenous sotalol has recently become widely available and limited studies have shown efficacy in termination of multiple types of refractory tachyarrhythmias, including AET, in the pediatric population [8–11].

Atrial Muscle Reentry There are numerous types of tachycardia related to reentry within the atrial myocardium.

1. *Classic Atrial Flutter*: This involves a macro reentry circuit through the right atrium and is rare in pediatrics outside of the newborn period. The rate varies from 280 to 500 bpm, generally 300 bpm, and is associated with the classic "saw tooth" flutter waves (Fig. 51.8). Conduction to the ventricles may vary from 1:1 to 3:1 or more, but most often there is a 2:1 block which may make recognition of the flutter waves difficult. Adenosine is extremely

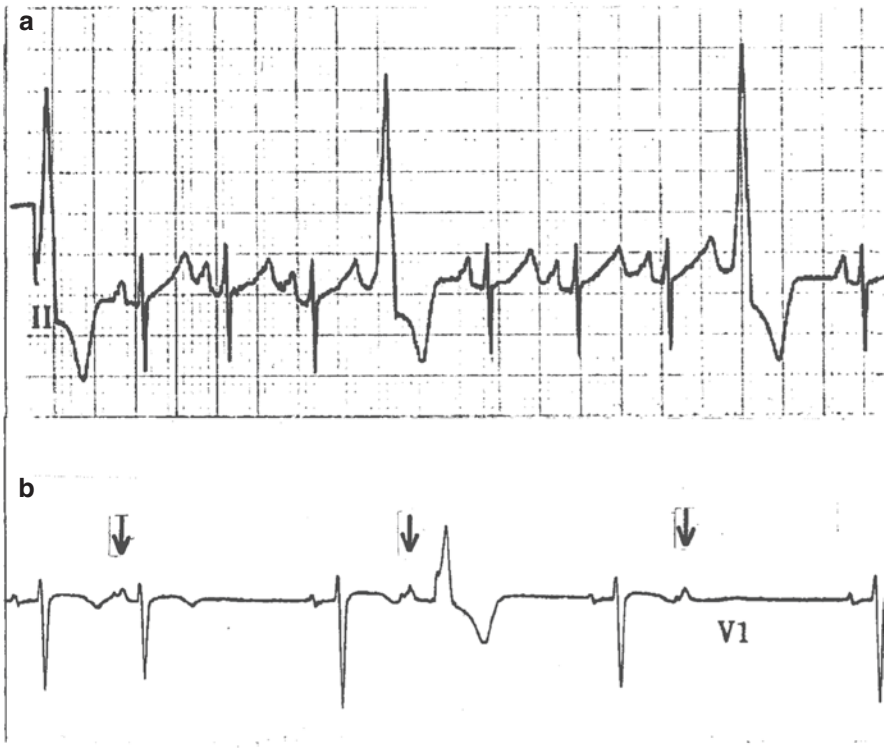

Fig. 51.6 (**a**, **b**) Premature ventricular and atrial beats. (**a**) Premature ventricular complexes demonstrating a wide QRS, abnormal T wave, and no preceding P wave; (**b**) premature atrial complexes (PAC) (*arrows*) showing three different ventricular responses: first arrow shows normal QRS, second arrow shows aberrant QRS with RBBB pattern, and third arrow shows nonconducted PAC resulting in a brief apparent sinus pause. *RBBB* right bundle branch block

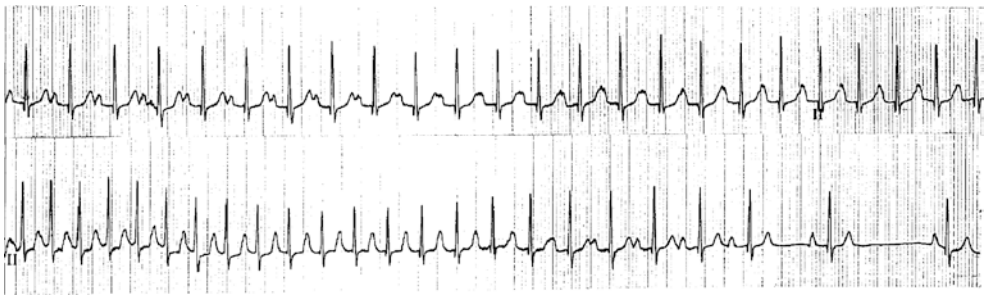

Fig. 51.7 Atrial ectopic tachycardia. Note P wave before every QRS and gradual "warm up" and "slow down" of tachycardia rate.

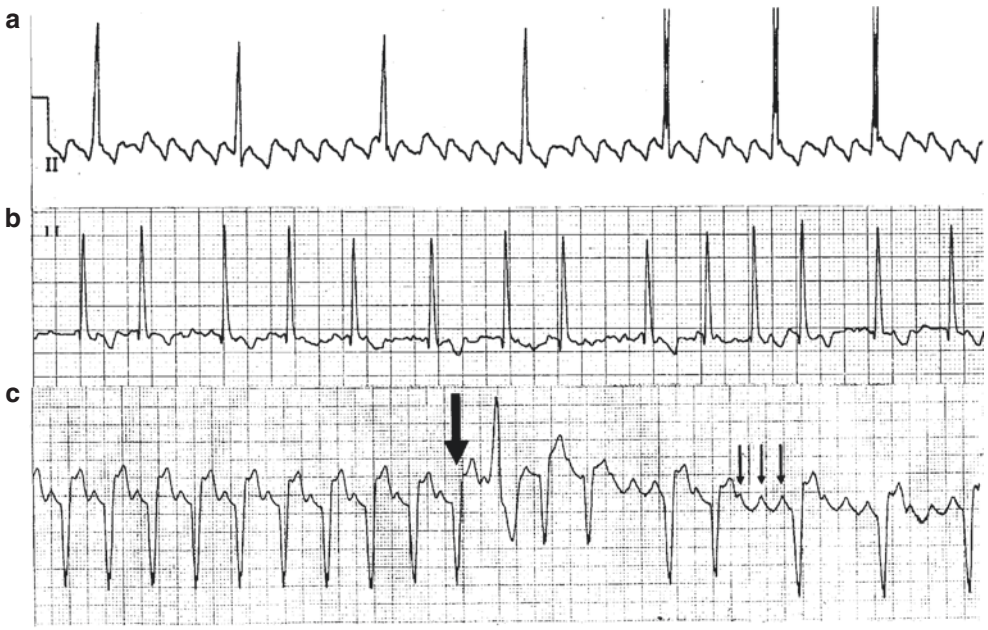

Fig. 51.8 (**a**–**c**) Atrial muscle reentry. (**a**) Atrial flutter with typical saw tooth pattern of atrial activity with variable AV block, (**b**) atrial fibrillation with irregularly irregular RR intervals and a coarse baseline, and (**c**) intra-atrial reentry tachycardia in a patient with Fontan procedure. Atrial rate not evident until onset of adenosine effect (*large arrow*), which increases AV block and reveals atrial rate of 250 bpm (*small arrows*)

helpful in unmasking the saw tooth wave pattern during the transient AV block that occurs seconds after the administration of this drug (Fig. 51.3).

Termination of atrial flutter can be performed with atrial overdrive pacing, synchronized cardioversion, or pharmacological cardioversion. AV nodal blocking agents are used if immediate rate control is required. Anticoagulation issues are important with atrial flutter, as they are with all sustained atrial arrhythmias [12], and are discussed below.

2. *Atrial Fibrillation*: This is the most common arrhythmia seen in the adult intensive care setting, but is extremely uncommon in the pediatric ICU. The characteristics include an irregular rhythm without a set pattern and a coarse baseline without consistent or well-formed P waves (Fig. 51.8b). It may occur in adolescents or adults with congenital heart disease and cardiac lesions resulting in long-standing atrial dilation or elevated atrial pressure. Hyperthyroidism should be considered in a patient with new onset atrial fibrillation and no underlying structural heart disease. Additionally, evidence suggests that in pediatric patients with lone atrial fibrillation that up to 39% will have a triggering, underlying SVT mechanism that degrades into atrial fibrillation [13, 14].

Treatment initially consists of rate control with digoxin, beta blockers, or calcium channel blockers. The calcium channel blocking agent diltiazem has become the drug of choice for rate control, as intravenous administration allows titration of the AV block. Thromboembolic complications are a risk if a rapid atrial arrhythmia persists for more than 24–36 h and anticoagulation with heparin should be considered. Conversion to sinus rhythm may occur with intravenous amiodarone, procainamide, ibutilide (a medication with a relatively high risk of torsade de pointes within the first several hours after administration) or sotalol. Synchronized DC cardioversion is generally effective, but the arrhythmia may be recurrent requiring suppressive therapy with amiodarone, procainamide, or sotalol.

3. *Intra-atrial Reentry Tachycardia (IART)*: This rhythm disorder, characterized by a reentry circuit within atrial myocardium circulating around natural barriers or scar tissue, is being seen with increasing frequency in adolescents and adults with repaired congenital heart disease. The rapidly enlarging population of patients who had Fontan procedures or atrial repairs for transposition of the great arteries (i.e., Mustard or Senning operations) is at the greatest risk for IART to develop years after the initial repair. However, this rhythm disturbance may be seen in anyone who had a previous atriotomy, even an uncomplicated ASD repair. IART is distinguished from classic atrial flutter because the rates are slower, ranging anywhere from 100 to 250 bpm, and P waves are discrete with abnormal morphology. As with atrial flutter, AV block is variable and 2:1 block may make the diagnosis difficult. Adenosine is useful in providing transient AV block allowing easy recognition of the atrial tachycardia (Fig. 51.8c).

Treatment initially consists of rate control, usually with diltiazem. If the duration of the arrhythmia is greater than 36 h or unknown, there is a risk of systemic emboli and stroke, particularly with conversion to sinus rhythm. In this situation, anticoagulation is necessary and cardioversion, electrical or pharmacologic, should be preceded by transesophageal echocardiography to rule out a thrombus within the heart. Alternatively, it may be reasonable to maintain therapeutic anticoagulation with Coumadin for 4 weeks before an attempt at conversion. Overdrive pacing and electrical synchronized DC cardioversion are very effective in acutely terminating the rhythm, but there is a strong tendency for recurrence and long-term antiarrhythmic therapy and or an attempt at ablation of the arrhythmia circuit is generally necessary [15]. For recalcitrant IART, a surgical MAZE procedure may need to be considered [16].

The *management of sustained atrial arrhythmias* is summarized in Table 51.3.

Junctional Arrhythmias

These arrhythmias involve AV nodal tissue or portions of the His bundle.

Paroxysmal Supraventricular Tachycardia (SVT) Paroxysmal SVT (Fig. 51.9) is due to reentry and is the most common arrhythmia requiring treatment in the pediatric population with no underlying structural heart disease. Any patient undergoing cardiac surgery who has the substrate for reentry SVT may have a recurrence in the postoperative state. This may cause significant and rapid hemodynamic distress in the setting of compromised myocardial function. Paroxysmal SVT can be easily recognized on the bedside monitor by the abrupt increase

Table 51.3 Management of atrial arrhythmias

1. Control ventricular rate by AV block
(a) Intravenous: Digoxin, beta blockers (esmolol), calcium channel blockers (diltiazem), dexmedetomidine (adjunctive)
2. Risk of thromboembolism
(a) Duration <36 h low risk
(b) If high risk: Transesophageal echocardiogram versus 4 weeks of anticoagulation
3. Conversion to sinus rhythm
(a) Pharmacologic – intravenous amiodarone, procainamide, ibutilide, sotalol
(b) Electrical DC conversion – 1 J/kg

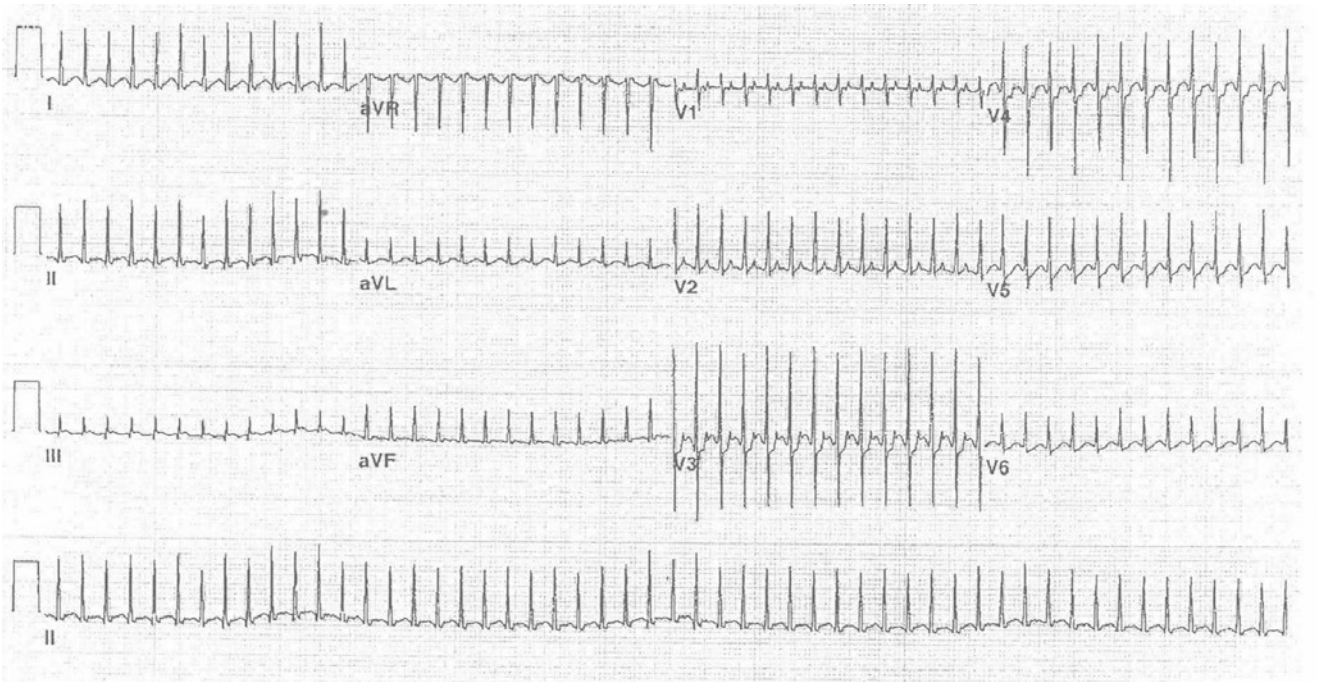

Fig. 51.9 (**a**) Supraventricular tachycardia. Note regular narrow complex tachycardia at a rate of 300 bpm

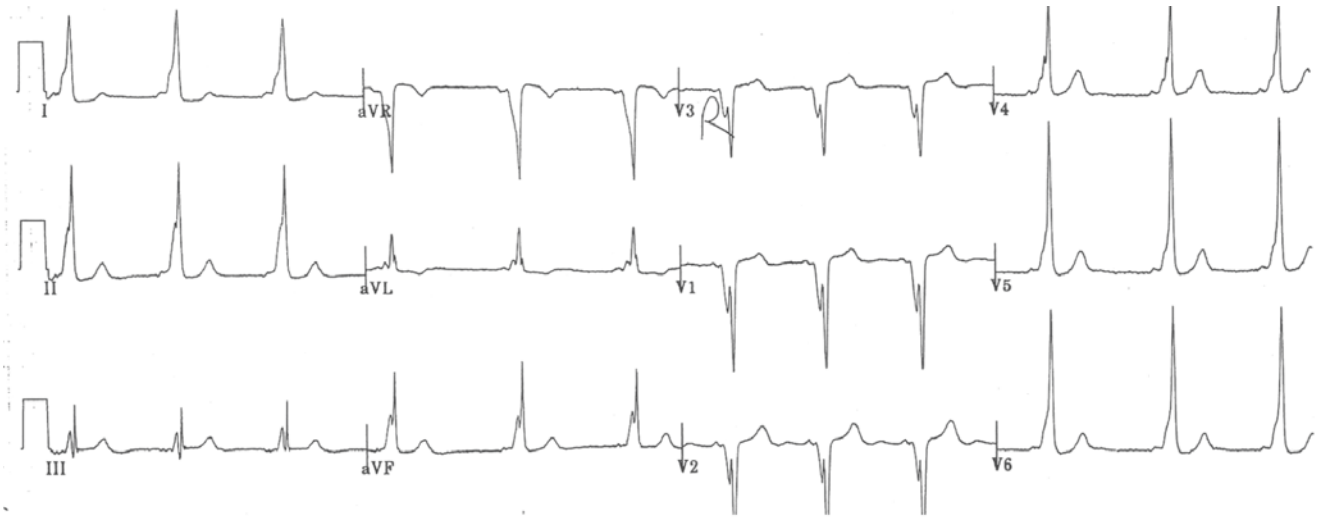

Fig. 51.10 Wolff–Parkinson–White syndrome. Note the short PR interval and slurred upstroke of the QRS typical of ventricular preexcitation

in heart rate to 180–300 bpm. This type of reentry tachycardia is either mediated through an accessory pathway (AV reentry) or via dual AV node pathways (AV node reentry). An accessory pathway consists of myocardial fibers bridging the fibrous AV annulus. These may be manifested with anterograde conduction resulting in preexcitation and constituting the Wolff–Parkinson–White (WPW) syndrome recognized by a delta wave in sinus rhythm (Fig. 51.10). However, these pathways often conduct only in a retrograde fashion, sometimes referred to as URAPs (unidirectional retrograde conducting accessory pathways) [5]. Therefore, they are not evident during sinus rhythm, but may still participate in a tachycardia circuit. Accessory pathway-mediated paroxysmal SVT predominates in younger individuals less than 10 years of age. After this age, AV node reentry utilizing fast and slow AV node pathways becomes more prevalent [5–7]. Regardless of the mechanism, the reentry circuit involves the AV node and this tachycardia is sensitive to any maneuver or drug that blocks conduction through the AV node. Although the mechanism of the SVT does not affect acute treatment choices, the use of the 12-lead ECG and an atrial recording can elucidate whether or not the SVT is mediated by an accessory pathway or AV node reentry.

If retrograde P waves are seen on the ST segment of the 12 lead, or if the RP interval on the atrial electrogram is greater than 80 ms, this implies the reentry circuit is relatively large involving an accessory pathway. A very short RP interval where the P wave occurs within the QRS generally indicates AV node reentry as the mechanism.

Treatment: If there is hemodynamic compromise, immediate synchronized cardioversion should be performed. If the situation is less critical, various vagal maneuvers can be tried such as the diving reflex with exposure of the face to ice water in a plastic bag. Adenosine is the drug of choice and is almost universally effective, at least transiently interrupting the tachycardia. However, in the presence of a high adrenergic state there may be a tendency for immediate recurrence of the SVT. This requires use of longer-acting medications such as digoxin, beta blockers, procainamide, or amiodarone. Sotalol can be considered for incessant or refractory episodes of SVT. Although digoxin should not be used long term in individuals with WPW because of its risk in enhancing AV conduction antegrade across the accessory pathway during atrial fibrillation, it is safe to use in the monitored critical care setting for paroxysmal SVT. Intravenous verapamil may be useful in patients over 1 year of age and who have preserved systolic ventricular function. While dexmedetomidine can terminate reentry tachycardias in certain cases, it may be more useful as an adjunct agent to slow or prevent recurrent episodes of SVT while awaiting effect of long-term agents. Overdrive atrial pacing with an esophageal pacing lead or atrial leads placed the time of surgery is also very effective in acutely terminating this arrhythmia.

Junctional Ectopic Tachycardia (JET) This is the most common hemodynamically important arrhythmia seen in the pediatric cardiac ICU [17–20]. JET generally has its onset in the first 24–48 h postoperatively and is usually transient, lasting 2–5 days. The incidence ranges from 5% to 8%, and risk factors include age less than 6 years, complex intraoperative repairs, duration of cardiopulmonary bypass, and requirement for relatively high-dose inotropic support. The defects that have most commonly been associated with postoperative JET include tetralogy of Fallot, total anomalous pulmonary venous return, transposition of the great arteries (arterial switch procedure), ventricular septal defect, AV septal defect, and hypoplastic left heart (stage 1 Norwood procedure). The mechanism remains unproven but is thought to be related to a combination of traction or trauma to the AV node and His bundle as well as ischemia during surgery. The hallmark of the diagnosis includes a junctional rhythm greater than 170 bpm usually associated with AV dissociation with the junctional rate being greater than the atrial rate. There may be occasional sinus capture beats causing irregular and shorter RR cycles. Occasionally there may be 1:1 VA conduction. The QRS morphology should be identical to the sinus QRS for this diagnosis to made confidently. Figure 51.11 shows tracings of JET, and Fig. 51.4a shows the use of an atrial electrogram to define the VA relationship.

Treatment: Adenosine is *ineffective* in eliminating the tachycardia but may produce transient VA dissociation with continuation of the tachycardia distinguishing it from a reentry SVT. The approach to this tachycardia should initially include avoiding hyperthermia, optimizing sedation and pain control, and minimizing inotropic support. Every effort should be made to normalize blood gases and electrolytes including calcium and magnesium. If this does not result in a decrease of the junctional rate, other maneuvers including drug therapy and cooling should be employed [17, 19, 21]. Our approach (outlined in Table 51.4) is to use amiodarone first with cooling added as necessary to decrease the junctional rate to a range that allows temporary atrial or AV sequential pacing to restore AV synchrony. R wave synchronized atrial pacing may also be attempted. Other medications have been used such as digoxin, intravenous beta blockers, dexmedetomidine, and procainamide. Although there is a risk of hypotension with intravenous amiodarone [22], this can be minimized by giving the bolus doses relatively slowly. It is important to remember that an ectopic rhythm such as JET usually does not abruptly terminate and convert to sinus rhythm with the above maneuvers, and the goal of therapy is to gradually suppress the rate to a tolerated level which allows overdrive atrial pacing. Generally, therapy needs to be continued for only 1–2 days as this arrhythmia usually resolves with gradual improvement in the underlying hemodynamic status of the patient. The incidence of postoperative JET can potentially be decreased with perioperative magnesium sulfate and dexmedetomidine administration and is standard procedure at our institution [23–25].

51.5.1.2 Ventricular Arrhythmias

Transient ventricular arrhythmias are not uncommon in the postoperative state or in the critically ill patient. Numerous conditions in this setting predispose the patient to ventricular irritability including electrolyte abnormalities (particularly potassium, calcium, and magnesium), hypoxia, mechanical irritation from catheters, drugs, edema, or acute inflammatory changes related to surgical manipulation. Furthermore, these patients often require inotropic drugs to support cardiac output, which enhance ventricular automaticity. The first approach to any ventricular arrhythmia is to try to correct any of the aforementioned causes.

Ventricular Ectopics This category includes isolated premature ventricular complexes (PVC), bigeminy and cou-

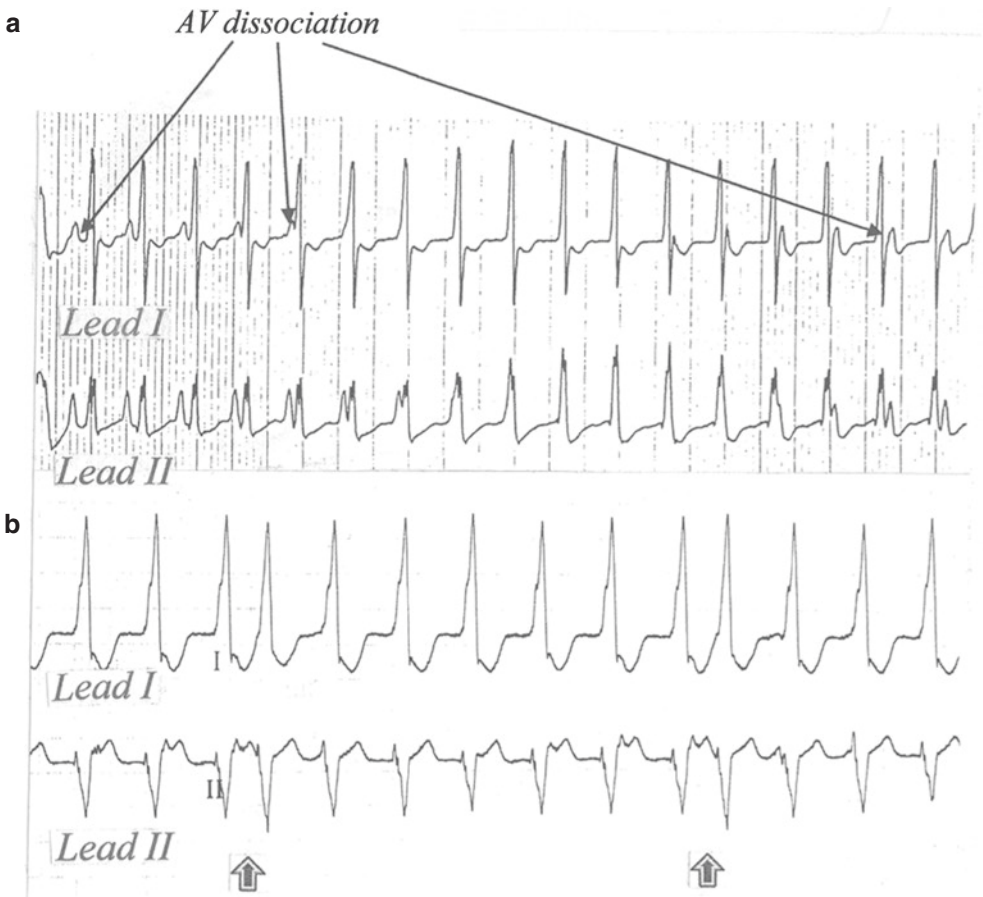

Fig. 51.11 (**a**, **b**) Junctional ectopic tachycardia (JET). (**a**) Rhythm strip demonstrates JET with AV dissociation (*arrows* identify P waves), (**b**) rhythm strip of JET with intermittent short RR intervals (*double arrows*) due to sinus capture beats

Table 51.4 Management of junctional ectopic tachycardia

1. General measures
(a) Optimize sedation/hemodynamics
(b) Decrease exogenous catecholamines
(c) Correct fever, establish normo- or mild hypothermia
(d) Optimize electrolytes (magnesium)
2. Rate control
(a) Drugs – intravenous amiodarone, procainamide, and/or dexmedetomidine
(b) If needed – moderate hypothermia, 35–36 °C
(c) Persistent tachycardia and/or side effects from amiodarone – intravenous procainamide
3. Establish AV synchrony
(a) Rate reduction plus atrial pacing or AV sequential pacing if AV block present

plets. Premature ventricular complexes (Fig. 51.6a) are recognized by their aberrant QRS, absence of a preceding P wave, occasionally a fully compensatory pause, and a morphology that is not typical for a bundle branch block pattern. A true compensatory pause (interval between the preceding normal QRS and post PVC normal beat being twice the normal RR interval) is frequently not seen because of underlying sinus arrhythmia. Morphology features favoring a ventricular origin include a very wide QRS, concordance of positivity (or negativity) of the QRS across the precordium, and an RSr' pattern in V1 with the R amplitude greater than the r'. Supraventricular origin of an aberrant complex is more likely when the QRS has a typical right bundle branch block or left bundle branch block morphology.

Treatment*:* Although isolated premature ventricular complexes do not merit antiarrhythmic therapy, certain features are worrisome and suggest the possibility of progression to a more complex and hemodynamically compromising ventricular arrhythmia. These include multiform morphology, increasing frequency of ectopy, R on T pattern, and nonsustained ventricular tachycardia.

Ventricular Tachycardia (VT) Nonsustained VT is defined as a run of 3 or more consecutive ventricular ectopics that spontaneously converts to sinus rhythm within 30 s. Sustained VT (Fig. 51.12) is a tachycardia that lasts greater than 30 s or requires immediate treatment because of hemodynamic collapse. VT may be monomorphic or polymorphic and can occur transiently in the postoperative state related to the predisposing factors mentioned above. *Monomorphic VT* is more likely to occur when there is a discrete scar focus related to underlying structural myocardial disease or prior

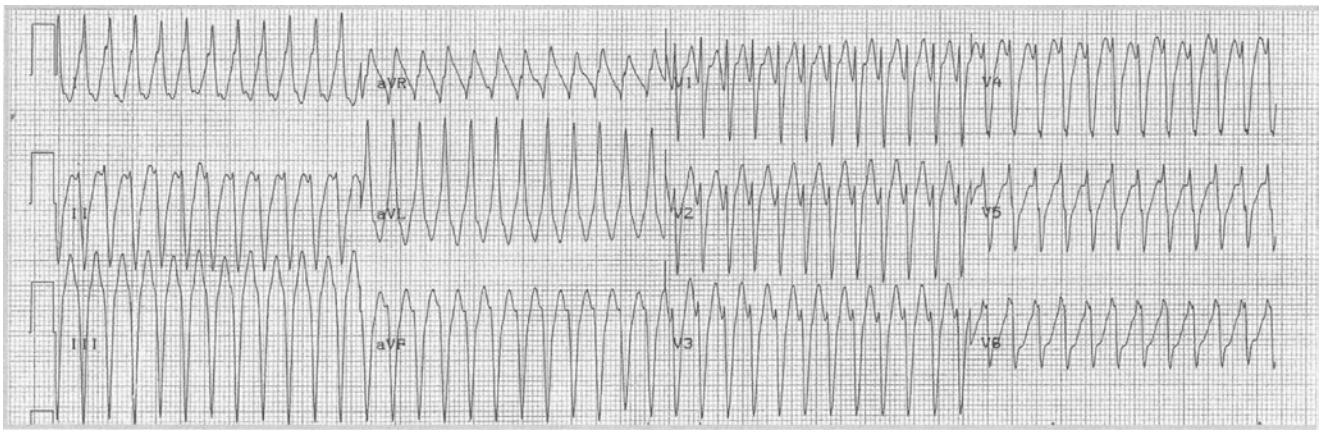

Fig. 51.12 Ventricular tachycardia. Note regular wide QRS tachycardia. P waves are not seen

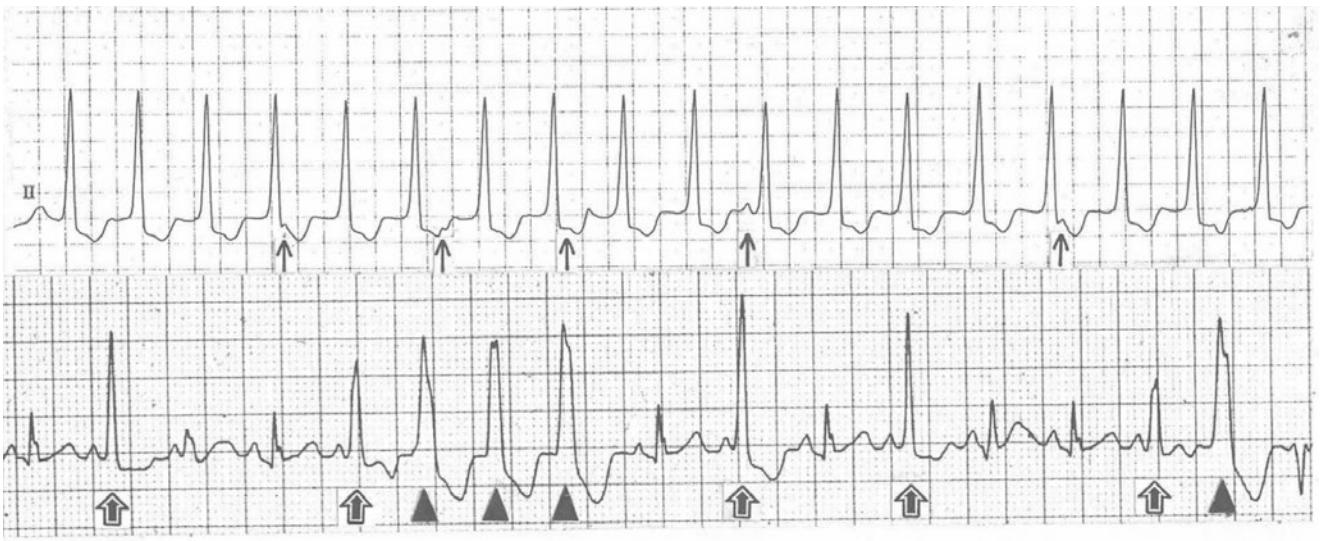

Fig. 51.13 Characteristics of ventricular tachycardia. (**a**) Rhythm strip of wide QRS tachycardia with AV dissociation showing P waves (*arrows*) are dissociated from ventricular activity, (**b**) rhythm strip showing frequent ventricular ectopics and a 4-beat run of nonsustained ventricular tachycardia. Note difference in morphology between pure PVC's (*triangles*) and fusion beats (*double arrows*), the latter beats representing ventricular depolarization from both the ectopic site and conduction through the normal AV conduction axis. *PVC* premature ventricular complex

cardiac surgery. The highest risk population of patients who had previous cardiac surgical repair include those with tetralogy of Fallot, transposition of the great arteries, or related lesions such as truncus arteriosus or double outlet right ventricle; and the risk increases proportionally to the time since surgery. *Polymorphic VT* is most often associated with acute ischemia or an acquired or congenital repolarization abnormality with prolongation of the QT interval. There are a number of congenital channelopathies and primary electrical diseases in addition to the long QT syndrome that may present with life-threatening ventricular arrhythmias, including catecholaminergic polymorphic VT and Brugada's syndrome [7]. In addition to VT, the differential diagnosis of a wide QRS tachycardia includes supraventricular tachycardia with aberrant conduction, antidromic SVT (anterograde conduction over an accessory pathway), and twin AV nodes in heterotaxy syndrome. The key diagnostic features indicating ventricular origin include AV dissociation, fusion, and capture beats (Fig. 51.13a, b). AV dissociation is not necessarily present, as each ventricular complex may retrogradely activate the atrium through the AV node resulting in a 1:1 VA relationship. Adenosine may be useful in this situation as it will transiently cause VA block confirming the ventricular origin of the tachycardia. Fusion beats represent dual activation of the ventricle from the ectopic site as well as capture of a portion of the myocardium from a nearly simultaneously conducted supraventricular impulse. Capture beats are infrequently noted, but are recognized as a normal QRS complex

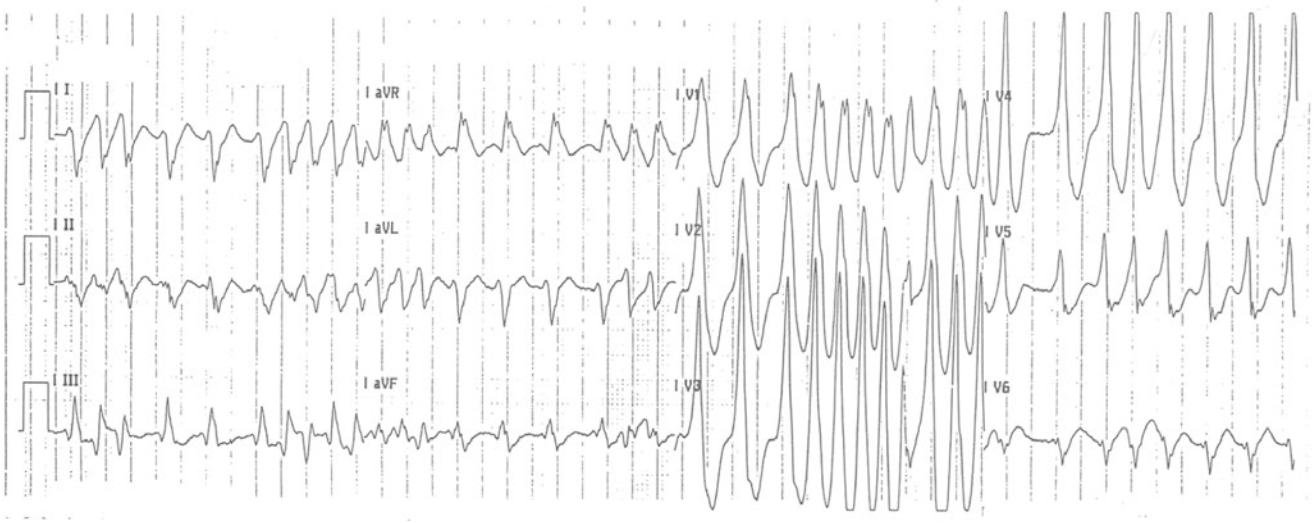

Fig. 51.14 Atrial fibrillation with WPW syndrome. Note the very rapid irregularly irregular wide QRS tachycardia in a patient with WPW syndrome. QRS complexes are wide due to anterograde conduction across an accessory pathway. The shortest RR intervals are 170–200 ms indicating a risk of deterioration of rhythm into ventricular fibrillation. *WPW* Wolff–Parkinson–White

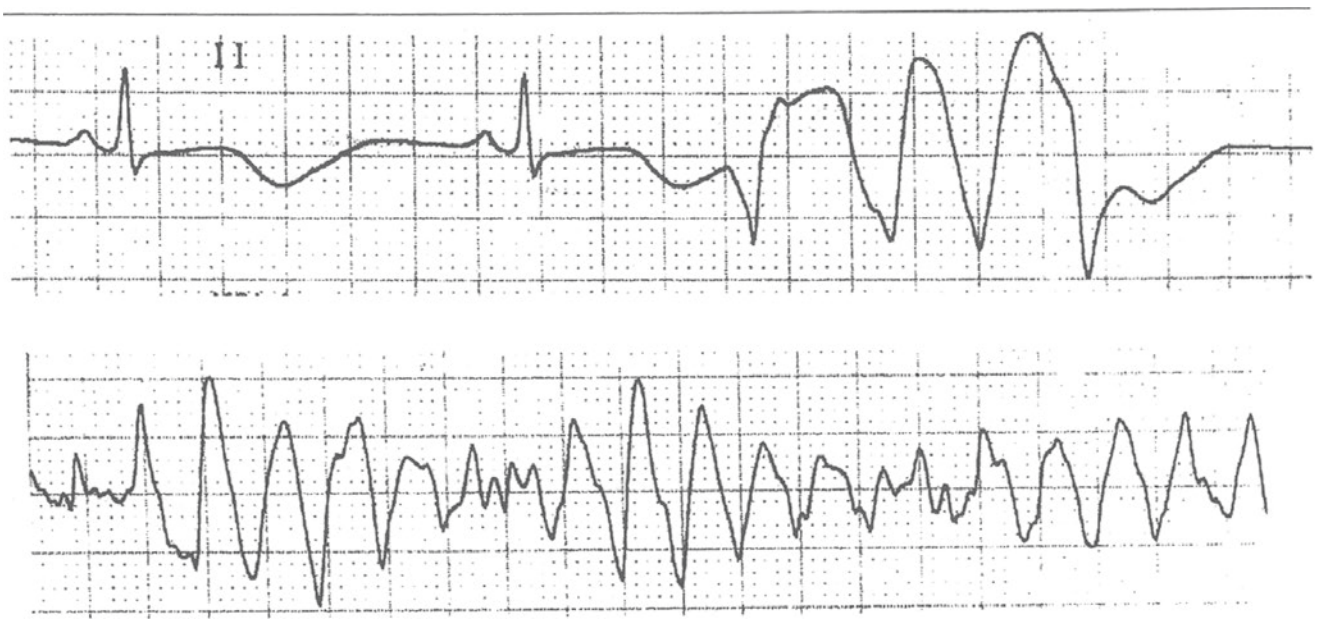

Fig. 51.15 Torsade de pointes. Note the prolonged QT interval on first 2 sinus beats on top tracing with initiation of the arrhythmia with R on T premature ventricular complex

within a relatively slow run of ventricular tachycardia. The most likely cause of a very rapid irregularly irregular wide QRS tachycardia is atrial fibrillation associated with an accessory pathway (Fig. 51.14). Polymorphic ventricular tachycardia may take the typical pattern of torsade de pointes with undulating variation in the QRS complexes (Fig. 51.15). This distinctive form of VT is almost always due to prolongation of the QT interval, either as a primary genetic channelopathy involving the sodium and potassium channels or secondary to drugs or electrolyte abnormalities such as low potassium, magnesium, or calcium.

Treatment: Treatment depends on the hemodynamic state of the patient. In the setting of hypotension and cardiovascular collapse, immediate synchronized cardioversion is indicated with a dose of 1–2 J/kg. If the patient remains relatively well perfused, a trial of medications is warranted. Intravenous magnesium is the treatment of choice for polymorphic ventricular tachycardia or torsade de pointes. Drugs available for acute treatment of ventricular tachycardia include lidocaine, procainamide, amiodarone, and sotalol. It is generally worth an initial trial of lidocaine, as the side effects are minimal and the effect

will be immediately apparent. If this is unsuccessful, our next choice would be intravenous amiodarone, although there is potential for hypotension if infused too rapidly. Amiodarone is generally tolerated better than intravenous procainamide in the setting of compromised myocardial function. Sotalol may be a useful alternative, however, use in pediatric patients with decreased myocardial function requires further evaluation.

Ventricular Flutter and Fibrillation These arrhythmias are usually the end result of sustained ventricular tachycardia with degeneration into a nonperfusing arrhythmia. Occasionally ventricular fibrillation will occur as a primary event.

Treatment: These lethal arrhythmias must be immediately treated with defibrillation (asynchronous delivery of 2 J/kg) as opposed to synchronized cardioversion.

51.5.2 Bradyarrhythmias

51.5.2.1 Sinus Node Dysfunction

Sometimes referred to as "sick sinus syndrome," this is a rhythm disturbance related to abnormal sinus node automaticity or perinodal conduction resulting in sinus bradycardia, long sinus pauses, sinoatrial exit block, or a junctional escape rhythm. This condition rarely occurs as a primary event in the pediatric population, but is not infrequently seen in postoperative patients. Acute sinus node dysfunction may be seen after any procedure involving manipulation of the right atrium including sinus venosus and atrial septal defect repairs, Fontan procedure, total anomalous pulmonary venous return, or orthotopic heart transplantation. Chronic sinus node dysfunction is common during long-term follow-up of patients who had a Mustard or Senning repair for transposition of the great arteries, a Fontan procedure, or closure of a sinus venosus atrial septal defect.

Treatment Isoproterenol infusion, temporary or permanent atrial pacing.

51.5.2.2 Atrioventricular Block (AVB)

First Degree AV Block

This consists of 1:1 AV conduction, but the PR interval is longer than normal for age and rate (Fig. 51.16a).

Treatment is not required.

Second Degree AV Block

This consists of conduction of some, but not all, atrial beats. There are two types of second degree block:

(a) Mobitz I (Wenckebach) block: There is progressive lengthening of the PR interval before a single blocked P wave, with the next impulse conducted with a relatively short PR interval (Fig. 51.16b). This block occurs in the AV node and is due to the property of decremental conduction inherent to nodal tissue. The etiology may be increased vagal tone, AV nodal injury, or ischemia or drugs (particularly beta blockers, calcium channel blocking agents, or digoxin).

Treatment is not necessary as long as an acceptable ventricular rate is maintained. If treatment is required, atropine, isoproterenol, and discontinuing offending medications are effective maneuvers.

(b) Mobitz II block: There are intermittent nonconducted P waves without any change in the PR interval of the conducted beats, before or after the blocked impulses (Fig. 51.16c). This block arises distal to the AV node, from the His bundle or below, and is an ominous sign of impending complete failure of AV conduction. It may be due to direct surgical injury, ischemia, or diffuse myocardial disease.

Treatment is indicated and urgent with a temporary pacemaker. If prolonged episodes of asystole are occurring before a pacemaker can be inserted, isoproterenol, or transcutaneous pacing should be instituted.

Note: It is not possible to definitively determine whether a *2:1 block* is Mobitz I or II. Indirect evidence favoring Mobitz I would be a normal QRS and absence of serious underlying heart disease, since Mobitz II block is usually associated with diffuse ventricular myocardial disease and aberrant QRS morphology.

Third Degree (Complete) AV Block

There is no conduction of any atrial impulses to the ventricle (Fig. 51.16d, e). Congenital AV block may occur in the absence of other structural abnormalities and may be related to maternal lupus antibodies. Certain types of congenital defects are highly associated with AV block including congenitally corrected transposition of the great arteries or the complex heterotaxy syndromes. Acquired AV block is more common in the intensive care setting and is usually related to surgical injury to the AV conduction axis.

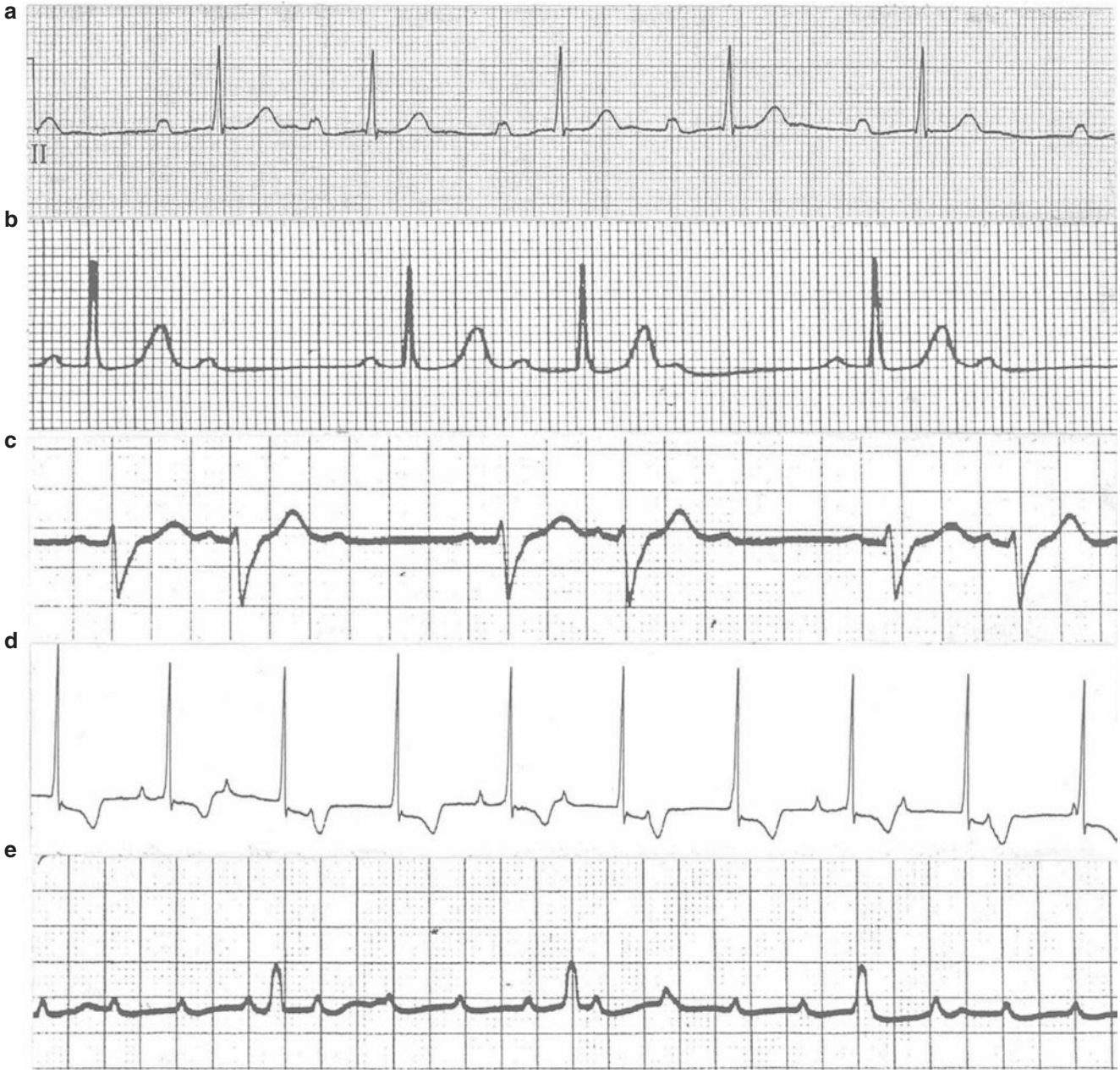

Fig. 51.16 (**a**–**e**) Types of AV block. (**a**) PR interval is prolonged, but every P wave is conducted; (**b**) second degree, Mobitz Type I (Wenckebach), block shows progressive prolongation of PR interval before a blocked P wave; (**c**) second degree, Mobitz Type II, block shows no change in PR interval before the blocked P wave. Note wide QRS which is frequently associated with more distal AV block, (**d**) third degree or complete AV block characterized by complete dissociation of atrial and ventricular activity. Narrow complex junctional escape rhythm suggests block is above the His bundle, (**e**) third degree AV block with slow wide QRS escape rhythm indicates block is below His bundle and is an indication for urgent intervention

Other causes of acquired heart block include myocarditis, Lyme disease, or acute rheumatic fever. A narrow QRS escape rhythm indicates block above the His bundle with a usually stable junctional rhythm (Fig. 51.16d), while a wide QRS escape generally indicates block below the His bundle, which is less stable (Fig. 51.16e). However, a wide QRS may be due to a bundle branch block rather than block below the His bundle.

Treatment is similar to that for sinus node dysfunction and includes temporizing measures with medication such as atropine or isoproterenol, followed by transcutaneous or temporary pacing. If the block is symptomatic or persistent,

permanent transvenous or epicardial pacemaker implantation is necessary. Postoperative AV block is effectively managed by temporary pacing utilizing surgically placed atrial and ventricular pacing wires. If block persists greater than 7 days, implantation of a permanent pacing system is generally warranted. Pacemaker therapy and indications for pacing are discussed in the following chapter of this book.

Note: It is important to understand the term "AV dissociation," as it is often used inappropriately. AV dissociation may be due to complete AV block, but it may also be due to isorhythmic (isochronic, interference) dissociation. In the latter situation, a lower focus, arising in the AV node or ventricle, demonstrates an intrinsic rate faster than the sinus rate. Therefore, most of the atrial complexes will encounter the AV node after it has already depolarized and is in a refractory state. This rhythm is usually characterized by intermittent short RR intervals due to sinus capture beats. Typical examples of AV dissociation not due to AV block include accelerated junctional or ventricular rhythm, and junctional ectopic or ventricular tachycardia.

51.6 Summary

Arrhythmias are a commonly encountered problem in the intensive care setting and in patients after cardiac surgery. Rapid and accurate diagnosis is required, particularly when hemodynamic compromise occurs. Multiple treatment modalities are available including optimizing the hemodynamic state and metabolic environment, medications (see Table 51.5 for doses of commonly used drugs), pacing, and cardioversion or defibrillation (Table 51.6).

Table 51.5 Common uses for antiarrhythmic medications

1. AV nodal blocking agents
Digoxin, beta blockers (esmolol), calcium channel blockers (diltiazem), dexmedetomidine
2. Ectopic (automatic) arrhythmias
Amiodarone, procainamide, beta blockers, dexmedetomidine, sotalol
Lidocaine (for ventricular arrhythmias)
3. Paroxysmal (reentry) arrhythmias
Atrial: amiodarone, procainamide, dexmedetomidine, sotalol
AV node: adenosine, verapamil or diltiazem, digoxin, beta blockers, procainamide, amiodarone, dexmedetomidine, sotalol
Ventricular: lidocaine, amiodarone, procainamide, sotalol
4. Differential diagnosis
Adenosine
Unmasking atrial tachyarrhythmias
Wide QRS tachycardia: SVT versus VT

Table 51.6 Dosages of common antiarrhythmics

Drug	Dose (intravenous doses)
Adenosine	Bolus: 100–300 μg/kg IV, up 12–15 mg
Amiodarone	Bolus: 5 mg/kg over 20 min, up to 20 mg/kg load
	Infusion: 5–20 μg/kg/min (10–15 mg/kg/24 h)
Esmolol	Bolus: 500 μg/kg
	Infusion: 50–200 μg/kg/min
Dexmedetomidine	Bolus: 0.1-1 μg/kg over 10 min
	Infusion: 0.2-0.7 μg/kg/hr
Digoxin	Bolus: 20 μg/kg, up to 0.5 mg
	TDD: 40 μg/kg/24 h, up to 1–1.5 mg
Diltiazem	Bolus: 0.25 mg/kg, up to 25 mg
	Infusion: 0.1–0.3 mg/kg/h, up to 10–15 mg/h
Lidocaine	Bolus: 1 mg/kg, up to 100 mg, repeat every 10 min × 2
	Infusion: 20–50 μg/kg/min
Procainamide	Bolus: 15 mg/kg over 30 min, up to 1 g (under one year reduce dose to 10 mg/kg)
	Infusion: 20–80 μg/kg/min
Propranolol	Bolus: 0.01 mg/kg, up to 0.5 mg, repeat up to 0.1 mg/kg if tolerated
Sotalol	Bolus: 1 mg/kg given over 1 hour
Verapamil	Bolus: 0.1 mg/kg, up to 5–10 mg; repeat in 15 min

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Chapter 52
Pacemakers (Temporary and Permanent), Implantable Cardioverter Defibrillators (ICDs), and Cardiac Resynchronization Therapy

Christopher W. Follansbee, Lee Beerman, and Gaurav Arora

Abstract Cardiac output is dependent on normal mechanical function of the heart, which in turn is dependent on normal functioning of the cardiac conduction system. When derangements of cardiac conduction occur, this can result in poor cardiac output acutely as well as poor cardiac reserve chronically. These derangements can occur as a result of bradyarrhythmia, tachyarrhythmia, or electrical dyssynchrony (atrioventricular [AV] or interventricular) of the heart.

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Different therapies have been developed to augment cardiac performance in times of electrical derangement, which include pacemakers (temporary or permanent) for bradycardic rhythms, antitachycardia pacemakers and implantable defibrillator devices for tachycardic rhythms, and, more recently, cardiac resynchronization therapy (CRT) for patients with evidence of dyssynchrony causing poor cardiac output.

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52.1 Basic Pacemaker Terminology and Definitions

Pacing can be performed in the atrium, the ventricle, or in both chambers sequentially. In addition, pacemakers can respond to intrinsic myocardial electrical activity or can operate without regard to native depolarization (asynchronous modes). The basic modes of pacing are based on a combined North American Society for Pacing and Electrophysiology (NASPE) and British Pacing and Electrophysiology Group (BPEG) consensus group, which formulated the generic pacing (NBG) nomenclature. An adaptation of the most revised version of this code is presented in Table 52.1 [1].

Successful pacing requires that electrical energy is successfully delivered from the generator to the myocardial tissue, allowing for electrical activation of the myocardium. Thus, failure in any part of the system (generator, lead, lead/myocardial interface, myocardial excitability) can lead to failure of pacing.

Common user-adjustable parameters in pacing include the lower and upper rates as well as the generator output. The threshold is defined as the lowest amount of energy required to successfully depolarize the myocardial tissue. Also, the sensing thresholds (level at which intrinsic depolarizations are sensed) can be adjusted. The timing of the heart rate is governed by setting of the atrioventricular (AV) delay (mimicking the native PR interval) as well as the postventricular atrial refractory period (PVARP). These factors govern the allowable upper rate based on the total atrial refractory period (TARP), which is the sum of the AV delay and PVARP. A full discussion of these parameters is beyond the scope of this text but may be read in any basic pacing textbook.

Leads may be unipolar or bipolar. Briefly, unipolar pacing occurs between the electrode tip and a ground electrode (either subcutaneous or the pacemaker generator). Bipolar pacing, on the other hand, occurs between two electrodes which are in close proximity (typically tip and ring electrodes at the tip of the lead). It is also helpful to know that

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Table 52.1 Basic generic pacemaker code (NBG); Adapted From [1]

I	II	III	IV	V
Chamber(s) paced	Chamber(s) sensed	Response to sensing	Rate modulation	Multisite pacing
O = none	O = none	O = none	O = none	O = none
A = atrium	A = atrium	T = triggered	R = rate modulation	A = atrium
V = ventricle	V = ventricle	I = inhibited		V = ventricle
D = dual (A + V)	D = dual (A + V)	D = dual (T + I)		D = dual (A + V)

unipolar pacing results in a larger stimulus artifact on the electrocardiogram or monitor, while a bipolar pacing spike is usually small in amplitude or sometimes inapparent.

With application of magnets, most pacemakers will revert to asynchronous pacing, while defibrillators will typically temporarily disable tachyarrhythmia therapies. However, devices respond differently to magnet applications depending on the brand, model, and programming mode so the specific response of each device must be confirmed before application of a magnet.

52.2 Pacemakers (Temporary and Permanent)

For over 50 years, pacemakers have been used in patients with bradycardic rhythms. In the current era, pacing can be accomplished temporarily or permanently. The primary methods for temporary pacing are transcutaneous, transvenous, or with epicardial wires, typically placed intra-op for use postoperatively. Permanent pacing involves implantation of a permanent pacemaker, typically using either transvenous endocardial or epicardial leads, although recently leadless pacemakers have become available.

Pacing requires a generator or battery to deliver electrical energy and a conduit to allow electrical energy to reach the heart. In most cases, the conduit takes the form of leads that are physically in contact with the heart.

52.2.1 Temporary Pacing

Typically, those patients who require temporary pacing are patients in whom a bradycardic rhythm is not tolerated hemodynamically, but in whom recovery of normal rhythm is expected. Another major category would be patients with infected pacing systems that need to be explanted until the infection has been completely cleared. Indications for temporary pacing are listed in Table 52.2.

Transcutaneous pacing relies on an external generator, which is typically an external defibrillator. Temporary pacing can be accomplished transcutaneously in an emergency. Energy is delivered to the heart using two external pads. The primary limitation to this approach is patient discomfort, as transcutaneous pacing is painful. In addition, the pads necessarily have a finite life span and need to be changed frequently. When using transcutaneous pacing, generator output is set at the minimum threshold required to have stimulation of superficial chest muscles. Successful pacing is measured by assessment of cardiac output, either via manual pulse check or invasive measures such as arterial blood pressure monitoring. With transcutaneous pacing, there are no lead-based parameters (e.g., sensitivity) to adjust. Due to patient discomfort, transcutaneous pacing is generally reserved for emergent resuscitation situations or self-limited episodes of bradyarrhythmia or asystole (e.g., profound bradycardia following cardioversion of a tachyarrhythmia).

Table 52.2 Indications for temporary pacing

Postsurgical bradycardia
Atrioventricular (AV) block
Sinus node dysfunction
Overdrive suppression of arrhythmias (atrial flutter)
Restoration of AV synchrony (e.g., junctional ectopic tachycardia)
Conditions that may be associated with AV block or sinus node dysfunction
Myocarditis
Endocarditis
Lyme disease
Rejection in posttransplant patients
Myocardial infarction
Active infection of pacemaker system in patients dependent on permanent pacing

Temporary transvenous pacing is the preferred mode for patients requiring pacing for only hours to days. Pacing is usually performed in the right ventricle and is continued until a sustainable perfusing rhythm is restored or another pacing modality is established. In most cases, the generator used is a specifically designed temporary pacemaker (Fig. 52.1). Various leads can be used for temporary transvenous pacing. In an emergency setting, balloon-tipped pacing catheters may be used for placement of a right ventricular pacemaker. In a more controlled setting, transvenous temporary leads with screw-in mechanisms to increase lead stability can be used. Temporary leads are inserted through a standard percutaneous approach with or without an intravenous sheath. The subclavian and internal jugular veins are most often utilized since the right ventricle can often easily be entered without

Fig. 52.1 Temporary dual-chamber and single-chamber pacemakers. (Reproduced with permission of Medtronic, Inc.)

fluoroscopy. The femoral venous approach is available, but often requires fluoroscopy, though echocardiography may be helpful in lead placement. If permanent transvenous pacing is anticipated, avoiding the subclavian vein is advisable to prevent thrombosis.

In the postoperative setting, the most common approach to temporary pacing is via the use of epicardial wires, which are placed directly onto the myocardium at the time of cardiac surgery. These wires can be placed in the atrium and/or ventricle, allowing for isolated single-chamber pacing or dual-chamber synchronous pacing. The atrial wires can also be used to obtain recordings of direct atrial activity during arrhythmias for diagnostic purposes. These wires may also be used for atrial overdrive pacing for atrial tachyarrhythmias, which are not uncommon in the postoperative setting (see Chap. 51 on "Arrhythmias in the Intensive Care Unit"). The same generator used for temporary transvenous pacing may be used for temporary epicardial pacing (Fig. 52.1). In patients requiring temporary pacing longer than 7 days, consideration should be given to implantation of a permanent pacemaker (see Sect. 52.2.2).

With both transvenous and epicardial temporary pacing, the pacemaker output is adjusted based on the threshold that is measured in milliamps (mA), which is different than permanent pacemakers where output is measured in volts (V). By convention, the output is set at twice the threshold or three times the pulse width to ensure an adequate safety margin. Thresholds will increase over time so they should be checked at least daily in all patients. In addition, the batteries in temporary pacemakers should be changed routinely, especially in patients who are pacemaker-dependent. Spare batteries should be readily available and the staff should be familiar with battery replacement. Alternatively, for patients who are pacemaker dependent, a spare temporary pacemaker with new battery should be kept at the bedside in case of failure of the in-use temporary generator.

Table 52.3 Common indications for permanent pacing in young patients

Advanced second- or third-degree AV block associated with symptomatic bradycardia, ventricular dysfunction, or low cardiac output
Postoperative advanced second- or third-degree AV block not expected to resolve or persistent at least 7 days after cardiac surgery
Congenital AV block with wide QRS escape rhythm, complex ventricular ectopy, or ventricular dysfunction
Congenital AV block in an infant with a structurally normal heart and heart rate <55 bpm
Congenital AV block in an infant with congenital heart disease and heart rate <70 bpm
Pause-dependent VT
Congenital AV block beyond 1 year of life with average heart rate <50 bpm, with abrupt pauses in ventricular rate that are 2–3x basic cycle length, or with symptoms secondary to chronotropic incompetence
Congenital long QT syndrome with AV block in high-risk patients
Asymptomatic sinus bradycardia in the child with complex heart disease and pauses longer than 3 s or resting heart rate <40 bpm
Patients with congenital heart disease and impaired hemodynamics due to sinus bradycardia or loss of AV synchrony
Sinus node dysfunction and symptomatic bradycardia

52.2.2 Permanent Pacemakers

Common indications for permanent pacing in young patients are given in Table 52.3 and are based on the consensus guidelines for pacing [2].

The primary modalities for permanent pacing are transvenous and epicardial systems. The choice of systems is based on patient size, anatomic issues (e.g., intracardiac shunts) vascular access, expected duration of pacing, and operator and center experience. Recently, leadless pacemaker technology has been developed and is undergoing trials in the adult population [3–6]. These small devices, such as the Medtronic Micra and St. Jude Nanostim (Fig. 52.2a–b), are attached to the ventricular endocardium via a transcatheter approach, though surgical implantation in pediatric patients has been proposed. While further studies evaluating efficacy and safety in the CHD population are ongoing, early limitations in the pediatric population include the large sheath size required for delivery (23 F and 16 F, respectively) as well as device retrieval at the time of replacement given the longer life expectancy of the pediatric population.

For patients with a permanent pacemaker who will be undergoing cardiac operations, knowledge of their pacemaker parameters before operation is essential to their post-

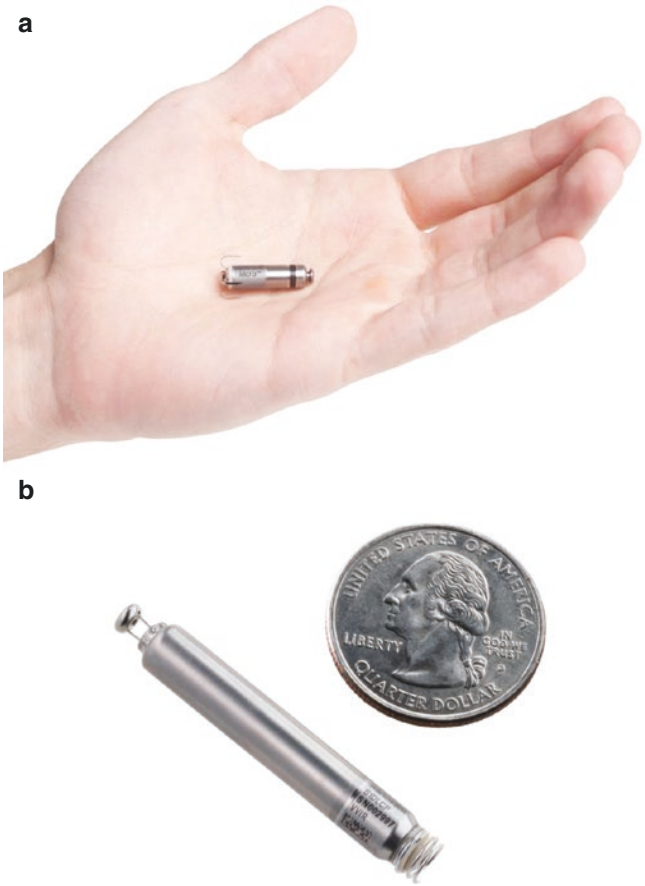

Fig. 52.2 Implantable transcatheter leadless pacemaker systems including the (**a**) Medtronic Micra and (**b**) St. Jude Nanostim. (Reproduced with permission of Medtronic, Inc. and St. Jude Medical, Inc.)

operative care. As a generalization, patients should have their devices interrogated before and after their surgery to ensure normal device function. In addition, the medical team caring for the patients should be aware of their device parameters (mode of pacing, lower rate, upper rate) in order to properly troubleshoot any issues that may arise, especially the magnet response of that specific device.

52.3 Implantable Cardioverter Defibrillators (ICDs)

In patients with potentially unstable tachyarrhythmias, defibrillators may be lifesaving. Currently, the most common application of this technology is implantable cardioverter defibrillators or ICDs. These may be implanted for secondary prevention in those patients who have survived a life-threatening ventricular arrhythmia or as primary prevention in individuals at risk for such arrhythmias. Consensus guidelines for ICD implantation relevant to pediatric patients are summarized in Table 52.4 [2].

Table 52.4 Indications for implantable cardioverter defibrillator (ICD) therapy

Cardiac arrest due to ventricular fibrillation (VF) or ventricular tachycardia (VT) not due to a transient or reversible cause
Spontaneous sustained VT in association with structural heart disease
Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study when drug therapy is ineffective, not tolerated or not preferred
Nonsustained VT in patients with prior myocardial infarction, LV dysfunction, and inducible VF or sustained VT at electrophysiological study that is not suppressible by a class I antiarrhythmic drug
Spontaneous sustained VT in patients without structural heart disease not amenable to other treatments
Adult patients with LV ejection fraction of less than or equal to 30%, at least 1-month postmyocardial infarction and 3 months postrevascularization surgery

Although ICDs are potentially lifesaving, their potential benefit must always be weighed against the known risks, which include infection, complication related to device placement, pneumothorax or hemothorax, lead fracture, inappropriate ICD shocks, other device malfunction, possible proarrhythmia, and potential psychological impact on patients [7]. In young patients, transvenous device placement, whether ICD or pacemaker, is limited by anatomic considerations of device size, increased risk of vessel thrombosis or occlusion, limited venous access, and in CHD risk of embolic disease with intracardiac shunts. Developments in surgical technique have recently demonstrated promising results in minimally invasive epicardial implantation via a limited thoracotomy [8]. Additionally, technological advances have led to subcutaneous ICDs, where the generator and lead are placed extracardiac and extrathoracic in the subcutaneous tissue. This offers the potential advantage of avoiding transvenous leads in smaller pediatric vessels or the need for thoracotomy, as well as potentially longer lead life span due to less mechanical stress and higher tensile strength. Limiting factors with early models include relatively large generator size due to significantly higher defibrillation thresholds and energy requirements, possibly limiting battery life [9–11].

Primary prevention of sudden death in patients with structural heart disease remains a significant challenge. It is clear that patients with repaired or palliated structural heart disease are at risk for sudden death. The lesions with highest risk for late onset life-threatening arrhythmias include tetralogy of Fallot, transposition of the great arteries status post atrial switch, and left-sided obstructive lesions [12]. However, there are no consensus guidelines for risk stratification in patients with structural heart disease. In addition, the patient population is quite heterogeneous, making it more difficult to have a unified approach based on type of heart disease. A prototype model for sudden death risk in patients with

structural heart disease is patients with tetralogy of Fallot. Established risk factors for sudden death include absolute QRS duration, rate of QRS change over time, prior palliation with a Blalock–Taussig shunt, older age of repair, and LVEDP >12 mmHg [13–14]. There is ongoing research in this area that is beyond the scope of this chapter, however, lack of consensus guidelines has left each practitioner and center to formulate their own strategy for primary prevention.

52.4 Cardiac Resynchronization Therapy (CRT)

Electrical dyssynchrony results in dyskinetic ventricular activation, which reduces left ventricular efficiency. This is often seen in patients with advanced heart failure. Recent adult data have shown that pacing can be used to restore electrical synchrony to hearts with significant dyssynchrony, termed CRT [15–19]. CRT involves placement of a lead in the left ventricle, typically via the coronary sinus, allowing for more uniform ventricular activation than by right ventricular pacing alone (Fig. 52.3). This has been shown to improve left ventricular ejection fraction, exercise tolerance, and all-cause mortality in various adult studies. Pediatric and adult CHD studies, both retrospective and prospective, have had mixed results likely due to the wide array of anatomies and physiologies in CHD combined with effects of surgical intervention, chronic volume or pressure loading, and varied cellular and myocardial remodeling [20–22]. Initial heterogenous studies showed chronic CRT was associated with improvements in ejection fraction and QRS duration. More recent studies have aimed at separating specific subpopulations, such as repaired tetralogy of Fallot with heart failure, with mixed results. Current evidence does suggest better outcomes in patients with systemic left ventricles and in pacing-induced dyssynchrony. Conversely, in the setting of systemic right ventricles or single ventricle physiology, the CRT outcomes have been mixed. Multisite single ventricle pacing, with multiple epicardial leads placed as far apart as possible on the same ventricle, has been explored with inconsistent results as well [20–24]. Recently, a consensus statement by Pediatric and Congenital Electrophysiology

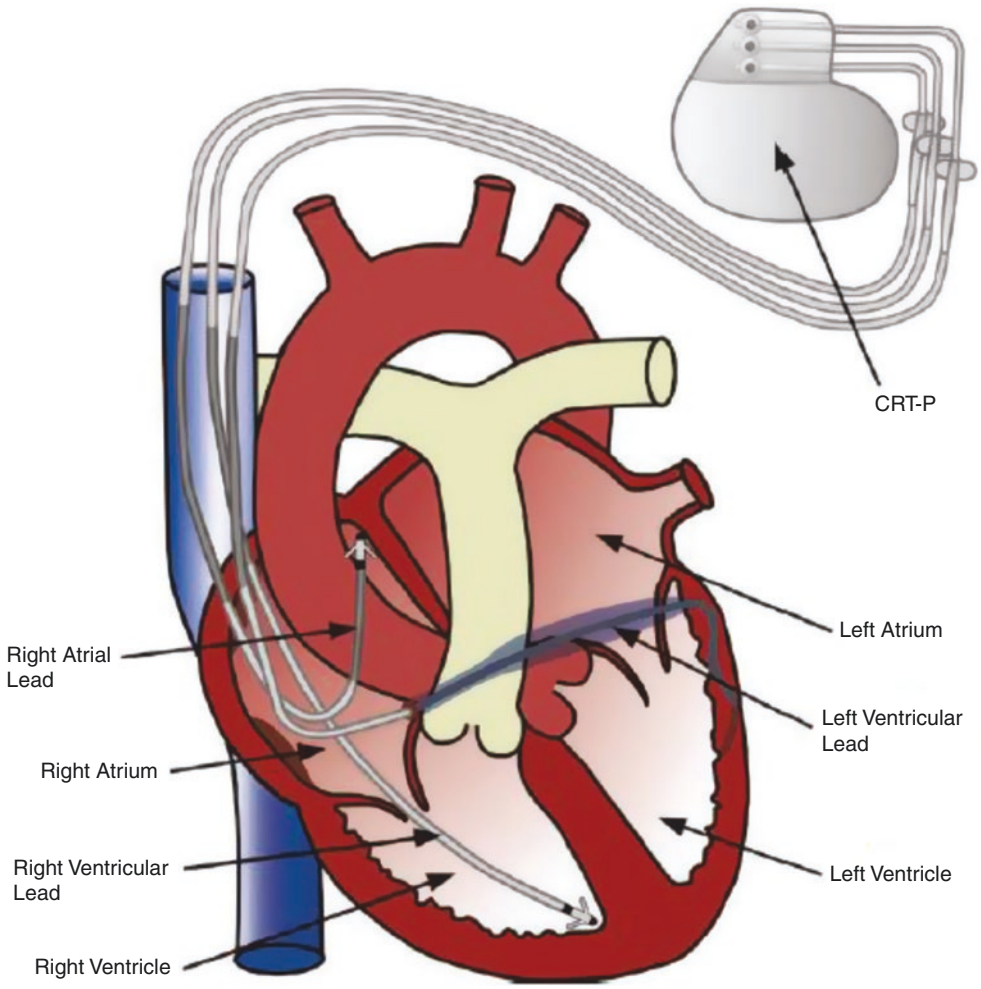

Fig. 52.3 Illustration of lead insertion in typical locations for cardiac resynchronization therapy (CRT). Locations include right atrium, right ventricle, and coronary sinus for left ventricular activation. (Reproduced with permission of Medtronic, Inc.)

Society and Heart Rhythm Society on arrhythmia management in the adult congenital heart disease (ACHD) population included guidelines for the use of CRT therapy modified from the adult algorithm [25].

The role of CRT in the management of pediatric and congenital heart disease patients is evolving and further studies are necessary to elucidate any consensus approach.

52.5 Troubleshooting

Device troubleshooting is a voluminous topic worthy of textbooks in their entirety. In this chapter, we will review two of the most commonly seen device issues and their management. For a more extensive discussion, please consult a pacing textbook. It is also important to note that modern pacemakers and ICDs are often equipped with remote interrogation and management capabilities. These features allow the provider to obtain the majority of information obtained by traditional in-person interrogation via analog or cellular wireless-based transmission. Features vary between brands and models. Use of remote interrogation has decreased clinic visit requirements, improved patient satisfaction, and allowed for earlier detection of actionable events [26].

With pacing, a failure to capture the myocardium may occur, which results in a missed depolarization and a subsequent pause in the ventricular rate. This is termed pacemaker noncapture. It is characterized on the monitor and electrocardiogram by the visualization of pacing artifact with no resultant electrical activity following. This may occur either in the atrium or the ventricle. When it occurs in the ventricle, the consequences are more severe as complete loss of cardiac output may ensue (Fig. 52.4). Once this is seen, the pacemaker (temporary or permanent) should be interrogated to evaluate the lead thresholds and device output. If the device output cannot be adjusted to provide an adequate safety margin, consideration should be given to the establishment of a more secure pacing modality.

Pacemaker oversensing can be similar in effect to noncapture. Pacemakers are often set to inhibit their activity in response to a sensed event. If the pacemaker falsely believes that an intrinsic depolarization has occurred, it will erroneously inhibit, resulting in a lack of depolarization and a resultant pause. This is deemed oversensing and can be distinguished from noncapture (Fig. 52.4) by the absence of pacemaker stimulus artifact compared to pacemaker noncapture where a stimulus artifact will often be visualized.

The peak heart rate supported by a pacemaker is primarily determined by two factors. The first factor is the programmable upper rate limit (URL) and many pacemakers have default settings which limit the URL to 180 bpm. The second factor is the TARP, as discussed at the beginning of this chapter, which is a calculated value composed of the AV delay and PVARP. When the URL is violated, pacemaker Wenckebach may ensure (Fig. 52.5), which is similar to native Wenckebach. In this scenario, a P wave falls in the PVARP and the ventricular lead is therefore unable to respond resulting in a dropped P wave. However, if the programming results in the heart rate violating TARP *before* reaching URL, then 2:1 AV block will ensue. Thus, it is important to program the device with the URL at a lower heart rate than the TARP rate to prevent abrupt 2:1 AV block. In the ICU postoperatively, the most common reason for reaching 2:1 AV block is incorrect programming of the temporary pacemaker, most likely to default nominal (adult) settings instead of age-specific for pediatric patients. Again, pacemaker programming is a complicated topic exceeding the scope of this chapter. For a more detailed discussion of these concepts, consult a pacing textbook.

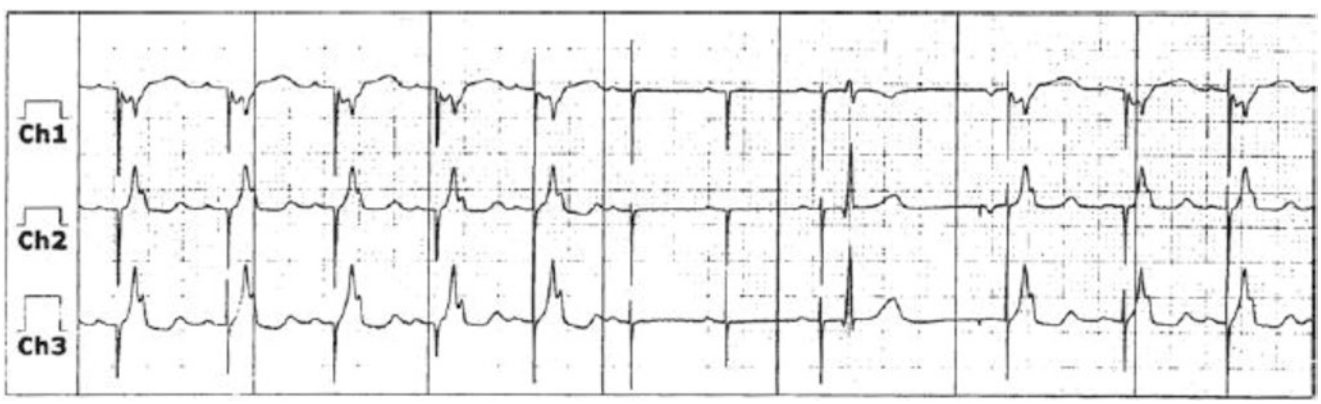

Fig. 52.4 Ventricular noncapture. Pacing spikes are initially followed by wide QRS complexes, indicating successful ventricular depolarization. In the middle of the strip, note the pacing spikes without QRS complexes, indicating noncapture. This is followed by a junctional escape beat (narrow complex)

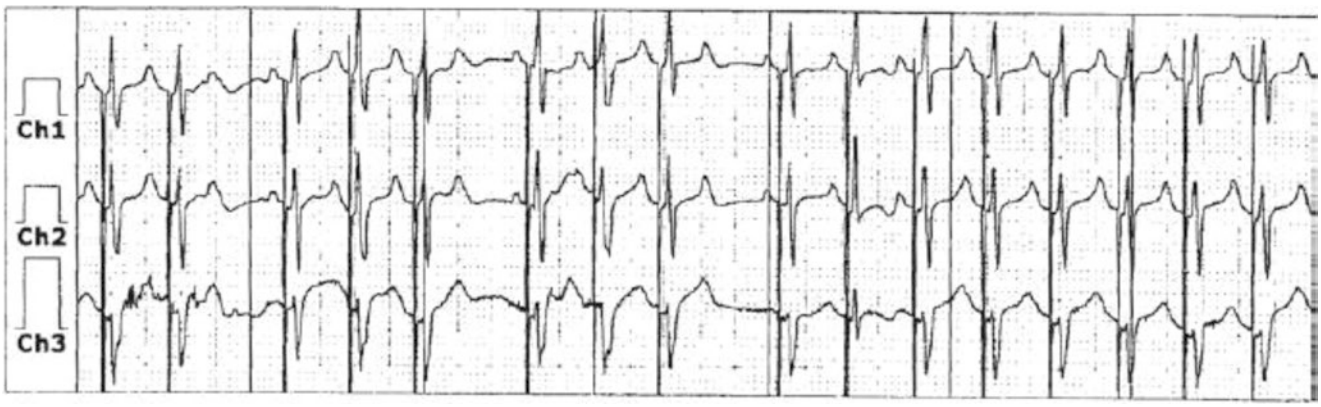

Fig. 52.5 Pacemaker Wenckebach. Initially atrial sensing with ventricular pacing (P waves followed by pacing artifact and QRS complexes). Occasional dropped beats indicate P waves that fall into the refractory period and are not responded to

An additional important note, there has been concern for electromagnetic interference with pacemaker and ICD function with the increase in handheld electronic devices. Recent studies have demonstrated that internal magnets in iPADs and portable headphones are capable of triggering magnet mode response in ICDs when in close proximity resulting in transient suspension of therapies [27–28]. Given the increasing frequency of contact with handheld devices, it is important to counsel patients/families to avoid placing devices close to their ICDs.

52.6 Summary

Electronic device therapies, including pacemakers, implantable cardioverter defibrillators, and CRT, provide important therapeutic options for pediatric and congenital heart disease patients.

Current usage should be based on published guidelines, as well as center and physician preference. Further studies are necessary to assist in formulation of a consensus approach to management of these entities.

Understanding of the basic indications and functioning of these therapies is imperative for anyone involved in the care of these patients, particularly in the intensive care unit setting.

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Chapter 53
Discontinuation of Life-Sustaining Therapy in Intensive Care: Ethical and Legal Issues

Pascale du Pré, Pierre Tissières, and Joe Brierley

Abstract This updated chapter addresses ethically challenging situations that can occur in pediatric intensive care. It begins with an introduction to medical ethics, continues by reviewing key issues in decision-making in pediatrics, and finally considers recent changes in end-of-life care (EOLC). It has taken into account developments in palliative care provision and the growing availability of ethical and other support mechanisms in decision-making, including the greater involvement of children and their families in shared decision-making even in the toughest situations.

53.1 Introduction to Medical Ethics

Ethics is the branch of philosophy dealing with matters of right and wrong, so medical ethics essentially considers what is right and wrong in medicine. However, things are not always so clear-cut in our modern intensive care units. As you will read throughout this book, modern cardiac intensive care practice with extracorporeal membrane oxygenation (ECMO), ventricular assist devices (VADS), heart transplants, and ever more complex operative interventions for congenital heart disease has been part of incredible successes, with children who only 20–30 years ago would have died now surviving and thriving. But, while survival rates have increased, the number of children discharged from ICU with severe neurodisability and/or ongoing need for life-sustaining therapy has also increased [1]. Of course, this reflects not only changes in medical practice but also changes in societal expectations and is outside the remit of this chapter; however, it is worth noting the increased prevalence of children living with life-limiting conditions in the community [2]. Tough decisions now seem to have to be made on what seems like a daily basis. How far should we push a child whose chance of survival is rapidly decreasing? How do we balance the burdens and benefits of possible interventions? How certain are we about the prognosis for the child and of our interventions? Who should make the final decision on whether to intervene: the clinicians, the multidisciplinary team, or the parents?

Pausing, reflecting, and considering the ethics of what we do promises a route to problem-solving, a technique to protect intensive care teams against moral distress and can facilitate our joint working with parents and children in the toughest of situations.

There are several meta-ethical theories which would be useful to understand for those who wish to explore further: *utilitarianism* suggests the greatest good for the greatest number of patients – perfect for ICU directors! *Deontology* is a rule-based theory that wants us to act in a way that if we all did it would be best but that also treat all people as vital human beings, not just a means to an end – perfect for fellows and bedside nurses. *Virtue ethics* asks us to do what the virtuous person would do and aim our good action between excesses – perfect for the cardiac surgeon. *The ethics of care* wants us to consider the crucial interpersonal relationships, so our child is not an isolated individual with rights, so much as a daughter or brother – perfect for our families [3]!

Of course, encountering different ethical standpoints can be a challenge, but also enriches the discussion and can lead to solutions. One approach to try and standardize ethical analysis has rather dominated medical ethical education and analysis over the last decades: *Principlism.* Beauchamp

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and Childress advocated four principles on which to base ethical analysis: respect for autonomy, beneficence, non-maleficence, and justice [4].

Respect for Autonomy This principle suggests that there is an obligation to respect the decision-making capacities of autonomous individuals. In pediatrics, this raises an obvious challenge: neonates and small children are clearly not autonomous individuals; therefore, parents are usually considered as their surrogates. But, as children develop, in most countries, their ability to consent to medical procedures increases, but different jurisdictions take different views on allowing children to refuse medical treatment which someone else consents to [5]. What is clear is that Article 12 of the Convention on the Rights of the Child states that children have the right to participate in decision-making processes that may be relevant in their lives and to influence decisions taken in their regard [6]! While short of autonomy, a degree of decision-making capacity is widely recognized and surely increases the older a child is. Parents usually consent to their child's treatment, but the extent to which they can override/determine clinical decision-making – supporting by international second opinions is one of the great contemporary controversies in pediatrics [7].

Beneficence This principle refers to a moral obligation to act for the benefit of the patient. Although this may seem self-evident, who ultimately determines what is beneficial, and must benefits be definite or possible? For example, parents might, understandably, want to try innovative, unproven, rescue therapies, if the alternative is death. Should clinicians always offer these, however, speculative?

Non-maleficence Often balanced with beneficence, non-maleficence suggests we avoid causing harm to patients. Ostensibly obvious, this is more complex in practice with different viewpoints about what is harmful, and about whether the best interests standard of the UNCRC should give way to a harm principle – that is, whether the operation planned should help the child or simply not cause undue harm. The latter gives far more importance to parents' decisions-making with a broadened zone of parental discretion, which not all ethicists support [8].

There is helpful multi-society guidance for "responding to requests for potentially inappropriate treatments in intensive care units," [9] which pushes away from the previous language of futility, reserving this for the truly physiologically futile.

So, while ventilation, with requisite sedation and suctioning, is recognized to be a somewhat painful life-sustaining intervention, if a parent's goal is continuation of life at all costs, for them ventilation is not *futile* even if it has little chance of restoring an acceptable quality of life or long-term survival, whereas continuing ECMO in the face of severe brain injury and continuing exsanguinating hemorrhage with an aim of recovery is truly futile.

Justice This principle mandates that we treat people equally and without discrimination. It raises challenging dilemmas for the modern healthcare team in terms of allocation of limited resources and the rights of individual to try expensive unproven treatment when they have no alternative. The use of innovative therapy has driven medicine forward arguably more than all the randomized controlled trials undertaken! Yet, how can we consider the resource element at an individual level? One approach is to openly consider this as part of an innovative therapy framework together with parents and children [10].

One classic consideration in this area is the provision of ventilation for premature infants at the limits of viability, where the ongoing burden of care for those infants with complications such as brain injury, short gut syndrome, and chronic lung disease is associated with significant ongoing national financial consequences at a time when some very expensive effective chemotherapies are not available for the entire population in most countries.

53.2 Essential Elements of Medical Decision-Making

Decision-making is one of the most challenging issues in modern pediatric intensive care. The overdue end of paternalism has been associated with the loss of physician/healthcare team autonomy. Concurrently, population shifts have brought a range of less familiar cultures and religious beliefs at a time of an emerging shared decision-making paradigm in healthcare. Values and beliefs are increasingly crucial in determining the course of action, not just clinical facts. This is not limited to the beliefs of patients but includes those of treating clinicians [11].

53.3 Informed Consent

Informed consent is a process in which patients are provided with adequate information to allow them to decide freely whether to accept or decline a recommended medical inter-

vention. As discussed, different jurisdictions have different standards about whether a child can consent or refuse medical treatments based on age and/or capacity. Parents are the usual surrogate decision-makers for their children, and so they can usually consent for treatment though again different countries consider the age at which children can, or should, consent instead differently. Informed consent must satisfy at three key requirements: competency, information provision and understanding, and freedom from undue influence.

Competency Most of our children in ICU are not competent due to sedation and the critical illness that they have been admitted with. Some may have contributed to decisions to plan surgery, and some may well be able to take part in decision-making if they are awake, for example, a child on VV ECMO without sedation. If competent, they may even be the primary provider of consent.

A competent individual has the capacity to understand the medical situation, consider the risks and benefits, make a choice among the alternatives, decide upon a course of action, and appreciate the consequences of the choice. However, it is more usual for the child's parent or someone with parental responsibility to provide consent for interventions or indeed for ongoing provision of ICU support.

As discussed, the generally accepted standard for decision-making in pediatrics is the best interests standard. So, decisions should be made on behalf of children by their parents and the healthcare team if they are in *the child's* best interests.

Information The information provided should allow the decision-maker to weigh the benefits and burdens of the proposed treatment options. It should be provided in a manner the patient (child) or their parents can understand. This might require translation services, videos, and a number of other techniques for children with disability that have the same rights to participate in decision-making as others.

Understanding While some of the complex situations in pediatric cardiology and intensive care might seem impossible to explain to lay people – the duty to do so – and to ensure that those providing consent fully understand what is proposed, any alternatives and the anticipated risk and benefits fall fully on the clinician.

In general, clinicians overestimate parental understanding, and some parents may not truly *hear* what is said due to a situational incapacity associated with the stress caused by their child's illness and the need to make emergency decisions [12].

53.4 Special Issues in Pediatric Intensive Care

53.4.1 Family Access to Their Child

Children do best in a family-centered environment, and the critically ill child is no different. Parents should have open access to their child as they are a crucial part of the team helping the child throughout their ICU stay and they provide a constant reassuring for the child as they emerge in the unfamiliar environment. Clear communication should occur between the parents and the medical teams about all matters affecting the child but especially the importance of parental involvement [13]. This can be best delivered by bespoke family-liaison nurses [14].

53.4.2 Family-Centered Care

Family-centered care is an approach to planning, delivery, and evaluation of healthcare grounded in mutually beneficial partnerships between healthcare providers and families [15]. Parents are acknowledged as the experts in the care of their child, and the perspectives and information they provide are acknowledged as important to clinical decision-making [16]. Not all accept this as optimal, as it arguably minimizes the concept of child-centered care and the role of the healthcare provider [17].

53.4.3 Shared Decision-Making

In order to determine the child's best interests, the team must weigh the burdens and benefits of providing (or withdrawing) treatment. The clinical team provides knowledge of the medical condition, prognosis, and prior experience with other similar cases, but the family brings unique knowledge of the child and their values and religious beliefs.

The two extremes that either the parent as surrogate should be the only decision-maker or that situational incapacity means that physicians should bear sole responsibility for the final decision are both clearly incorrect. In most situations, however challenging, a shared decision between expert parents and expert clinical teams can be made in the child's best interest. If disagreement persists – most frequently encountered in withdrawing life-sustaining therapies on the ICU – then a number of support mechanisms are available including ethics committees, chaplaincy, medication, external second opinions, and ultimately the courts [18].

53.4.4 Participation in Care

The role of caregiver can be hard for parents to maintain in the unfamiliar ICU environment, especially at a time of great stress. One of the most crucial roles for the bedside nurse is helping parents, who may feel frightened by their child's appearance or overwhelmed by technology, to overcome these issues and take on the parenting role within ICU. This can be as simple as holding their child's hand despite all the machines, assisting with tracheal suctioning, positioning, or even bathing and massage [19].

53.4.5 Presence of Parents in Rounds

The presence of parents during ICU rounds is encouraged in many institutions and suggested as a right by some medical societies [20]. Concerns about increased time required for rounds and the inhibition of open discussion among staff are not born out in the literature [21], although some families may be intimidated by the medical staff or their own lack of medical training [22]. Clearly, ward rounds are not the best place to convey sensitive information or to obtain family input into difficult decision-making.

53.4.6 Presence of Family Members During Resuscitation and Cardiopulmonary Resuscitation (CPR)

Traditionally parents/family member presence during CPR has been controversial. Does parent presence affect the performance of resuscitation staff? Is witnessing CPR on their child damaging to parents' emotional and psychological outcome? Such concerns are not supported by the admittedly scanty literature [23]. However, family member presence during episodes of CPR has become the norm, although this is not quite (yet) the case for ICU thoracotomy…

53.5 Essential Elements of End-of-Life Care

End-of-life care in the ICU has improved dramatically over the last decade, with routine palliative care rounds [24], transfer out for one way wean of life-sustaining therapy to offer a choice in place of death [25]. Organ donation is now a routine part of end-of-life care in the ICU, both following brain death and – depending on national standards – following circulatory determination of death. Traditional concerns about invasive postmortem investigation are being addressed by novel end-of-life investigations such as minimally invasive or limited autopsy and postmortem imaging [26].

53.5.1 Optimal Care for Dying Children in the PICU

The steady increase over the last decade in the number of children living with life-limiting conditions in the community underpins a stark change in healthcare [27]; many children with existing palliative care needs are now admitted to ICU [28]. Palliative care teams refer children for ICU, as well as becoming involved during an episode of critical illness. Integration of specialist palliative care teams with modern ICU has led to routine ward rounds, goal-directed care for resuscitation with advanced care plans and a holistic compassionate approach to the dying child both within and outside the ICU.

Situations in which individual children should be spared inappropriate invasive procedures:

(i) For children who cannot benefit from a period of organ support, ICU admission should be avoided.
(ii) For children who die in ICU, the mode of death varies between different countries – based on the cultural approach to death. In US and Northern European countries, around 10% are brain dead and around 25% die with full resuscitation ongoing. Of the remainder, half die after withdrawal of life-sustaining therapies and half after withholding or a ceiling of treatment has been established; in Southern Europe and elsewhere, withdrawal of LST is less frequent [29].

53.6 Preparation of the Child, His or Her Family, and the Clinical Team

This preparation is based on open transparent communication and an understanding of the child and family's needs. Thoughtful care of the parents and relatives, with respect for cultural and spiritual norms in dying and post death care are crucial, but the child's comfort and care must be the primary focus of caregivers. The needs of the clinical team are also important and excellent care at the end of life should be recognized as an institutional priority, with adequate opportunities for training and appropriate debriefing.

53.7 Providing Palliative Care

Parallel planning is increasingly the norm, even in ICU. The traditional curative model, with criteria related to the degree to which interventions will contribute to recovery from illness coexisting, for those with end of life needs, with the palliative model where criteria are related to whether interventions will provide symptoms relief – with relief of pain and anxiety a priority, improved functional status, or ameliorate emotional, psychological, or spiritual concerns [30].

The increased use of validated pain, anxiety, and delirium scales has provided for better quantification even in neonates and small infants and facilitates more sensitive use of both nonpharmacologic and pharmacologic approaches.

The Doctrine of Double Effect is often suggested as an ethical tool to facilitate adequate analgesia at the end of life. Here, an agent such as morphine can ethically be given to the dying patient even if the respiratory suppression might hasten death, because the intention of the clinician is to provide analgesia. Of the double effect, only one is intended. Despite the fact that this is rather redundant as effective analgesia in dying patients actually prolongs life, and as intensivist, the actions and side effects of the drugs we use are part of our treatment plans. Still, if this allows adequate analgesia to be provided to dying children, esthetic objections can be waived.

Of course, in some jurisdictions, euthanasia as well as assisted dying for children is lawful, though there are no reports of this within an intensive care environment.

53.8 Withholding and Withdrawing Life Support

Decisions to withhold, withdraw, or limit life-sustaining treatment in children with life-limiting or life-threatening illness may still prove contentious, difficult, and emotive.

Withholding treatments is often considered easier than withdrawing them: deciding not to intubate a child who cannot recover and extubating a child who has failed to recover despite a period of ventilation are philosophically the same, yet emotionally and often legally different.

The types of treatment that can be withheld and withdrawn as well as the type of situations in which this may be considered are delineated in a useful UK RCPCH framework freely available online [16].

It has been shown that parents who were with their child at the time of death did not regret having been present, whereas parents who were not present later wished they had been.

53.9 Communication

Communication consistently emerges as an important, and indeed perhaps the most critical determinant of the satisfaction of parents with the care of their dying children. In some studies, parents rated parents–doctors communication as the principal determinant of high-quality physician care. Problems in communication lie at the heart of many conflicts that occur between families and clinicians in the ICU. In most cases, with effective communication the clinical team and parents do reach agreement. In those rare cases where this does not prove possible, the Court should be approached to give a determinative opinion.

Parents always welcome the opportunity for scheduled meetings with clinicians. Some parents want to reduce the potential for contradictory information by having a single point person to communicate with. Others prefer to hear from multiple perspectives.

53.9.1 Legal Issues

The Law surrounding discontinuation of life-sustaining treatments is highly dependent upon the legislation of the country in question. In many Western countries, there is consensus in the law that parents have the authority to consent to medical treatments in the best interests of their children and to make decisions that are in accord with their own values. Parents cannot, however, demand treatments that the clinical team does not think are in the *best interests* of the child, although they can try to find other teams that will. One of the most interesting questions for the immediate future is whether in the age of the internet and modern communication, this remains limited by national boundaries, and what the financial implications of this are given different national healthcare funding models.

In general, healthcare professionals must obtain the consent of the parents (those with parental responsibility) before giving any treatment to a child, or of the child if they are able to lawfully provide it. Parents, however, cannot insist on medical treatment that clinicians do not think is in the child's best interests, though the clinician has a moral duty to make reasonable efforts to seek another who might be willing to do so. Conversely, clinicians can only override parental decision-making with a court order or in a genuine emergency where agreement cannot be reached to enable life-sustaining measures to be used before the courts are approached.

Involving the legal system is often a very stressful experience for both the child's family and the clinical team and it is costly. It certainly warrants further ethical consideration regarding allocation of resources and other techniques such as clinical ethics services are strongly recommended.

53.10 Conclusion

Advances in pediatric intensive care medicine have also led to ethical and legal challenges for a small number of children who have prolonged admissions with persisting technological dependence both in ICU and at home. They and others have recurrent ICU admissions that have led to significant concerns for critical care providers. One of the most striking changes is that the majority of deaths in the ICU now occur following the decision to withdraw or withhold life-sustaining treatments, so they are managed deaths. This fact heightens the importance of competence in end-of-life decision-making and timely introduction of parallel palliative care provision by all practitioners working in pediatric ICUs and pediatric cardiac ICUs.

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Part IV

The Challenge of Extra-cardiac Complications

Chapter 54
Respiratory Complications: Acute Respiratory Distress Syndrome, Chylothorax, Diaphragmatic Palsy and Paresis, Respiratory Physiotherapy, and Tracheostomy

Jiuann-Huey Ivy Lin, Jennifer Exo, and Ricardo A. Munoz

Abstract This chapter addresses the respiratory complications/issues that can occur in pediatric cardiac intensive care unit. Pulmonary complications are prevalent in the critically ill cardiac patients, and the acute respiratory distress syndrome (ARDS), chylothorax, and diaphragmatic dysfunction after cardiac surgery are frequently encountered in pediatric cardiac intensive care unit.

54.1 Acute Respiratory Distress Syndrome (ARDS)

54.1.1 Introduction

Acute respiratory distress syndrome (ARDS) is a clinical syndrome of noncardiogenic pulmonary edema that is an uncommon postoperative complication after pediatric cardiac surgery, heart transplantation, and cardiopulmonary bypass. Children with ARDS are some of the most challenging patients to manage in the ICU. It is necessary for those caring for critically ill children with heart disease to understand the pathophysiology, clinical course, and therapies used to treat ARDS.

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54.1.2 Definition

The definition of ARDS has evolved with our understanding of the disease. ARDS was first called "adult respiratory distress syndrome" by Ashbaugh et al. in 1967 [1], the authors reported 12 patients (five between 11 and 19 years of age) with tachypnea, hypoxemia and diffuse opacities on chest radiographs, with hyaline membranes lining the alveolar spaces in postmortem studies in 6 of the 7 patients. The pathological findings were thought to be specific for the respiratory distress syndrome of the neonates at that time. The title of ARDS was changed to "acute respiratory distress syndrome" after being recognized in newborns and children. In 1994, the American-European Consensus Conference (AECC) [2] developed the widely accepted definition for ARDS and acute lung injury (ALI): ALI is defined as an acute onset of respiratory distress and hypoxemia (defined as a P_{aO2}/F_{iO2} ratio $\leq$ 300), bilateral infiltrates on a chest X-ray, pulmonary wedge pressure $\leq$ 18 mmHg, or absence of clinical evidence of left atrial hypertension. ARDS is characterized by the same chest X-ray findings and pulmonary wedge pressure findings, but with more severe hypoxemia (defined as a P_{aO2}/F_{iO2} ratio $\leq$ 200).

The Pediatric Acute Lung Injury Consensus Conference (PALICC) published the first pediatric-focused definition for pediatric acute lung injury and ARDS (Fig. 54.1) in 2015 [3]. Some of the key elements of this consensus document include: (1) creation of criteria to define ARDS in patients with cyanotic congenital heart diseases (acute onset, a known clinical insult, new onset pulmonary parenchymal disease, acute deterioration on oxygenation not explained by the underlying cardiac disease); (2) inclusion of patients with unilateral lung disease; (3) stratification of the severity of lung injury based on an oxygenation deficit, as defined by the oxygenation index (OI, $F_{iO2} \times$ mean airway pressure $\times$ 100/P_{aO2}) or oxygen saturation index (OSI, $F_{iO2} \times$ mean airway pressure $\times$ 100/S_{po2}) with minimum positive end-expiratory pressure (PEEP); (4) utilization of pulse oximetry-based metrics when P_{aO2}

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a **Pediatric acute respiraotry distress syndrome (PARDS)**

Age	Exclude patients with peri-natal related lung disease			
Timing	Within 7 days of known clinical insult			
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	**Non Invasive mechanical ventilation**	**Invasive mechanical ventilation**		
	PARDS (No severity stratification)	Mild	Moderate	Severe
	Full face-mask bi-level ventilation or CPAP ≥ 5 cm H_2O [2] PF ratio ≤ 300 SF ratio ≤ 264 [1]	4 ≤ OI < 8 5 ≤ OSI < 7.5[1]	8 ≤ OI < 16 7.5 ≤ OSI > 12.3[1]	OI ≥ 16 OSI ≥ 12.3[1]
Special Populations				
Cyanotic Heart Disease	Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease.[3]			
Chronic Lung Disease	Standard Criteria above for age, timing, and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline whic meet oxygenation criteria above.[3]			
Left Ventricular dysfunction	Standard Criteria for age, timing and origin of edema with chest imaging chenges consistent with new infiltrate and acute deterioration in oxygenation whic meet criteria above not explained by left ventricular dysfunction.			

b **At risk of pediatric acute respiratory distress syndrome (PARDS) definition**

Age	Exclude patients with peri-natal related lung disease		
Timing	Within 7 days of known clinical insult		
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload		
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease		
Oxygenation	**Non Invasive mechanical ventilation**		**Invasive mechanical ventilation**
	Nasal mask CPAP or BiPAP	Oxygen via mask, nasal cannula or High Flow	Oxygen supplementation to maintain spO_2 ≥ 88% but OI < 4 or OSI < 5[1]
	FiO_2 ≥ 40% to attain spO_2 88-97%	SpO_2 88-97% with oxygen supplementation at minimum flow[2]: < 1 year: 2 L/min 1 – 5 years: 4 L/min 5 – 10 years; 6 L/min >10 years: 8 L/min	

Fig. 54.1 (**a**) Pediatric acute respiratory distress syndrome (PARDS) definition. [1]Use P_{aO2}-based metric when available. If P_{aO2} is not available, wean F_{IO2} to maintain $S_{pO2} \leq 97\%$ to calculate oxygen saturation index (OSI; [F_{IO2} × mean airway pressure × 100]/S_{pO2}) or S_{pO2}:F_{IO2} (SF) ratio. [2]For non intubated patients treated with supplemental oxygen or nasal modes of noninvasive ventilation, see (**b**) for "at-risk" criteria. [3]Acute respiratory distress syndrome severity groups stratified by oxygenation index (OI; [F_{IO2} × mean airway pressure × 100]/P_{aO2}) or OSI should not be applied to children with chronic lung disease who normally receive invasive mechanical ventilation or children with cyanotic congenital heart disease. CPAP = continuous positive airway pressure, PF = P_{aO2}:F_{IO2}. (**b**) At risk of pediatric acute respiratory distress syndrome (PARDS) definition. [1]If P_{aO2} is not available, wean F_{IO2} to maintain $S_{pO2} \leq 97\%$ to calculate oxygen saturation index (OSI). [2]Given lack of available data, for patients on an oxygen blender, flow for at-risk calculation = F_{IO2} × flow rate (L/min) (e.g., 6 L/min flow at 0.35 F_{IO2} = 2.1 L/min). BiPAP bilevel positive airway pressure, CPAP continuous positive airway pressure, OI oxygenation index. (By permission from Ref. [3])

is not available; (5) additional diagnostic consideration for patients with chronic lung disease, including those treated with supplemental oxygen, noninvasive ventilation, or invasive ventilation via a tracheostomy; and (6) elimination of age criteria, with the exception of perinatal-related lung injury, which recognizes the unique physiology of the transition from fetal circulation to newborn circulation and the postnatal lung growth and development. The PALICC consensus recommendations also expanded the definition of pediatric ARDS to consider the type of respiratory support (invasive versus noninvasive) required by the patient. Children receiving invasive mechanical ventilation with an OI greater than or equal to 4, or an OSI greater than or equal to 5 fulfill the criteria for the diagnosis of pediatric ARDS. Children being treated with full face mask noninvasive ventilation (BiPAP or CPAP) with a minimum CPAP of 5 cm H_2o who have a

P/F (P_{aO2}/F_{iO2}) ratio less than or equal to 300 or an S/F (S_{pO2}/F_{iO2}) ratio less than or equal to 264 also meet the diagnostic criteria for ARDS. The category of "acute lung injury" (ALI) was eliminated and replaced with a grading of ARDS severity. The grading system is preferentially based on OI or OSI criteria rather than the PF ratio, with pediatric ARDS being described as mild (OI = 4–8), moderate (OI = 8–16), or severe (OI > 16). Although the diagnosis of pediatric ARDS remains clinical, the adoption of a consensus definition will facilitate earlier recognition of severe pediatric respiratory disease, standardize optimal treatment priorities and identify knowledge gaps for future research.

54.1.3 Pathophysiology

A pair of newborn lungs contain approximately 50 million alveoli, increasing to approximately 500 million (range: 274–790 million) alveoli in fully mature human lungs. The pulmonary vasculature starts as a duplicate network and matures into a single network [4]. Pediatric studies suggest similarity in the pathophysiology of ARDS in children and adults, but studies have not been performed to evaluate the impact of different stages of pulmonary development on ARDS, which would have the potential to develop the best therapeutic strategies for ARDS with increasing age. Several contributing mechanisms have been associated with ARDS [4].

1. Inflammatory Dysfunction: The initial exudative phase of ARDS is characterized by the loss of the epithelial-endothelial permeability barrier and accumulation of edema fluid within the interstitium and alveolus mediated by innate immune cells [5]. The development of ARDS appears to be caused by direct injury to the alveolar epithelium and capillary endothelium (infectious agents, toxins) or "indirect" insult to the lung (trauma, transfusion, nonpulmonary sepsis, pancreatitis, or cardiopulmonary bypass). Neutrophils migrate into the alveolar compartment to defend against infection but produce several proinflammatory substances, including leukotrienes, proteases, reactive oxygen, and nitrogen species, which serve to propagate lung damage. Resident alveolar macrophages detect the presence of microbial components (such as lipopolysaccharide (LPS)) or tissue injury (damage/danger-associated molecular patterns (DAMPS) such as heart shock proteins, histones, and mitochondrial DNA) using pattern recognition receptors (Toll-like receptors) and promote the inflammatory response through the mitogen-activated protein kinase (MAPK) pathway and the transcription factor, nuclear factor κβ (NFκβ) [6, 7]. These responses result in the increased expression of cytokines and chemokines [6, 7]. Several biomarkers, including pulmonary microvascular endothelial markers related to inflammation (tumor necrosis factor [TNF]-α, interleukin [IL]-6, IL-8, IL-1β) [8, 9] and proteases (the antimicrobial agents released by neutrophils to protect the host) [10] have been implicated in adults with ARDS.
2. Loss of Integrity of Alveolar Epithelial/Endothelial Permeability: The alveolar epithelial/endothelial barrier consists of alveolar epithelium, pulmonary capillary endothelium and epithelial basement membrane (Fig. 54.2). Changes in capillary endothelial integrity allow protein-rich fluid to leak from the plasma into the lung interstitium and airspaces [5]. This results in changes in pulmonary mechanics (decreased compliance), pulmonary function (decreased functional residual capacity and forced vital capacity) and impaired oxygenation [4, 11]. In addition, concentrations of cytokine (such as IL-1, IL-8 and TNFα) and lipid mediator (such as leukotriene B4) are significantly elevated.
3. Alveolar Epithelial Dysfunction: Under normal conditions, the lung epithelial barrier is much less permeable than the endothelial barrier. There are two types of pulmonary epithelial cells: (1) Alveolar type (AT)-1 cells, which make up 90% of the alveolar surface and are easily injured; (2) cuboidal AT-II cells, which are more resistant to injury. AT-II cells can produce surfactant and differentiate into type I cells after injury [12]. The damage of the lung epithelium during ARDS compromises the ability of the lungs to (1) maintain a permeability barrier and (2) remove excess alveolar fluid. The ability of the alveolar epithelial cells to mediate sodium-dependent intracellular transport across the epithelium is associated with improved outcome in ARDS [13]. The rate of alveolar fluid clearance can be accelerated by cAMP agonists (including elevated endogenous levels of epinephrine or the exogenous administration of β2 adrenergic agonists) [14] or catecholamine-independent pathways (glucocorticoids, thyroid hormone, and keratinocyte growth factor) [15]. However, the use of the aerosolized β2 adrenergic agonist albuterol failed to prove efficacious in adults with ARDS in a randomized trial [16]. Elevated serum levels of lung proteins including Krebs Vonden Lungen (KL)-6 (a glycoprotein on AT-II, a marker of epithelial cell damage and regeneration) [17], SP-D [18] and receptor for advanced glycation end products (RAGE) [19] have been observed in adults and children with lung injury.
4. Pulmonary Endothelial Dysfunction: The pulmonary endothelium is a component of the alveolar-capillary unit; it is vulnerable to mechanical, chemical, or cellular injuries mediated by inhaled compounds or delivered through the pulmonary circulation [4]. Activated pulmonary endothelium induces changes in vascular tone and integrity, activates the proinflammatory process and becomes procoagulant [20]. Elevated serum levels of

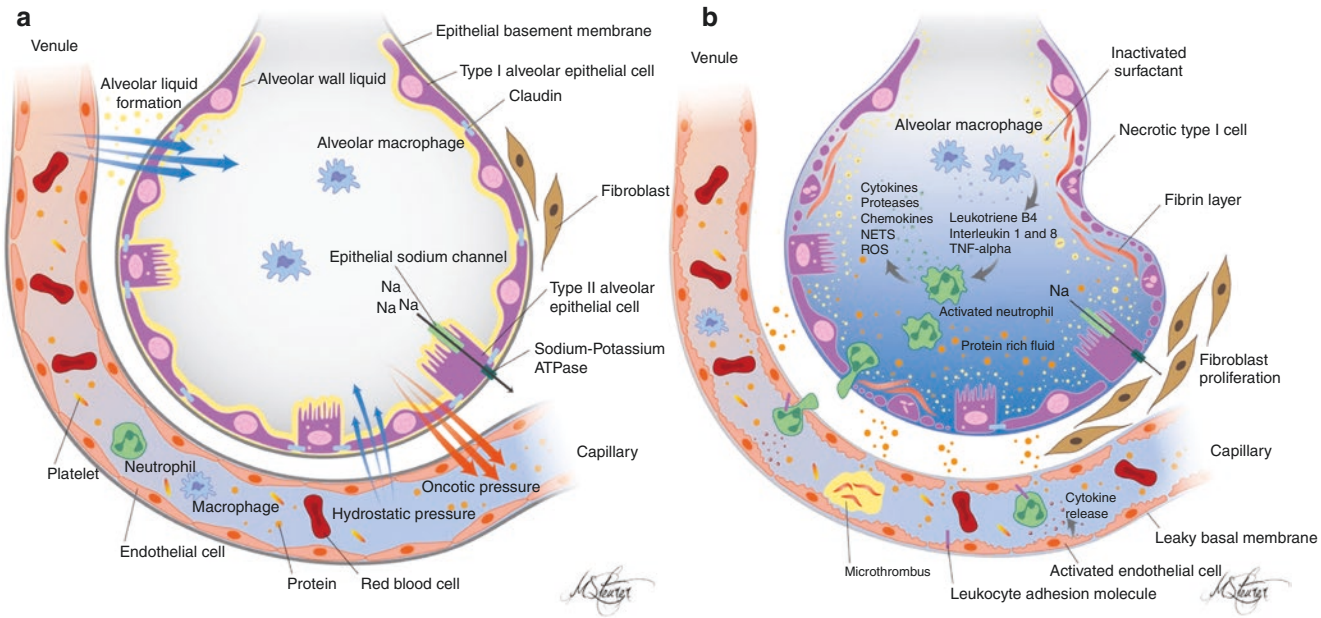

Fig. 54.2 (**a**) Schematic of a healthy alveolus. The alveolar epithelium and capillary endothelium are intact. The characteristics of the pulmonary circulation and intact epithelial endothelial barrier allow for formation of the alveolar wall liquid (AWL) while maintaining the air-filled, fluid-free; status of the alveoli. The AWL facilitates gas exchange and is a medium for the dispersal of surfactant and alveolar macrophages, which is essential for maintaining alveolar stability and host defenses. The intact sodium-dependent vectoral transport across type II alveolar epithelial cells regulates the removal of excess alveolar fluid. (**b**) Schematic of the pathophysiology in acute respiratory distress syndrome. There is a loss of epithelial and endothelial barrier integrity and a loss of function leading to increased permeability pulmonary edema. Solutes and large molecules such as albumin enter the alveolar space. In the presence of proinflammatory mediators and activated endothelium leukocytes traffic into the pulmonary interstitium and alveoli. There is activation of coagulation and deposition of fibrin in the capillaries and alveoli with increased concentrations of fibrinogen and fibrin-degradation products in the edema fluid. Surfactant depletion and degradation result in large increases in surface tension and a loss of alveolar shape and integrity. Recovery is preceded by fibroblast proliferation. NETs neutrophil extracellular traps, ROS reactive oxygen species, TNF tumor necrosis factor. (By permission from Ref. [4])

endothelial-specific proteins such as soluble thrombomodulin [21], von-Willebrand factor (Vwf) [22], angiotensin-converting enzyme (ACE) [23], and tissue factor pathway inhibitor (TFPI) [24] have been noted in children and adults with ARDS. Persistent pulmonary endothelial dysfunction and hypoxic vasoconstriction can increase pulmonary vascular resistance. Elevated pulmonary and arterial pressures contribute to the development of pulmonary hypertension, which can cause shunting of the blood from the right to the left side of the heart if a direct connection is present or compromise cardiac output if no such connection exists. Prolonged pulmonary hypertension also contributes to the development of right ventricular dysfunction and failure.

5. Surfactant Dysfunction: Surfactant is essential for maintaining normal lung physiology; it lowers surface tension within the alveoli. Alveolar epithelial injury causes necrosis and sloughing of type I alveolar cells, protein influx and damage to Type II alveolar epithelial cells, which alters the production and function of surfactant, decreasing lung compliance [4]. Polymorphisms of SP-B, a major protein of surfactant, has been associated with more severe lung injury in African American children with pneumonia [25].
6. Thrombosis and Fibrinolysis Dysfunction: The lung endothelium provides the surface that integrates the inflammatory pathways and the coagulation cascade [26]. During ARDS, neutrophils release platelet-activating factor (PAF) along with other procoagulant inflammatory factors. The balance of coagulation and fibrinolysis is altered, resulting in the development of systemic microthrombi, occlusion of vascular remodeling, and the development of pulmonary hypertension.
7. Finally, mechanical ventilation itself can contribute to lung injury by producing barotrauma (elevated peak/plateau airway pressure), volutrauma (high tidal volume/over-distention) and/or atelectrauma (repetitive opening and closing of alveoli). In addition to the toxic effects of prolonged ventilation with high fractions of inspired oxygen, the mechanical stress of artificial ventilation applied to susceptible alveoli amplifies inflammation. Since the amount of lung available for oxygenation and ventilation is greatly reduced in ARDS, the volume and pressure applied by mechanical ventilation causes the overdistension of uninjured alveoli. Repeated collapsing and reopening of alveoli also stimulate the release of inflammatory cytokines. Together, these changes cause

the impaired gas exchange and altered lung mechanics that characterize the acute phase of ARDS.

54.1.3.1 Resolution of ARDS

Timely resolution of these pathological processes is required for recovery during the second/ proliferative phase of ARDS. The return of normal structure and function involves the resolution of inflammation, repair of the lung epithelium and capillary endothelium, and removal of fluid, without the generation of fibrotic tissue. Excess neutrophils undergo apoptosis and phagocytosis by lung macrophages. Active transport of sodium and chloride from the alveoli into the interstitium facilitates the resolution of alveolar edema. Water passively follows these ions through aquaporins, located primarily on Type I alveolar cells. Insoluble proteins are then removed by local cell endocytosis and phagocytosis, making it possible to rebuild the alveolar hyaline membrane framework. Type II alveolar cells multiply, migrate on the damaged framework, and then differentiate into type I cells [27]. Recent studies in animal models suggest that other lung progenitor cells are involved in repairing epithelium, including Clara cells and integrin α6β4 alveolar epithelial cells [28]. The type I cells restore alveolar structure and the alveolar-capillary barrier, new blood vessels form, and normal gas exchange and lung mechanics are restored.

Many patients experience substantial improvement within the first week of ARDS, while others develop fibrosing alveolitis, the final/fibrotic phase of ARDS [5]. Progression into fibrotic lung disease usually occurs 5–20 days after disease onset; the fibrotic phase does not occur in all patients with ARDS, but excessive fibrosis is associated with increased mortality. In the fibrotic phase, alveolar edema and inflammation become less prominent. Instead, granulation tissue, rich in collagen and fibrin, is deposited. This granulation tissue, along with fibroblasts and procollagen III peptide, fill the alveolar spaces, making the lungs less compliant and susceptible to further injury. The fibrotic phase is usually prolonged, increasing the risk of developing nosocomial infections, organ failure, and respiratory muscle deconditioning. The progressive fibrosis further reduces lung compliance, rendering PEEP less effective at recruitment of the collapsed alveoli and contributing to carbon dioxide retention. Patients in this stage often require weeks of mechanical ventilation, and after recovery, they are at risk of increased bronchial reactivity and extrapulmonary complications (muscle wasting and weakness). Most patients who survive ARDS do not have long-term lifestyle limitations or severe chronic pulmonary disease, but lung abnormalities, particularly involving gas exchange, may persist for an extended period.

54.1.4 Treatment

The priority in the care of children with ARDS is identification and treatment of the underlying causes and maintaining reasonable oxygenation and ventilation. The onset of ARDS is characterized by the rapid development of respiratory distress, hypoxemia that responds poorly to oxygen and infiltrates on chest X-rays and pleural effusions. Alveolar and interstitial edema can increase the effort of breathing by increasing resistance to airflow and decreasing lung compliance. When combined with respiratory muscle fatigue, intubation, and mechanical ventilation are often necessary. Computed tomography of the chest of an ARDS patient often reveals heterogeneous disease with areas of normal lung interspersed with regions of consolidation and collapse. The areas of lung with normal compliance can become overdistended as more of each breath is delivered preferentially to them instead of their stiff, damaged counterparts. This further reduces the functional residual capacity of the lung and increases intrapulmonary shunting.

54.1.4.1 Ventilation and Oxygenation Strategies

Survival of patients with ARDS often requires intubation and mechanical ventilation. Supportive therapy for ARDS is focused on limiting further lung damage through lung-protective ventilation and meticulous fluid management [5]. The optimal approach to lung-protective ventilation is unknown but experimental and human research suggests using specific oxygenation and ventilation strategies. Traditionally, mechanical ventilation is titrated to achieve normal arterial blood gases; this is often accomplished by using tidal volumes measuring 10–15 ml/kg of predicted body weight. Numerous studies have shown that excessive tidal volumes damage consolidated (low volume/ poor compliance) lungs. The physiological tidal volumes in a normal person (including neonates) are in the ranges of 6–8 ml/kg [29, 30]. Trials using lower ventilator settings at the expense of gas exchange were undertaken, and a landmark ARDS network study demonstrated that low tidal volume lung protective strategies improved outcome [31]. The NIH ARDS network compared 6 versus 12 ml/kg of tidal volume and positive plateau pressure less than 30 cm H_2O (lung protective group) versus less than 50 cm H_2O (control group). Oxygen saturation was maintained between 88% and 95% by adjusting PEEP to maintain minimal F_{iO2}. The levels of arterial carbon dioxide could rise if arterial pH remained higher than 7.15 (permissive hypercarbia). The pH was maintained by increasing the ventilator respiratory rate and by titration of a sodium

bicarbonate infusion. The patients ventilated with the lower tidal volume strategy had significantly reduced mortality, increased ventilator-free days, and reduced incidence of extrapulmonary organ failure in the first 28 days of their hospital stay when compared with the traditional ventilation group (control arm). However, this study was criticized for using supranormal tidal volumes in the control arm. Notably, a subgroup analysis from the same NIH ARDS network trial [31] comparing patients with low versus high respiratory compliance (using a compliance of 0.6 ml/cm H_2O/kg as a cutoff point) demonstrated that only patients with poor lung compliance at study entry had a survival benefit when randomized to the 6 ml/kg study arm [32]. A similar finding was reported in a pediatric group with an inverse relationship to mortality with tidal volumes but a direct relationship with airway pressures [33]. These observations support the concept of keeping lung tissue strain (the ratio between inflated volume and functional residual capacity) low to protect the lung [34]. PALICC recommends targeting tidal volumes of 3–6 ml/kg predicted body weight for patients with poor lung compliance and closer to the physiological range (5–8 ml/kg ideal body weight) for patients with better compliance [35]. Various methods have been used to estimate the ideal body weight of infants and children, most of them based on gender and height measurements [36] or ulnar length [37] inpatients with skeletal anomalies.

An important consequence of using lung protective strategies is the development of hypercapnia. Ideally, the $PaCO_2$ will rise no more than 5 mmHg per hour. $PaCO_2$ levels of 65–85 mmHg are considered acceptable, and bicarbonate is used to maintain a desirable pH. An increasing amount of sedation may be required to reduce the patient dyspnea and air hunger that result from rising levels of carbon dioxide. Hypercapnia can increase pulmonary capillary resistance and mean pulmonary arterial pressure, which is an important consideration in patients with heart disease.

Manipulation of positive end-expiratory pressure (PEEP) has been shown to improve outcome in ARDS [5]. Application of PEEP minimizes oxygen toxicity and decreasing the need for a high fraction of inspired oxygen [35]. A positive effect of higher levels of PEEP was observed as part of a lung protective strategy in adult patients with ARDS [38, 39] but this benefit of PEEP was not observed in patients with milder forms of acute lung injury [35]. Excessive levels of PEEP can overdistend areas of normal lung and negatively impact hemodynamic function. This has led researchers to seek the "ideal" PEEP, in which compliance and oxygenation are maximized while overdistension and undesirable hemodynamic effects are minimized. The recommendations from PALICC are (1) moderately elevated levels of PEEP (10–15 cm H_2O) or PEEP level greater than 15 cm H_2O may be needed to titrate to the desired oxygenation level; (2) oxygen delivery, plateau pressure/respiratory system compliance, and hemodynamics should be appropriately monitored in patients as PEEP is increased; (3) PEEP should be set to prevent alveoli collapse at end-expiration and avoid tidal recruitment at each breath cycle (atelectrauma) [35, 40].

High-frequency oscillatory ventilation (HFOV) can be used to minimize hypercapnia and maximize lung inflation and oxygenation. HFOV should be considered as an alternative in patients with hypoxic respiratory failure in whom plateau airway pressure exceeds 28 cm H_2O in the absence of clinical evidence of reduced chest wall compliance [35]. By adjusting the amplitude of the oscillation, lung ventilation is improved, and hypercapnia is reduced. The mean airway pressure can be adjusted to maximize oxygenation and minimize the inspired fraction of oxygen. By using smaller tidal volumes and maintaining alveolar volume, HFOV has been shown to improve short-term physiological endpoints [35]. However, the use of HFOV in pediatric and adult ARDS patients has not yet demonstrated significant improvements in clinically meaningful outcome measurements such as 30-day mortality [35].

The ventilator strategy should be tailored to specific pathophysiological conditions:

1. Left ventricular (LV) dysfunction: Positive ventilation decreases both the venous return (decreased preload) and the afterload of the left ventricle. PEEP and tidal volume should be titrated to prevent atelectasis and maintain end-expiratory lung volume (EELV) near the functional reserve capacity (FRC).
2. Right ventricular (RV) dysfunction: Cardiovascular interaction should be manipulated to optimize the RV preload and minimize the RV afterload. The RV afterload can be reduced by adequate oxygenation and alkalization. It is crucial to keep the EELV near the FRC because an EELV less than the FRC (resulting in atelectasis) or greater than the FRC (resulting in alveolar overdistension) will result in elevated pulmonary vascular resistance (PVR). Since most pulmonary flow occurs during expiration, the expiratory time should be longer than the inspiratory time. Patients with ARDS and RV dysfunction may benefit from ventilator strategies to decrease the intrathoracic pressure and maintain an adequate intravascular volume (preload).
3. Pulmonary hypertension: Ventilator strategies should aim to maintain a normal pH, decreasing $PaCO_2$ and increasing both alveolar oxygen (P_{AO2}) and arterial oxygen (P_{aO2}). Patients with pulmonary hypertension may benefit from hyperventilation and maintaining the EELV near the FRC, but clinicians should avoid the detrimental effects of elevated mean airway pressure on right ventricular filling and pulmonary vascular resistance.

54.1.4.2 Other Therapies

Several other therapies are useful in the treatment of ARDS. Because patients with bronchiolitis, pneumonia, and sepsis are more likely to develop ARDS, prompt use of antibiotic therapy is important.

Nitric oxide (NO), a known pulmonary vasodilator, may be used in the treatment of ARDS. Its acts to relax the vascular smooth muscle by increasing the intracellular cyclic guanosine monophosphate (cGMP) levels. Inhaled nitric oxide increases pulmonary blood flow to the normal ventilated lung tissue, and therefore improves ventilation-perfusion matching by reducing dead-space ventilation. Nitric oxide improves oxygenation in pediatric ARDS, but a recent systematic review found there was no significant improvement in mortality, duration of mechanical ventilation, or length of the hospital/ICU stay [41]. The routine use of inhaled nitric oxide (iNO) is not recommended in pediatric ARDS, its use can be considered in patients with pulmonary hypertension or severe right ventricular dysfunction or as a rescue from or bridge to extracorporeal life support [42].

Assessment and management of the fluid status is also important in the treatment of ARDS. Aggressive treatment of concomitant septic shock, and the development of capillary leak can increase the extravascular lung water. Diuresis is useful for treating persistent pulmonary edema, however it must be used carefully, because rapid diuresis can compromise cardiac output and tissue perfusion.

Because the levels of surfactant are reduced, and the surfactant produced is functionally abnormal, administration of exogenous surfactant may improve lung compliance and allow the recruitment of collapsed alveoli. The largest non-neonatal pediatric trial ($n = 153$) from a multicenter, prospective, randomized study demonstrated that patients with ALI and ARDS treated with surfactant had improved oxygenation and decreased mortality when compared with the control group [43]. However, there was an unequal distribution of immunocompromised patients in this study. A subsequent study in an international, multicenter placebo-controlled trial of calfactant in ARDS treatment was closed prematurely for both adult and pediatric patients when no improvement was found in either oxygenation or mortality [44].

Steroids are also used to treat the inflammation associated with ARDS, although the benefit of steroid administration in ARDS remains controversial. High-dose, short-course corticosteroids given in early ARDS failed to improve survival, and an ARDS network late steroid rescue study showed that late administration of steroids also did not improve survival [45]. There was insufficient data for PALICC to make recommendations for routine use in patients with ARDS [42].

Prone positioning has been used to recruit collapsed alveoli. This position is also thought to improve ventilation-perfusion matching, increase end-expiratory lung volume, create positive changes in chest-wall mechanics, and enhance oxygenation with acute hypoxemic respiratory failure. These effects may result in a more uniform distribution of ventilation and less compression of the left lung by the heart [5]. Prone positioning has been associated with reduced mortality [46] and is recommended for patients with moderate-to-severe ARDS with P_{aO2}/F_{iO2} less than 120 mmHg, according to the guidelines of the American Thoracic Society, the European Society of Intensive Care Medicine and the Society of Critical Care Medicine [5]. Although prone positioning is not recommended as routine therapy in pediatric ARDS, it should be considered an option for severe pediatric ARDS [42].

Extracorporeal membrane oxygenation (ECMO) is reserved for patients with very severe ARDS [5]. There are no published consensus criteria for the provision of ECMO support for children with ARDS. A failure to maintain clinical stability within the "lung protective strategy" for maintaining adequate gas exchange and oxygenation is an indication for consideration of ECMO support in the absence of contraindications [47].

Mortality

Since the 1990s, pediatric ARDS has been associated with a significant but highly variable mortality rate although there appears to be an overall decrease in mortality over time [48]. Parvathaneni et al. reported that applying the PALICC definition of pediatric ARDS has the potential to identify an increased number of acute respiratory distress syndrome patients with a mortality rate of 22.7%. The presence of severe acute respiratory distress 24 h after the onset of respiratory failure was associated with nearly 50% mortality [49]. The trigger for the development of ARDS also influences outcomes, with particularly high mortality (65–70%) rates in patients with sepsis-induced ARDS [48].

Conclusion

Although relatively uncommon, it is necessary to understand the physiology and treatment of pediatric patients with ARDS. For patients with concomitant heart disease, gentle ventilation strategies and adjunctive therapies can be applied with special consideration given to their cardiovascular effects, thereby hastening recovery from ARDS.

54.2 Chylothorax

Chylothorax is a well-recognized complication of cardiothoracic procedures. Chylothorax is defined by the presence of chyle in the pleural space. Chest tube drainage may be persistent and creamy in appearance if the patient is

receiving enteral nutrition with long-chain fatty acids. In fasting patients, drainage may appear serosanguinous with a normal triglyceride level. Chylothorax can be confirmed if the pleural fluid triglyceride levels are >1.2 mmol/l (110 mg/dl) and/ or the total fluid cell count is >1000 cells/µl (high percentage of lymphocytes >70%) and/or chylomicrons are present.

A report from the Pediatric Cardiac Critical Care Consortium (PC4) database [50] and the Pediatric Health Information system (PHIS) [51] found that the overall incidence of chylothorax in pediatric patients after congenital heart surgery or heart transplantation was 2.8% and 3.8%, with higher rates observed in neonates (6.9%) and in patients with single ventricle physiology (6.9%), chromosomal/genetic abnormalities (5.2%) and major noncardiac anomalies (6.4%) [50]. Neonates were four to seven times more likely to develop postoperative chylothorax compared with older children [50, 51]. Patients with neck or upper extremity vein thrombosis were four to seven times more likely to develop chylothorax after a cardiac procedure [50, 51]. The incidence of chylothorax increased from 2% in 2004 to 3.7% in 2011 in the PHIS database, with possible attribution to early enteral feeding and increased complexity of pediatric cardiac surgical procedures and increased invasive line utilization [51]. The development of chylothorax is associated with increased rates of infection, increased duration of mechanical ventilation and ICU stay, and mortality. In-patient mortality was reported in 10% of patients who developed chylothorax after cardiac surgery compared with 3% of the patients without chylothorax [50].

Given the proximity of lymphatic vessels to cardiac structures, trauma to the thoracic duct can occur during surgical correction of congenital heart defects, especially during aortic arch reconstruction and repair. Abnormally increased venous pressure is common after congenital heart surgery. In the normal lung, the pulmonary arterial pressure and pulmonary capillary wedge pressure are higher than the systemic central venous pressure. In the Glenn and Fontan circulations, the lung interstitium is still subjected to a normal hydrostatic pressure because more than 80% of the total lung arterial flow returns to the heart via pulmonary veins. However, pulmonary lymph is required to drain at a higher-pressure secondary to elevated central venous pressure. The increase in resistance to lymphatic drainage results in lymphatic endothelial cell adherence, and lymph that is not effectively removed from the interstitium. The congested lung seen in the early Glenn/Fontan patient is often related to lymph formation and accumulation, with pleural effusion/chylothorax as a manifestation of this imbalance [52].

Dori et al. identified three possible mechanisms of persistent chylothorax after cardiac surgery using lymphatic imaging (excluding the patients with postoperative chylothorax who improved quickly) [53]:

1. Traumatic leak from a thoracic duct branch;
2. Pulmonary lymphatic perfusion syndrome: retrograde flow from the thoracic duct to the lung or mediastinum;
3. Central lymphatic flow disorder (CLFD), a newly characterized condition with abnormally low or absent central lymphatic flow, effusions in more than one compartment, and dermal backflow through abdominal lymphatic collaterals. The patients with CLFD were notably younger in age (median age: 0.3 years), were resistant to intervention (100% had continued chylothorax) and had high mortality rates (88.9%).

Most patients with chylothorax from thoracic duct leakage or pulmonary lymphatic perfusion syndrome had increased central venous pressure and impaired secondary lymphatic drainage; all of them responded well to lymphatic intervention and all of them survived to discharge [53].

The development of a large chylous effusion can result in compromised pulmonary function as well as significant loss of immunoglobulins, T-lymphocytes, albumin, coagulation factors and anticoagulation factors and electrolytes. Standard therapies include:

1. Decreasing chyle production
2. Draining the pleural fluid
3. Providing adequate nutrition and fluid replacement
4. Thoracic duct embolization, selective lymphatic duct embolization [53]
5. Surgical intervention
   (a) Thoracic duct ligation
   (b) Pleurodesis with talc or fibrin
   (c) Pleuro-peritoneal shunt

Most patients in the PHIS database with chylothorax were treated with conservative management with 8.9% patients having surgical treatment (thoracic duct ligation, pleurodesis) [51], 10% of patients in the PC4 database had thoracic duct ligation, and 4% had pleurodesis) [50]. However, surgical interventions are frequently ineffective and chemical pleurodesis often leads to the formation of aortopulmonary chest wall collaterals [52]. Dori and coauthors suggested that surgical procedures make patients with chylothorax and CLFD worse and should be avoided [53]. In addition, eliminating fat from the diet during the critical growing stages of infancy and childhood and medical therapy with octreotide had significant unwanted

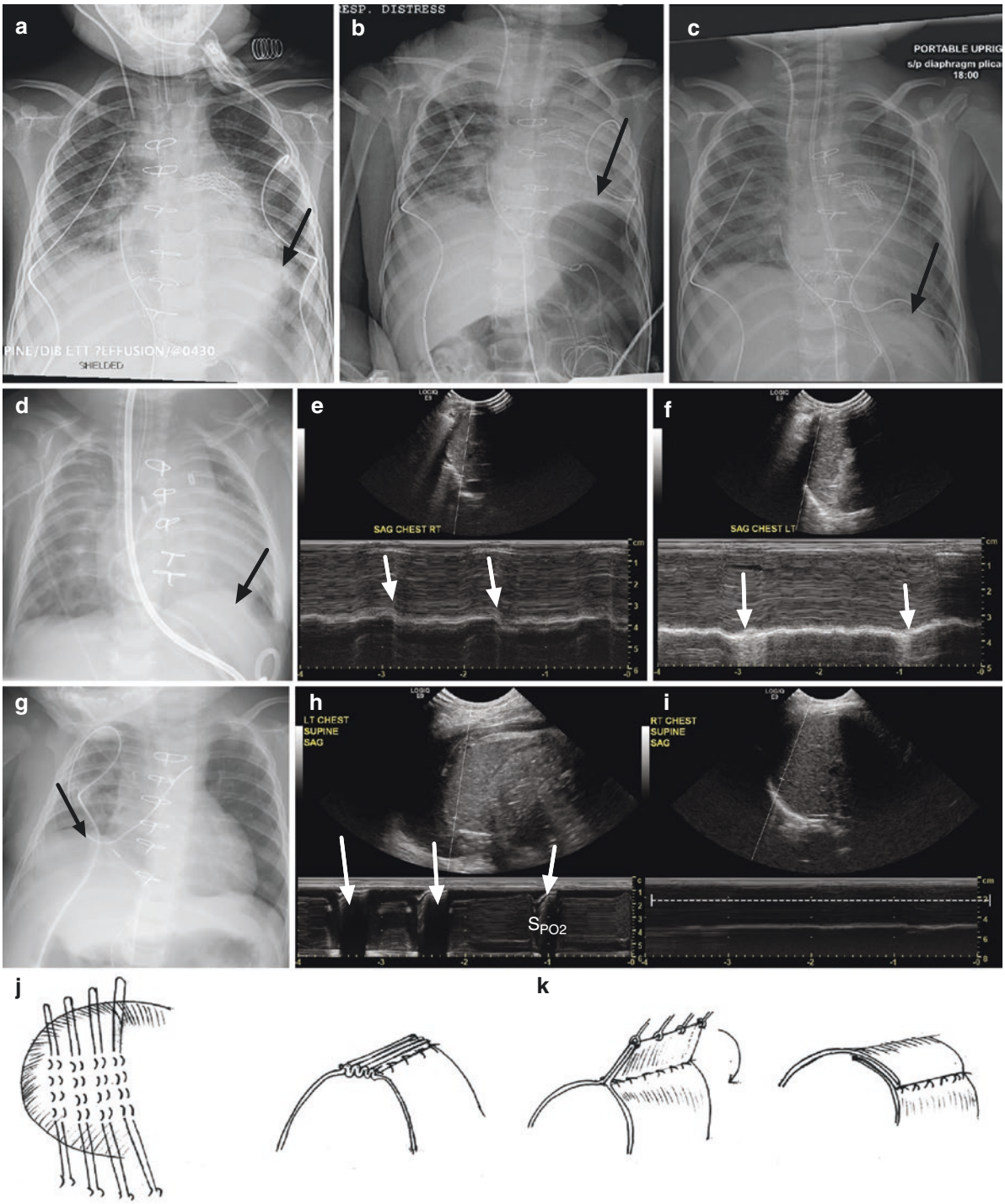

Fig. 54.3 (**a**–**c**) Chest X-rays of a patients with left hemidiaphragm paralysis after Fontan operation: (**b**) compared with chest X-ray during intubation (**a**), elevation of the left hemidiaphragm (arrow) was noted after extubation with segmental atelectasis of left lung; (**c**) Chest X-ray after diaphragmatic plication, demonstrated improved left lung aeration, patient was immediately extubated in the operation room after plication. (**d**–**f**) A 1-month-old baby with left hemidiaphragm paralysis: (**d**) Chest X-ray demonstrated the elevation of left diaphragm (arrow), (**e**) M-mode of right diaphragm showed the diaphragm moved toward the transducer during inspiration (white arrow). (**f**) M-mode of left diaphragm showed paradoxical movement with diaphragm moved away from the transducer during inspiration (white arrow); (**g**–**i**) A 5-month-old infant with right hemidiaphragm palsy: (**g**) Chest X-ray showed elevated right hemidiaphragm, (**h**) M-mode of normal left hemidiaphragm movement: the diaphragm movement during inspiration was toward the transducer with an excursion more than 4 mm (white arrow). (**i**) M-mode of right hemidiaphragm showed no movement and a straight line: "akinetic" (white dash line). (**j**) illustrated the technique of diaphragmatic plication with placement of multiple rows of sutures (**k**) illustrated another technique of diaphragmatic plication. (Figure **j** and **k**: by permission from Ref. [57])

side effects [52]. The use of dynamic contrast-enhanced magnetic resonance lymphangiography to understand the pathophysiology of these lymphatic disorders after congenital heart surgery allowed effective therapy, as reported by Dori et al. [53], shedding light on lymphatic disorders after cardiac surgery.

54.3 Diaphragmatic Palsy and Paralysis

Injury to the phrenic nerve (usually the left) can occur during surgeries involving the dissection of the branch pulmonary arteries and manipulation of the aortic arch and superior vena cava. Reoperations in the presence of adhesion and scarring, which obscure landmarks, can also make inadvertent injury to the phrenic nerve more likely. Phrenic nerve injury resulting in paralysis (paradoxical movement) (Fig. 54.3a–f) and diaphragmatic palsy (reduced motion) (Fig. 54.3g–i) is a cause of respiratory failure requiring positive pressure ventilation in the postoperative period. An incidence of 0.3–12.8% of diaphragmatic paralysis has been reported, with higher incidences of diaphragmatic paralysis after bidirectional Glenn shunt, arterial switch, correction of tetralogy of Fallot, ventricular septal defect closure with pulmonary artery patch plasty and Blalock-Taussig shunt [54–57]. Unilateral diaphragm paralysis reduced global lung function in the sitting position by an average of about 25% in adults and usual does not cause a significant problem [58]. Neonates and young infants are particularly at risk for respiratory failure from diaphragm palsy and paralysis. This population relies heavily on the diaphragm to breathe, whereas older children or adults use intercostal and accessory muscles to assist in the work of breathing. Injury to the phrenic nerve is part of the differential diagnosis of a postoperative patient struggling to wean from positive pressure ventilation. Symptoms include increased work of breathing on low ventilator settings, respiratory distress after extubation, and persistent atelectasis and oxygen requirement. An elevated hemi-diaphragm may be visible on chest X-ray (Fig. 54.3b, d, g), although a film taken during peak positive ventilation may obscure this finding. Ultrasonography (Fig. 54.3e, f, h, i) or fluoroscopy can be used to identify evidence of reduced or paradoxical diaphragm movement. Evoked responses and diaphragmatic electromyogram (EMG) may also provide useful diagnostic information. It is important that these tests are performed in the absence of positive pressure ventilation, as this can cause a false negative test result. Recovery from phrenic injury was reported to be 56.5% over the first several years [55]. Surgical plication (Fig. 54.3j, k) is indicated for failure to wean from positive pressure ventilation or significant respiratory compromise after extubation especially in patients under 6 months of age [55–57].

54.4 Respiratory Physiotherapy

Clearance of respiratory secretions and the prevention and treatment of atelectasis are critical components of postoperative recovery. Prolonged intubation, acquisition of pulmonary infections, respiratory muscle weakness, and inadequate nutrition can make airway clearance difficult. Chest physiotherapy and tracheal suctioning are often initiated for patients who are intubated or are unable to cough effectively. Tracheal suctioning allows the clearance of tracheal secretions, but may cause airway mucosal injury, arrhythmia and hypoxia. Chest physiotherapy consists of postural drainage and chest percussion or vibration. Fresh chest wounds, coagulopathy, and a tenuous hemodynamic status may be prohibitive. Several devices are used in conjunction with suctioning and traditional chest physiotherapy. These include an intrapulmonary percussive ventilator (IPV) [59], intermittent positive pressure breathing (IPPB) [60], pneumatic chest high- frequency oscillation physiotherapy (Metaneb®) [61], and a mechanical insufflator-exsufflator (CoughAssist®) [62]. These devices, in conjunction with tracheal suctioning, transitional chest physiotherapy, and inhaled mucolytics, can be helpful in the maintenance of pulmonary hygiene and increase the chance of respiratory recovery.

54.5 Tracheostomy

With the advance of pediatric cardiovascular surgery and perioperative care, mortality rates from congenital heart surgery have been declining. Surgical repair/palliation is now offered to patients with complex underlying cardiac anatomies with coexistent noncardiac morbidity at most centers. Many of these patients may not have had any intervention in the past. With these high-risk, complicated patients, the incidence of tracheostomy after cardiac surgery has increased seven-fold from 0.11% in 2000 to 0.76% in 2012, according to the Society of Thoracic Surgeons (STS) congenial heart database [63]. Consistent with the STS database, Prodhan et al. reported that the tracheostomy rate of patients with hypoplastic left heart syndrome was increased from 1.9% in 2004 to 2006 to 3% in 2010 to 2013 [64]. Genetics and noncardiac anomalies were present in 40–60% of the patients [63, 65], with a high operative mortality of 25% [63]. Tetralogy of Fallot variants (29%) and coarctation with or without ventricular septal defect (21%) accounted for most of the biventricular lesions with tracheostomy [65]. Hypoplastic left heart syndrome with the Norwood procedure carried the highest overall mortality compared to the other patients who required tracheostomy, at 22–44% [64]. An elegant study from Cotts and coauthors found a 92% chance of hospital survival and a 38% chance to complete the Fontan procedure if single

ventricle patients required tracheostomy for a mechanical airway issue; however, if single ventricle patients received tracheostomy for cardiorespiratory failure and were unable to wean from mechanical ventilation, the hospital survive rate decreased to 58%, with only one patient (8%) getting through Fontan completion [65]. This prognosis related to the etiology of respiratory failure of hypoplastic left heart syndrome needing tracheostomy has been replicated [64]. To assist caregivers in decision making, long-term follow-up data for a large cohort of these patients who require tracheostomy after cardiovascular operations will be extremely helpful.

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Chapter 55
Gastrointestinal Complications: Necrotizing Enterocolitis, Malrotation, Protein-Losing Enteropathy, and Nasogastric Tube Syndrome

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Abstract This chapter addresses the gastrointestinal complications that can occur in pediatric cardiac intensive care unit. Gastrointestinal complications are not uncommon in the critically ill cardiac patients and are associated with prolong ICU stay and hospital length of stay as well as poor growth and development.

55.1 Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is the most common and devastating intestinal disease in neonates in which the mucosal barrier of the gut is damaged and breached, resulting in intestinal injury [1]. NEC is characterized by variable damage to the intestinal tract, which ranges from mucosal injury to full-thickness necrosis and perforation. The terminal ileum, cecum, and proximal ascending colon are the most common sites of NEC [2]. The disease may involve a single isolated lesion, multiple discontinuous areas, or in rare instances pan-necrosis. In 1978, Bell et al. classified NEC into three stages by using a combination of clinical and radiographic criteria [3]. The Bell's criteria for NEC have been widely accepted and used ever since, with one modification to distinguish between perforated and non-perforated cases [4] (Table 55.1)

The risk of developing NEC is more prevalent among very low-birth-weight infants and is inversely related to gestational age at birth [6]. The incidence of NEC is reported to be 1–5% of neonatal intensive care unit admissions [7], and this incidence increases to 5–15% of infants born at less than 30 weeks gestational age or less than 1500 g birth weight [8]. Approximately, 7–15% of neonates with NEC are born at term or late pre-term [9, 10]. This epidemiologic factor suggests that immaturity of the gut mucosa is an important predisposing factor. In term infants, congenital heart disease is a well-known risk factor for NEC, with a reported incidence between 3.3% and 6.8%, which is 10–100-fold higher than that of the normal newborn population [10–12]. The most commonly associated congenital heart defects are hypoplastic left heart syndrome (HLHS), truncus arteriosus, and aortic arch anomalies which result in intestinal hypoperfusion [11, 12]. Episodes of shock and younger gestational age but not body weight were reported to be associated with NEC in infants with CHD admitted to the cardiovascular intensive care unit [12]. A high index of suspicion for NEC is critical in infants with CHD, ranging from patent ductus arteriosus

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Table 55.1 Modified Bell staging criteria for necrotizing enterocolitis

Stage	Classification	Systemic signs	Intestine signs	Radiologic signs
1a	Suspected NEC	Temperature instability, apnea, bradycardia, lethargy	Elevated residuals, mild abdominal distention, emesis, guaiac-positive stool	Normal or intestinal dilation, mild ileus
1b	Suspected NEC	Same as 1a	Bright-red blood from rectum	Same as 1a
2a	Proven NEC – mildly ill	Same as 1b	Same as 1b, plus absent bowel sounds, with or without abdominal distention	Intestinal dilation, ileus, pneumatosis intestinalis
2b	Proven NEC – moderately ill	Same as 2a, plus mild metabolic acidosis, mild thrombocytopenia	Same as 2a, plus definite abdominal tenderness, with or without abdominal cellulitis or right lower quadrant mass	Same as 2a, plus portal vein gas with or without ascites
3a	Advanced NEC – severely ill, bowel intact	Same as 2b, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, disseminated intravascular coagulation, and neutropenia	Same as 2b, plus signs of generalized peritonitis, marked tenderness and abdominal distention	Same as 2b, plus definite ascites
3b	Advanced NEC – severely ill, bowel perforated	Same as 3a	Same as 3a	Same as 3a, plus pneumoperitoneum

By permission from Ref. [5]

(PDA) to HLHS. Surgical intervention to correct any form of CHD may be a predisposing factor for NEC. Intestinal mucosal ischemia, although frequently transient, can occur in infants during and after cardiopulmonary bypass. In contrast, a patient with coarctation of aorta may have increased renin release, which results in the shunting of blood from mesenteric arteries (mesenteric arteritis syndrome), a defined component of post-coarctectomy syndrome [13].

The presence of a PDA is also a risk factor for the development of NEC [14]. Ibuprofen is the pharmacological agent most frequently used for nonsurgical closure of a PDA in premature infants. Compared with indomethacin, ibuprofen reduces the risk of NEC but still carries the risk of inducing a reduction in mesenteric blood flow, which further compromises bowel perfusion in the presence of a hemodynamically significant ductus [15].

55.1.1 Pathophysiology

The pathogenesis of NEC is still incompletely understood. Several factors are involved in the pathophysiology of NEC, including immaturity of the neonatal gut mucosa, tissue hypoperfusion and hypoxia, enteral alimentation, imbalance in microvascular tone, microbes, and the prematurity of the host immunologic system [9, 16]. A generally accepted hypothesis regarding the development of NEC involves the immature host immunologic response in an immature intestinal mucosa [9, 16] (Fig. 55.1). An initial insult such as mesenteric ischemia or the presence of infectious or toxic agents can lead to a loss of the intestinal mucosal integrity/epithelial barrier [17]. After the initiation of feeding, there is a substrate available for the bacterial proliferation. Bacteria may invade the injured mucosa which induces the production of pro-inflammatory cytokines [9]. The pro-inflammatory/inflammatory response results in further injury to the mucosal barrier, which in turn may progress to bowel necrosis, systemic inflammation, shock, sepsis, and death [16, 17].

55.1.2 Clinical Presentation

The clinical presentation of NEC ranges from nonspecific signs such as vomiting, diarrhea, and feeding intolerance, to fulminant gastrointestinal complications (acute abdomen, bowel perforation), then progress to multiple organ failure and shock [9, 16]. More specific symptoms include abdominal distention and frank or occult blood in the stools. Of note, occult stool blood diagnosed by a hemoccult test correlates poorly with NEC [18] (Fig. 55.2c). When the stomach is involved, NEC can present as bloody emesis or a bloody gastric residual [19]. NEC can present with bloody stools (hematochezia) when NEC involves the distal colon. If the jejunum and terminal ileum are the predominant sites of NEC, then emesis, increased gastric residuals and abdominal distention may be evident [9]. With disease progression, abdominal tenderness, abdominal wall edema and erythema, or palpable bowel loops may become apparent. An isolated intestinal perforation with a shiny, dicoloration and distended abdomen may be indistinguishable from that in an infant with NEC (Fig. 55.2a). Erythema or bluish discoloration of the scrotum may appear in a male patient with an inguinal hernia if peritoneal fluid from the perforated bowel enters the scrotum [9] (Fig. 55.2b). Apnea, bradycardia, lethargy, labile body temperature, hypoglycemia, and shock are signs of advanced disease. The clinical presentation of NEC is different in extreme premature infants compared to preterm or term infants (Fig. 55.2c, d). In term and late-term infants, the most common presenting symptom is hematochezia followed by radiographic changes [20] (Fig. 55.2c). In extremely premature infants, abdominal distention and ileus are present in more than 50% of cases with NEC

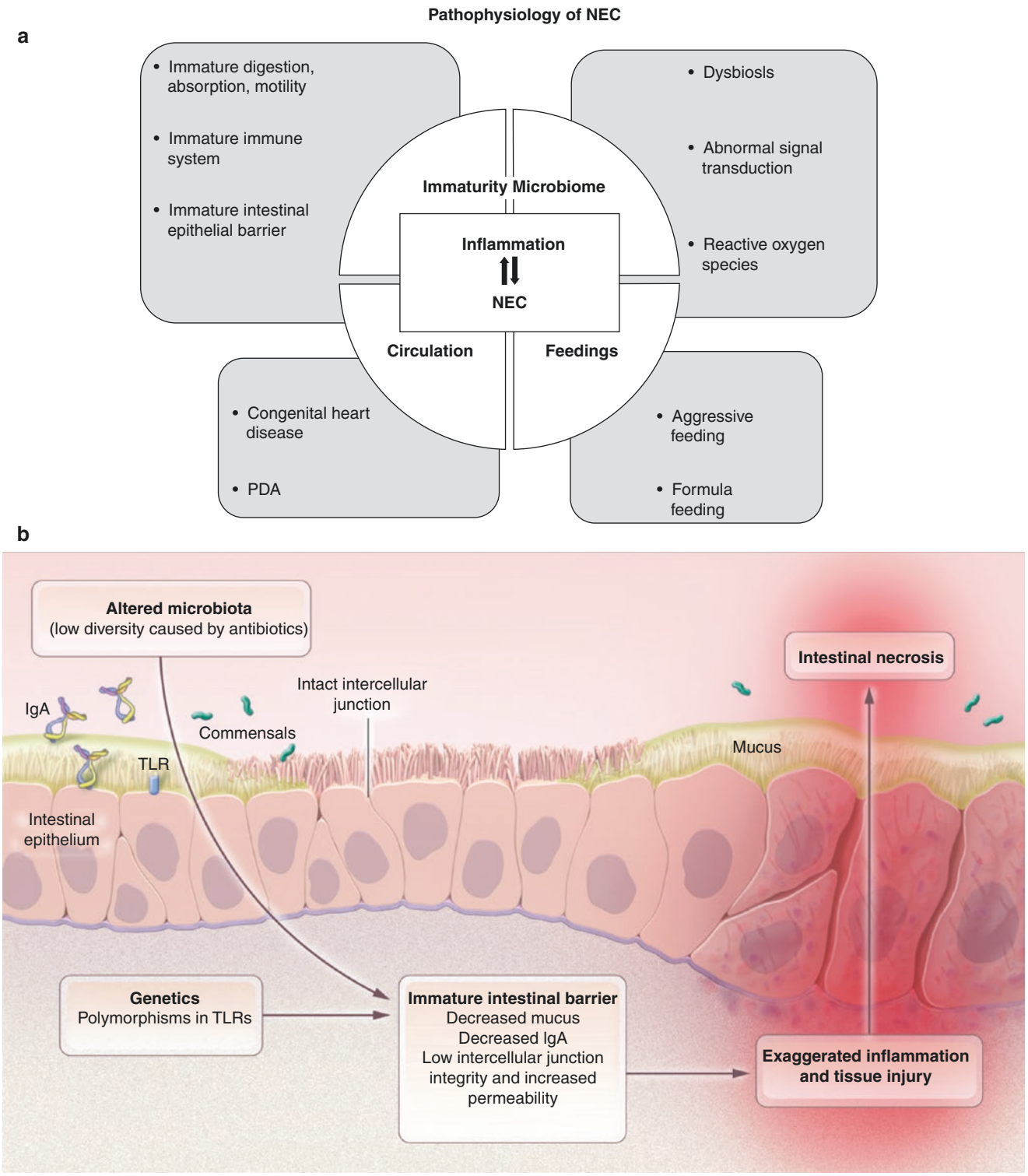

Fig. 55.1 Pathophysiology of NEC. (**a**) Scheme illustrating pathophysiology of NEC (By permission from Ref. [9]). (**b**) Factors conferring a predisposition to necrotizing enterocolitis include genetic factors and several immature characteristics of the fetal intestine, including altered microbiota, inadequate intestinal barrier function, and an excessive inflammatory response. These factors contribute to the severe necrosis of the small intestine that is characteristic of this disease. TLR denotes Toll-like receptor. (By permission from Ref. [16])

(Fig. 55.2d) with less than 50% of infants with NEC presenting with intramural gas or portal venous gas (Fig. 55.2c) [6]. In premature infants, the clinical presentation of NEC typically occurs 20 days after birth, when infants have overcome the acute respiratory issues associated with premature lung diseases, are taking feedings and are in a "feeding and growing" mode toward discharge [19]. In contrast to premature infants, term infants with NEC present with the onset of

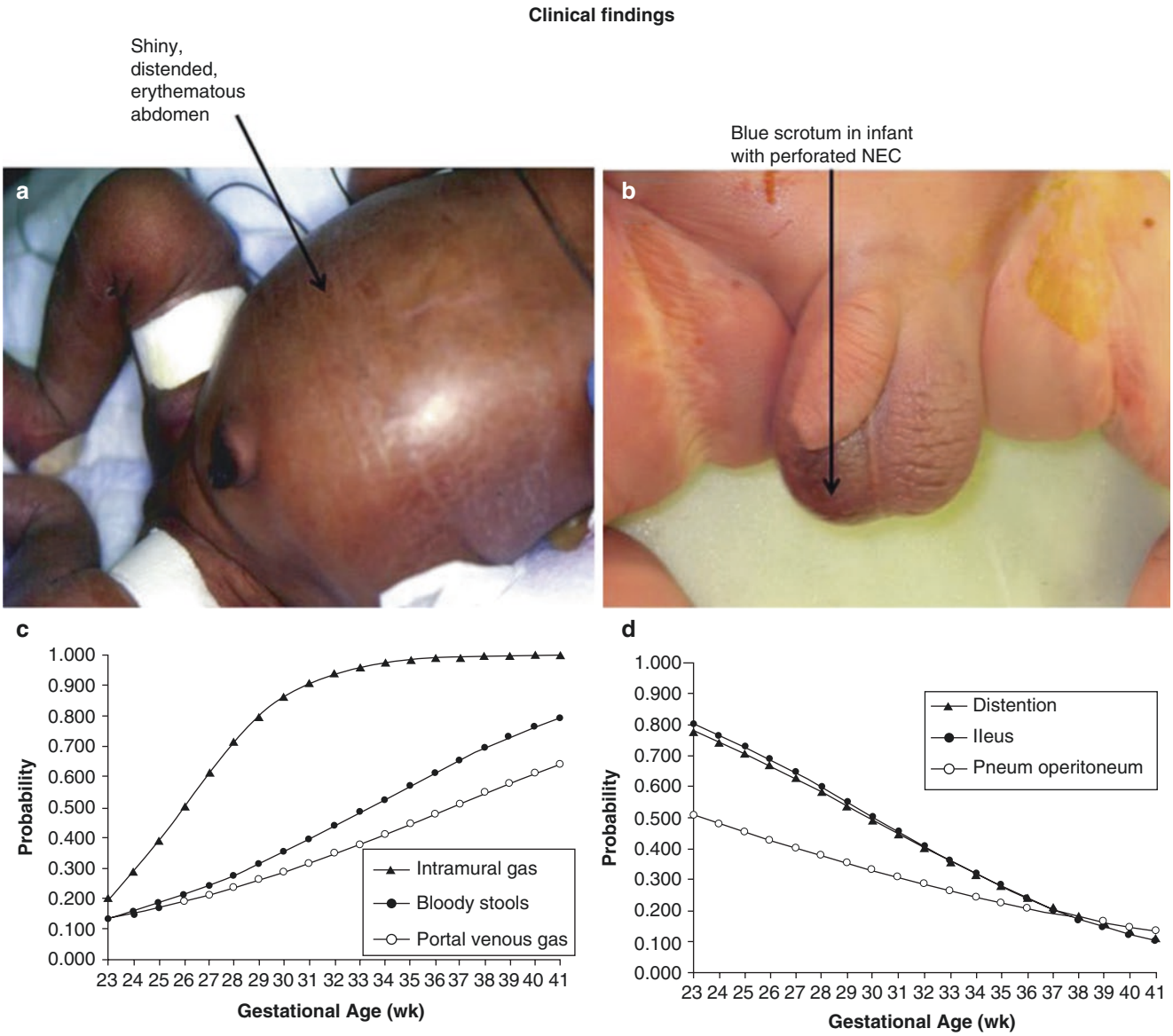

Fig. 55.2 (**a**) A shiny, distended, erythematous abdomen (arrow) of an infant with advanced NEC in frog-leg position (By permission from Ref. [9]). (**b**) Discolored scrotum (arrow) in an infant with perforated advanced NEC; no pneumoperitoneum was seen in abdominal radiographs (By permission from Ref. [9]). (**c**) Probability by gestational age (GA) that an infant with NEC will present with intramural gas, portal venous gas, or bloody stools (By permission from Ref. [6]). There is less than 50% probability for an extremely premature infant to manifest intramural gas. (**d**) Signs that are less probably manifested with advancing GA. There is more than 50% probability that extremely premature infants will present with abdominal distention and ileus. (By permission from Ref. [6])

NEC at an earlier age (7 days vs. 2–3 weeks) [20] and are associated with other problems, such as maternal illicit drug abuse, intestinal anomalies, congenital heart diseases, and perinatal stress, which may affect mesenteric blood flow [21]. The recurrence rate of NEC is reported to be 5–6% of cases [22, 23], and an increased risk if an initial episode of NEC is associated with congenital heart disease, with rotavirus infection, with cow milk protein allergy [24] or without specific risk factors [22, 23]. Among premature infants, spontaneous intestinal perforation represents a different disease entity with minimal intestinal inflammation and necrosis, it usually occurs in the first several days after birth and is not associated with feedings [5].

55.1.3 Diagnosis

55.1.3.1 Laboratory Test

In any infant with a suspicion of NEC, the initial laboratory tests should include a complete blood count (CBC), basic metabolic panel (BMP), and blood culture. A CBC may

demonstrate elevated, normal, or low white blood cell (WBC) counts. An elevated hemoglobin level and hematocrit may mark hemoconcentration due to a notable accumulation of extravascular fluid. However, the infant may be anemic if clinically significant gastrointestinal (GI) blood loss has occurred secondary to hematochezia. Thrombocytopenia is the most frequent hematologic abnormality: more than 80% of patients have platelet counts of less than 150,000/μL. Thrombocytopenia appears to be a reaction to Gram-negative bacterial endotoxin. Obtaining a blood culture prior to the initiation of antibiotics is recommended, with a reported 40–60% prevalence of concurrent bacteremia and sepsis in NEC [9, 25]. A basic metabolic panel may show electrolyte abnormalities consistent with metabolic acidosis and unexplained hyponatremia [9]. These abnormal lab results are common and may represent intestinal ischemia, hypoperfusion, and hypovolemia.

55.1.3.2 Radiography

Plain abdominal radiography is the mainstay in confirming the diagnosis of NEC (Fig. 55.3). Pneumatosis intestinalis or intramural gas (Fig. 55.3c–i) and/or portal venous gas (Figs. 55.3d, i, and 55.4f) with an appropriate clinical presentation is diagnostic of NEC. Pneumatosis is present in over 50% of the patients with NEC [26] (Fig. 55.2c), which indicates that the absence of these radiographic signs cannot rule out the absence of NEC. Early imaging signs include "loss of the mosaic pattern" of abdominal gas, dilated loops of bowel, a paucity (Fig. 55.3b) of gas, and gas-filled loops of bowel that are not altered on repeated plain abdominal radiography (fixed-loop). Pneumatosis (Fig. 55.3) c–i may occur as a cystic form and has a foamy appearance, or as the linear form, in which the gas accumulates in the subserosal layer. The gas is principally hydrogen, secondary to bacterial metabolism in the bowel wall. Pneumoperitoneum is pathognomonic for intestinal perforation and is best seen on an abdominal film performed in the left decubitus position. Free air may also be identified as a "football sign" on supine views, as free air outlines the falciform ligament (Fig. 55.3g) or "Rigler's sign" ("double-wall sign") (Fig. 55.3h), as the air is present on both sides of the intestine [26]. The amount and degree of intramural gas are not always related to the clinical severity of NEC [26]. Portal venous gas (Figs. 55.3d, i, and 55.4f) presents as linear branching streaks overlying the liver and is caused by gas produced by bacteria in the portal vein or by transmigration of gas from the bowel wall, through mesenteric veins and into the portal vein [26]. Although nonspecific, bowel dilatation (Fig. 55.3b) is an early sign of NEC and present in more than 90% of the infants with NEC. The degree and severity of dilatation correlate well with the clinical severity of NEC, and the distribution of the dilated bowel loops in serial abdominal radiographs is associated with clinical progression. Resolution of NEC is related to the resolution of dilated bowl to a more normal appearance [27]. Persistence of bowel dilatation, especially in a localized area of abdomen indicates failure of response to medical treatment or deterioration [27]. The change from generalized bowel dilatation to an asymmetric distribution is worrisome and is an ominous sign if the asymmetric pattern persists and the dilated loops maintain and appear as fixed loops on follow-up radiographs. This may suggest the development of intestinal necrosis [27]. Therefore, the pattern and degree of bowel loop dilatation are the most important signs for early diagnosis of NEC and are important to monitor the degree of distension and to observe for any fixed or dilated loops of bowel in the follow-up abdominal radiographs [27]. Air-fluid levels and bowel wall edema (Fig. 55.5) may also develop. The timing of follow-up plain abdominal radiographs relies on the severity of NEC and may range from 6 to 24 hours as well as at any time of acute clinical deterioration [26]. The time interval between plain abdominal radiographs can be extended in those infants with an improving clinical status [26].

Ascites can occur in advanced cases of NEC. The ascites is often purulent. Ascites is suggested by a generalized opacification of the abdomen with medial displacement of bowel loops. A paracentesis with a positive Gram stain for Gram-negative bacteria is an operative indication for NEC.

Adnominal ultrasound (US) (Fig. 55.4) is useful for identifying gas in the portal venous system as well as pneumatosis intestinalis and has been reported to be more sensitive than plain radiography for the detection of these findings. Ultrasonography appears to be most useful in neonates with an equivocal clinical picture for NEC and normal or nonspecific plain radiographic findings [26]. Abdominal ultrasound can detect intramural gas (Fig. 55.4b, d, e, f, g); intramural gas will not change position with abdominal compression with the transducer as the inter-luminal gas dose [26]. In addition, the advantage of abdominal ultrasound over plain abdominal radiography is its ability to depict abdominal fluid (Fig. 55.4c) with its location, and whether it is in the peritoneal cavity or a more localized fluid collection, ultrasound also facilitates localization of paracentesis and percutaneous abscess drainage [26]. The second advantage of abdominal ultrasound in NEC is it can visualize the bowel wall directly and assess the bowel wall thickness, echogenicity, and peristalsis. The normal bowel echogenicity (gut signature) in neonates showed a prominent hypoechoic rim or halo, which was thought to present the muscularis propria (Fig. 55.4a). There was no significant interference from the presence of normal bowel gas [26]. Thickening or thinning of abdominal wall is observed in infants with NEC (Figs. 55.4b, and 55.5) [26, 27]. The third advantage of abdominal ultrasound is the ability to directly assess arterial

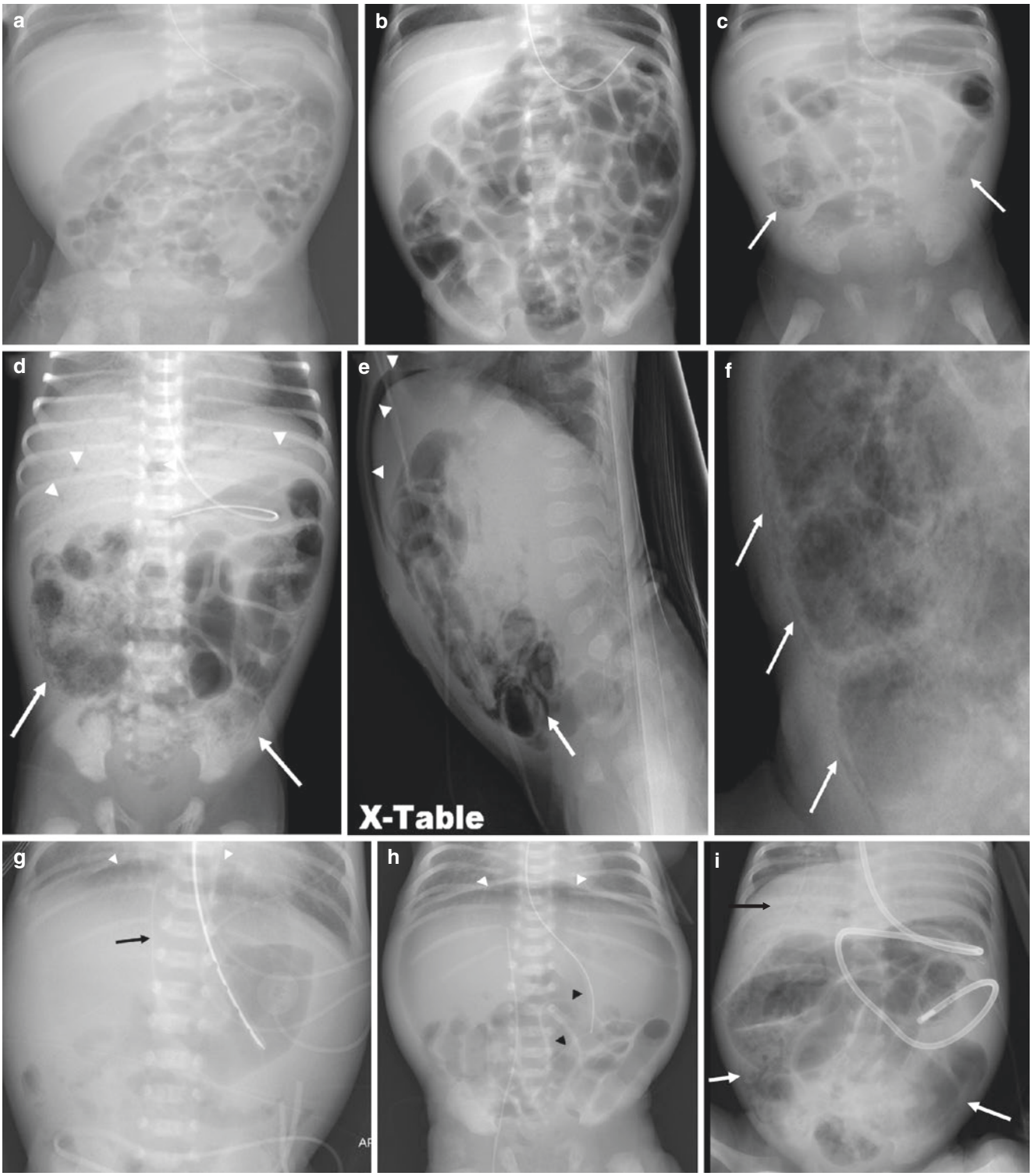

Fig. 55.3 Abdominal radiograph: (**a**) Normal bowel gas pattern, with non-dilated loops of bowel. (**b**) Demonstrates mild diffuse gaseous bowel distention, which can be the first abnormality seen in an infant with early NEC. (**c**) and (**d**) show pneumatosis intestinalis (white arrows), which linear lucencies within the bowel wall. (**d**) also demonstrates extensive portal venous gas throughout the liver (arrowheads). (**e**) Pneumatosis intestinalis (arrow) and pneumoperitoneum (arrowheads) are seen on this cross-table lateral radiograph of an infant with perforated NEC. (**f**) shows a magnified view of peripheral linear lucencies of pneumatosis intestinalis. (**g**) Large pneumoperitoneum is demonstrated with the falcifom ligament (black arrow) and subdiaphragmatic lucency (arrowheads) which combine to create the "football sign." (**h**) demonstrates marked subdiaphragmatic lucency (white arrowheads) of massive free air and Rigler's sign (double-wall sign, the air is present on both sides of the intestine) (black arrowheads) are demonstrated. (**i**) demonstrates pneumatosis intestinalis (white arrows) and branching and linear lucencies of portal venous gas (black arrow)

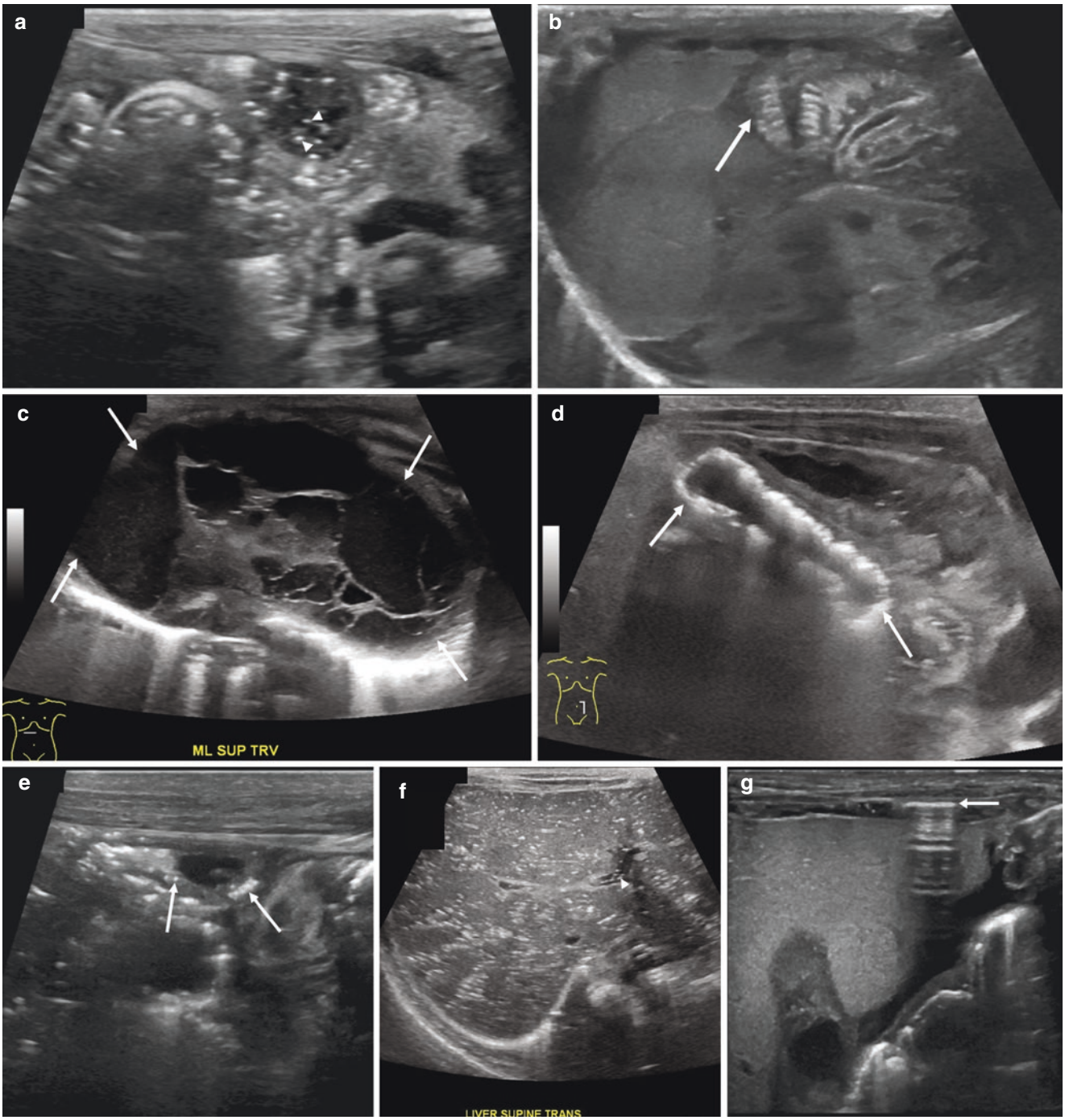

Fig. 55.4 Grayscale abdominal ultrasound images performed in neonates. (**a**) demonstrates a normal loop of small bowel, with small foci of normal intraluminal gas (arrowheads). (**b**) demonstrates the "tiger stripe" or "zebra stripe" appearance (arrow) of early NEC with thick-walled bowel. (**c**) demonstrates a large complex fluid collection (arrows), which has been shown to have high specificity for necrotizing enterocolitis, in an infant with perforated NEC. (**d**) shows the "ring sign" of pneumatosis intestinalis, with extensive submucosal air (arrows). (**e**) demonstrates intramural and subserosal gas bubbles (arrows), although to a lesser extent than (**d**). (**f**) demonstrates a "fruit pulp" appearance (heterogeneous regions of increased echogenicity within the parenchyma) of the liver in a neonate with large portal venous gas. Small bubbles of mobile gas (arrowhead) can also be seen at the portal vein bifurcation. (**g**) demonstrates the "peritoneal stripe" sign (arrow) of pneumoperitoneum, with free air anterior to the liver, with ring-down artifact

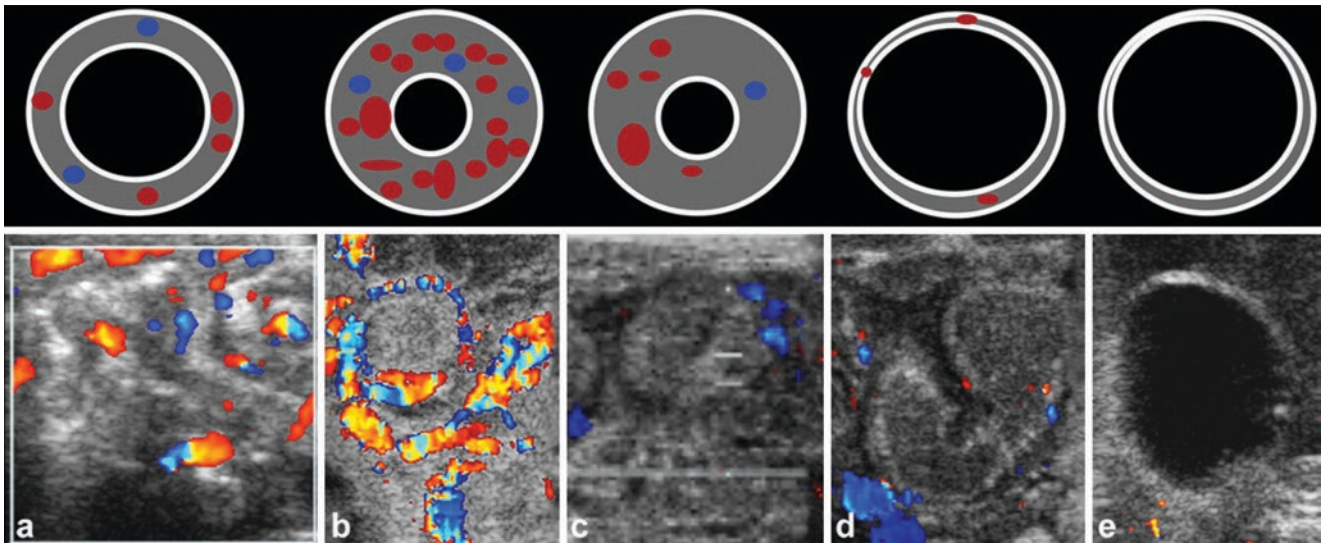

Fig. 55.5 Summary of the concept of the sequence of changes in bowel wall thickness and perfusion in NEC. The sequence is depicted with simplified diagrams of a transverse section of a bowel loop (top) and color Doppler sonograms (bottom). (**a**) There is normal flow to normal bowel. The diagram shows normal bowel wall thickness and perfusion. (**b**) The changes of NEC are shown with bowel wall thickening and hyperemia. (**c**) The bowel wall thickening persists, but the perfusion has diminished. (**d**) As the process progresses in more severely affected neonates, the mucosa starts to slough, and the bowel wall becomes much thinner, although some perfusion persists. (**e**) Sloughing continues, the bowel wall becomes asymmetrically thinned, and blood flow ceases. The authors believe that progression from the phase of bowel wall thickening and hyperemia (**b**) to bowel wall thinning and absent perfusion (**e**) may take a variable time in different patients. However, it may be an extremely rapid process, and the latter findings may indeed be present on abdominal sonograms at presentation. (By permission from Ref. [26])

perfusion (flow) of bowel wall which is impossible with plain abdominal radiography [26, 27]. The changes in bowel wall thickness, echogenicity, and perfusion are summarized in Fig. 55.5. Please refer to the excellent review by Epelman et al. for more details [26].

55.1.4 Treatment

55.1.4.1 Nonoperative Management

The mainstay of treatment for patients with early-stage NEC is medical management. The typical course of treatment consists of cessation of enteral feeds, nasogastric decompression, and broad-spectrum antibiotics. Historically, antibiotic coverage has consisted of ampicillin, gentamicin, and either clindamycin or metronidazole, although the specific regimen used should be tailored to the most common nosocomial organisms found in the Neonatal or Cardiac Intensive Care Unit. In addition, a strong index of suspicion for fungal septicemia must be maintained, especially in infants with a deteriorating condition and negative bacterial cultures.

Infants with early-stage disease, improved abdominal symptoms, and a negative sepsis workup can resume feeds in 7–10 days. The infant should be fed slowly, with careful monitoring for distension, emesis, and other signs of intolerance or recurrent NEC. Large-volume feedings and highly concentrated formulas should be avoided when feeds are initiated. We developed feeding protocols according to the low-, moderate-, or high-risk patients (Figs. 55.6, 55.7, and 55.8).

Patients with more extensive NEC and those who do not demonstrate clinical improvement may need intense supportive care, including ventilatory support and aggressive resuscitation. These patients require urgent surgical evaluation and management.

55.1.4.2 Surgical Management

Surgery is indicated in the medically treated patient whose clinical condition deteriorates [29]. An absolute indication for surgery is free air resulting from a perforated viscus or frank peritonitis. Relative indications for surgery include the presence of portal venous gas, worsening abdominal cellulitis, progressive and intractable acidosis, persistent thrombocytopenia, rising leukocytosis or worsening leukopenia, and hemodynamic instability despite medical therapy.

Surgical options for advanced NEC include laparotomy (abdominal exploration) and primary peritoneal drainage without laparotomy [16]. Peritoneal drainage is often selected for very low-birth-weight infants (<1000 g) or those infants too ill to tolerate a laparotomy [29]. For infants with

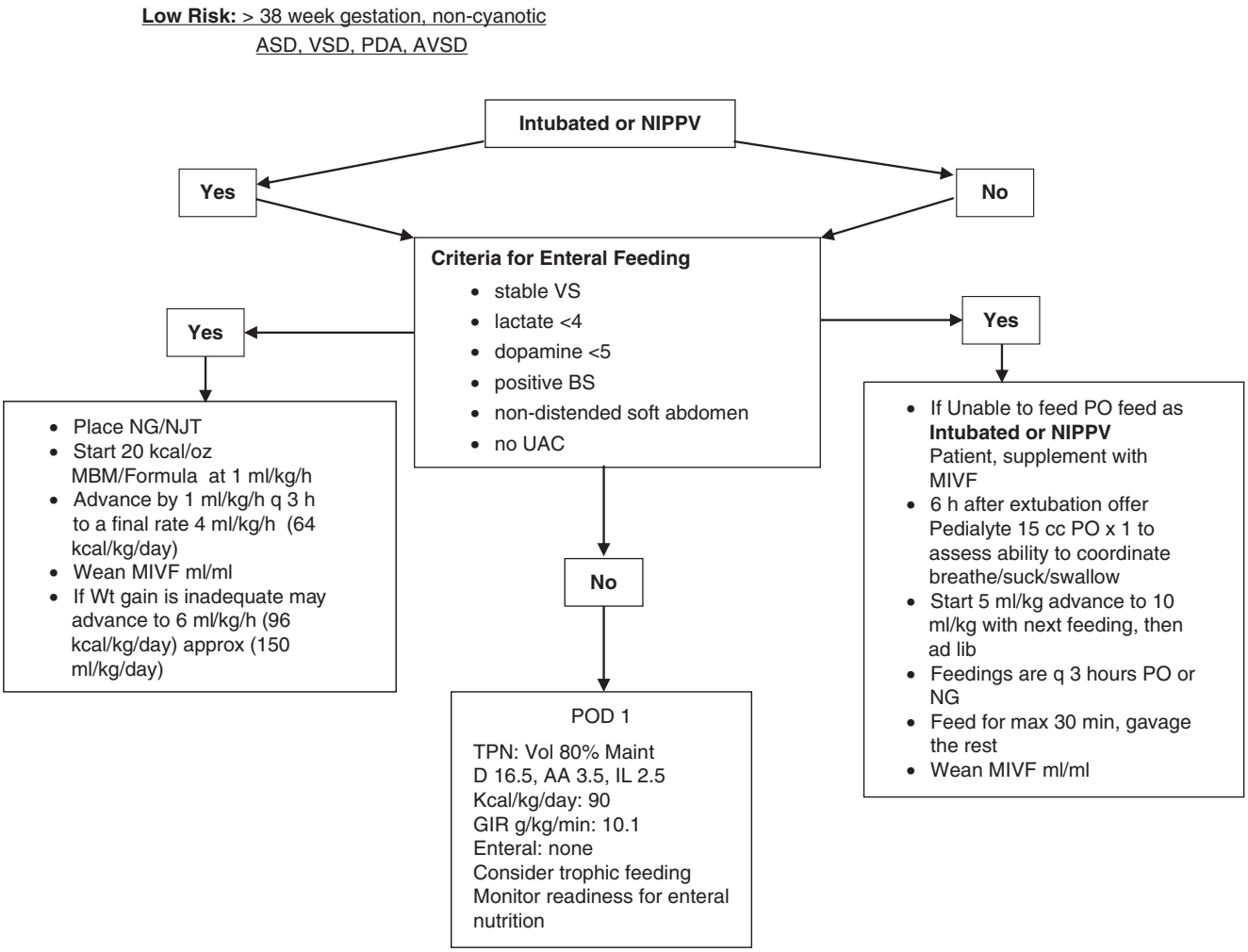

Fig. 55.6 Protocol for initiation and advancement of nutrition for low-risk patients

multi-segmental disease and pan-necrosis, peritoneal drainage is often inadequate, and these infants will require subsequent abdominal exploration.

Peritoneal drainage [30] can be performed at the bedside with adequate anesthesia. The site of drainage is usually in one or both lower quadrants. A Penrose drain is passed from the right to the left lower quadrant and secured in place. Upon entering the peritoneum, there is often a rush of air. The drain will remain in place until drainage ceases. It is not unusual for a drain site to mature into an enterocutaneous fistula that will require subsequent surgical resection or to restore intestinal continuity.

Abdominal exploration is performed through an upper quadrant transverse laparotomy incision. Upon entry into the peritoneal cavity, the liver is quickly identified and gently retracted out of the field of view. A sub-capsular liver hematoma can be a fatal complication of abdominal exploration in an infant. Therefore, it is imperative that any manipulation of the liver is performed very carefully.

The bowel is eviscerated from the peritoneal cavity and inspected for necrosis and perforation. Although the terminal ileum is the most common site of necrosis and perforation, the entire length of bowel must be evaluated due to a high incidence of discontinuous necrosis. The surgical goal is resection of all nonviable intestine with preservation of the overall intestinal length. Bowel with liquefactive necrosis and/or frank perforation must be resected. Questionably, viable bowel is often left in situ for a second-look evaluation within 24–48 hours of the original laparotomy. A proximal enterostomy is created at the most proximal site of intestinal resection. Distal discontinuous segments can be left in situ, reanastomosed, or brought out through the skin as a mucous fistula.

Primary anastomosis may be considered in select cases of isolated intestinal perforation in an otherwise stable infant. In these infants, there is minimal peritoneal contamination and overall excellent bowel viability.

Enterostomy closure to restore intestinal continuity is usually performed 6–8 weeks after the initial surgical

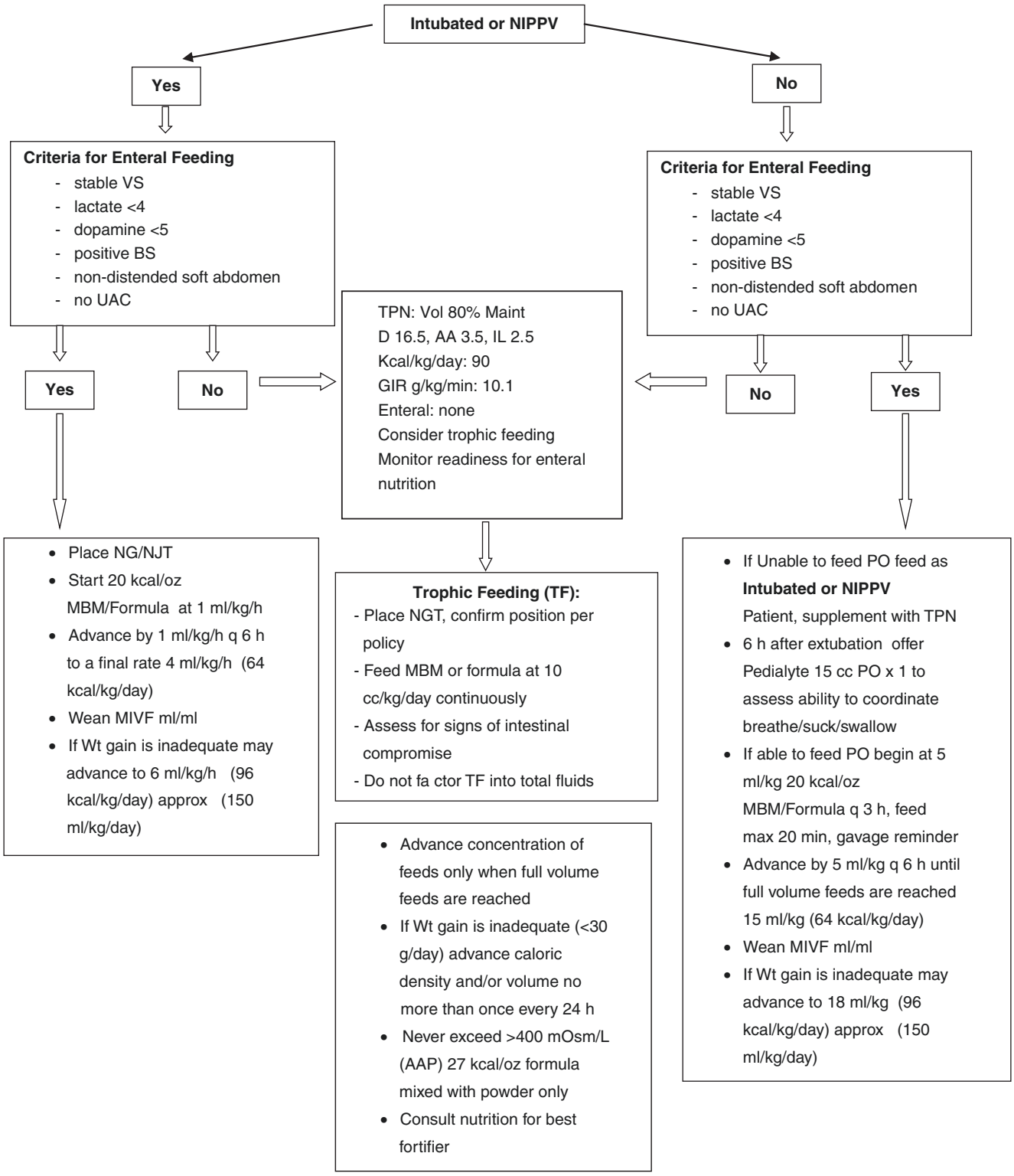

Fig. 55.7 Protocol for initiation and advancement of nutrition for moderate-risk patients

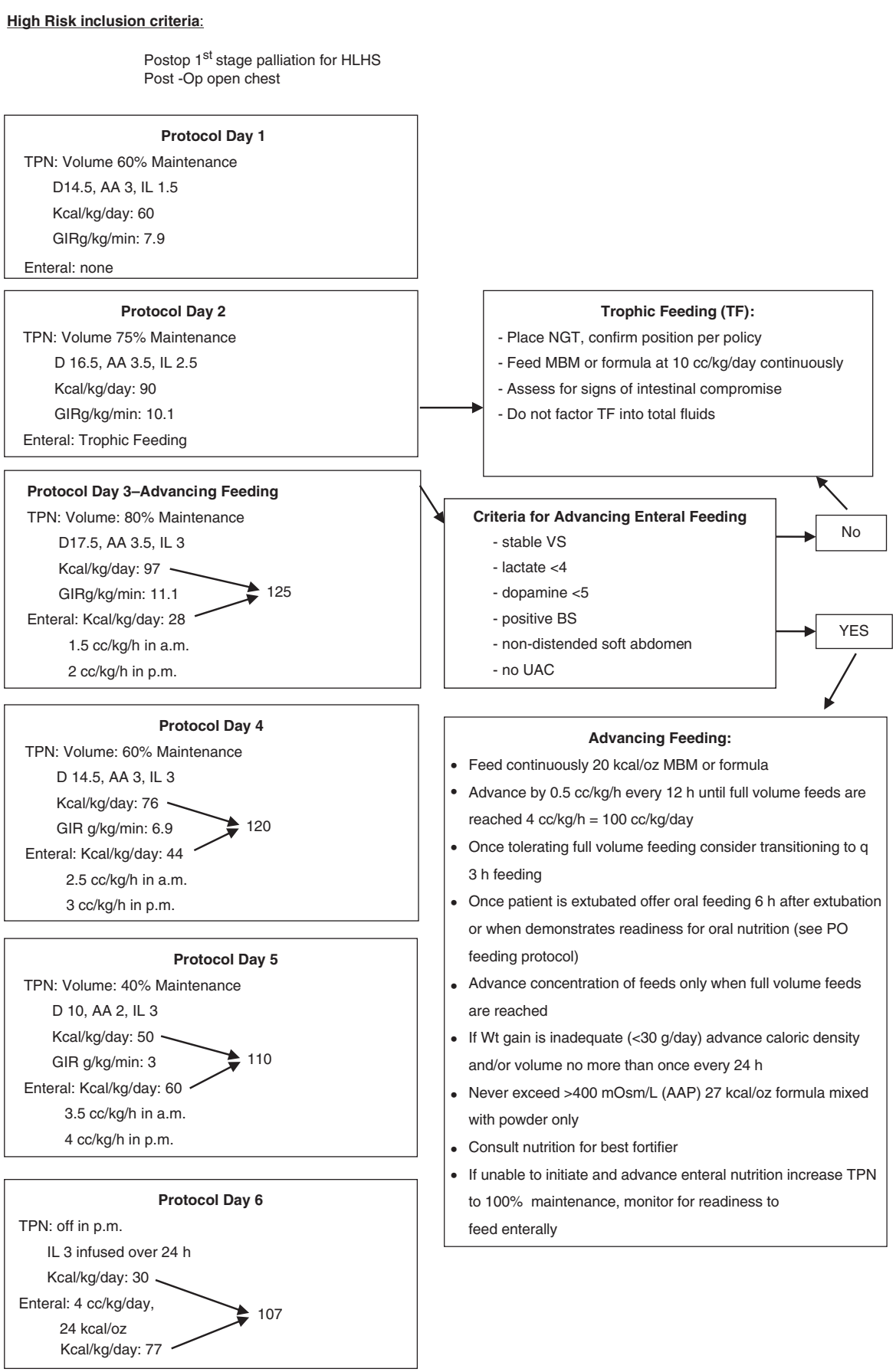

Fig. 55.8 Protocol for initiation and advancement of nutrition for high-risk patients

intervention. All bowel distal to the stoma must be imaged with a contrast enema before closure of the stoma to ensure there are no distal strictures in the remaining bowel.

Abnormally high ostomy output may indicate a need for early ostomy closure. A patient with a high jejunostomy output may have substantial loss of fluid and electrolytes, with consequences such as failure to thrive and peri-stomal skin injury. These patients may benefit from early ostomy closure with attendant colonic water absorption. However, infants with a high ostomy output and extensive ileal resection (particularly involving the ileocecal valve) who undergo ostomy closure may have considerable secretory diarrhea. Regardless, patients must be monitored after ostomy closure for stool output and electrolyte abnormalities. All patients with remaining intestine after an initial operation for NEC must be examined with a contrast-enhanced enema of the colon to identify any areas of stricture before ostomy closure. If any strictured areas are present, they will need to be addressed when the re-anastomosis is performed.

55.1.4.3 Postoperative Management

The most common complication after NEC is intestinal stricture, which occurs when an area of intestinal ischemia heals with resultant fibrosis and scar formation that impinges on the diameter of the lumen. The most common site of stricture is the left colon, followed by the terminal ileum. Intestinal stricture is most common in infants treated nonoperatively and should be suspected in any infant that was treated with nonoperative management for NEC and subsequently fails to tolerate enteral feeds and/or has recurrent bloody stools or bowel obstruction after the resumption of feeds.

Intestinal malabsorption is caused by loss of bowel length with a decreased absorptive surface area, vitamin B12 deficiency, bile salt deficiency, bacterial overgrowth, and intestinal hypermotility. Short gut syndrome is the most serious postoperative complication, occurring in as many as 27% of patients after intestinal resection [31]. Cholestatic liver disease is a multifactorial condition caused by prolonged fasting and total parental nutrition. The disease is characterized by hepatomegaly and elevated aminotransferase and direct bilirubin levels. The treatment involves initiating enteral feedings as early as possible to stimulate bile flow. Patients with intestinal failure requiring chronic parental nutrition should be managed by a multidisciplinary team consisting of a nutritionist, gastroenterologist, and pediatric surgeon.

55.1.5 Long-Term Outlook

The estimated rate of mortality associated with NEC ranges between 20% and 40%, with the highest rates among infants requiring abdominal surgery; the mortality rate approaches 100% in infants with the most severe form of the disease [20, 32, 33]. For infants with hypoplastic left heart syndrome who develop NEC, mortality has been reported to be as high as nearly 40%, and mortality increases to 75% when NEC is severe enough to cause pneumatosis intestinalis [34]. Infants who survive NEC are at increased risk for developmental delay. Infants with NEC are significantly more likely than infants of a similar age and gestation who do not develop NEC to be neuro-developmentally impaired, exhibiting a high risk of cerebral palsy and visual, cognitive, and psychomotor impairments. NEC is associated with worse neurodevelopmental outcome than prematurity alone [21, 35].

55.1.6 Prevention

Despite decades of research, preventive strategies for NEC remains elusive. There are numerous approaches proposed for the prevention of NEC [16], which include feeding the infant with maternal breast milk [36] or donor breast milk, administrating probiotics, and advancing enteral feedings slowly. The common practice of withholding enteral feeds in infants with NEC comes from clinical experience and retrospective reviews that suggest a rapid increase in feedings increases the likelihood of NEC [37]. Reflecting this practice, in the cohort from the Pediatric Cardiac Critical Care Consortium (PC4) registry, only half of the neonates with congenital heart disease received preoperative enteral nutrition and 3.2% of the patients developing NEC – three preoperatively and five postoperatively [38]. Multi-institutional collaboration is needed to develop feeding strategies associated with the best clinical outcomes in neonates with congenital heart diseases.

Human milk is the gold standard for healthy infants, as well as for those who are premature or critically ill. There has been no research to date evaluating the benefits of human milk and risks of artificial human milk in the population of infants with congenital heart disease. To provide adequate nutrition to these infants, the current recommendation is to first offer the mother's own milk, if available, pasteurized human milk second, and artificial human milk third [39]. Infants with congenital heart disease are at an extremely high risk for morbidity and mortality related to NEC. The protective components present in human milk are not present in artificial human milk. These components can decrease the inflammatory response triggered by Toll-like receptor 4 (TLR4), promote epithelial cell growth, and decrease intestinal permeability to harmful bacteria [40].

55.2 Malrotation

Malrotation is an anatomical defect that occurs during embryonic intestinal rotation and fixation within the abdomen. Intestinal rotation and fixation begin in the fifth

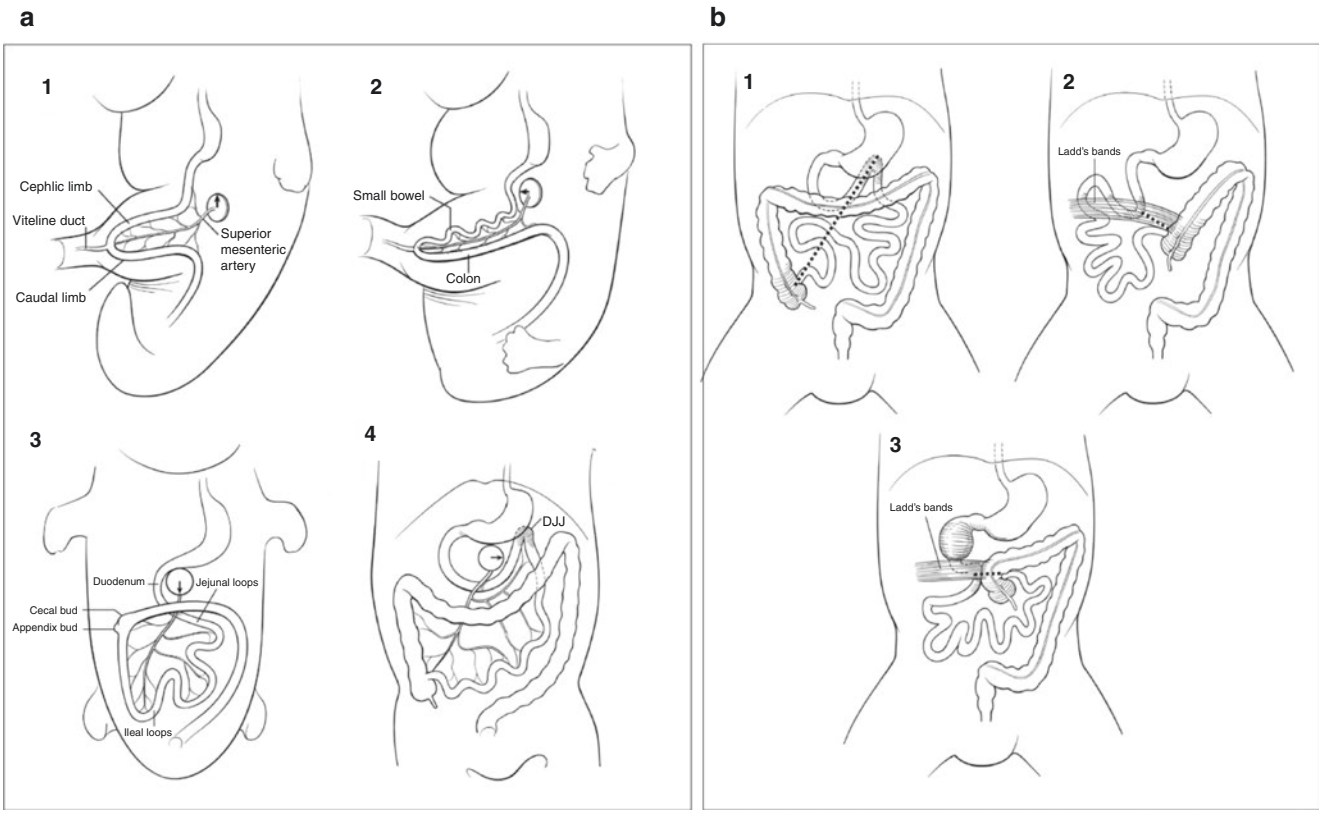

Fig. 55.9 (**a**) Normal intestinal rotation and fixation. (1) At week 6 of gestation, the bowel loops elongate and herniate in a U-shaped loop through the umbilicus (U) to the primitive extraembryonic celom. (2) During weeks 6–10 of gestation, the bowel loops (mainly the cephalic limb of the primitive gut) rotate counterclockwise 90°. (3) In week 10 of gestation, the cecum can be appreciated and the intestine reenters the abdominal cavity completing 180° of counterclockwise rotation. (4) At 12 weeks of gestation, the counterclockwise rotation (270°) of the intestine is complete. The duodenum extends retroperitoneally behind the SMA, and the duodenojejunal junction (DJJ) is fixated by the ligament of Treitz to the left of the spine at the level of the pylorus. Throughout the remainder of gestation and first few months of life, the colon continues to elongate, and the cecum descends into the right lower quadrant. DJJ, duodenojejunal junction; SMA, superior mesenteric artery (By permission from Ref. [28]). (**b**) Normal and rotational abnormalities of the intestine. (1) Normal position of the DJJ and the cecum with a broad mesenteric root. (2) Nonrotation with the entire small bowel in the right abdomen and the colon in the left abdomen. Ladd bands may be present. Mesenteric root is wide if the cecum is located in the lower abdomen or the pelvis and the risk of volvulus is low. However, midgut volvulus is still of some concern if the cecum is high with a shorter mesenteric root as shown in (2). (3) Incomplete rotation with the DJJ to the right of midline and high position of the cecum. There is a short mesenteric root predisposing to volvulus and Ladd bands, which may cause obstruction. DJJ duodenojejunal junction. (By permission from Ref. [28])

gestational week, with completion by the tenth gestational week [28, 41].

There have been several categorizations of the exact steps involved in this process, but it is logical to consider the event as a continuum rather than occurring in distinct phases (Fig. 55.9). Most simply, the embryonic gut begins as a short, straight continuous tube (Fig. 55.9a1). The entire intestine must rotate counterclockwise for a total of 270° around the axis of the superior mesenteric artery (SMA). The duodenojejunal loop originates anterior to the SMA (Fig. 55.9a2). It initially rotates to the right of the artery and then travels under and finally across the spine and upward, so that the duodenojejunal junction lies to the left of the SMA and spine (Fig. 55.9a4). The ceco-colic loop originates beneath the SMA (Fig. 55.9a2) and rotates counterclockwise. It initially rotates to the left of the SMA, then above it (Fig. 55.9a3) and finally to the right and downward (Fig. 55.9a4) to create the typical configuration of the colon. Normal intestinal rotation leads to a retroperitoneal duodenum, with a fixed point in the left upper quadrant where the duodenum transitions to the jejunum (Fig. 55.9a4). This fixed point is known as the ligament of Treitz (LT). The small bowel is then located throughout the center of the abdomen (Fig. 55.10c), arising from a broad mesentery that has a second fixed point in the right lower quadrant. Incomplete rotation results in a shortened distance between the LT and the cecum and therefore a narrowed mesenteric root. Fixation is initiated during rotation but continues even after rotation is complete. Fixation ensures the secure anchoring of the intestine to the posterior abdominal wall [28, 42]. Arrest of development anywhere along this continuous process will result in incomplete rotation with varying degrees of intestinal fixation termed "malrotation" (Fig. 55.9b) [42]. In intestinal malrotation, the duodenum is not retroperitoneal and has no point of fixation

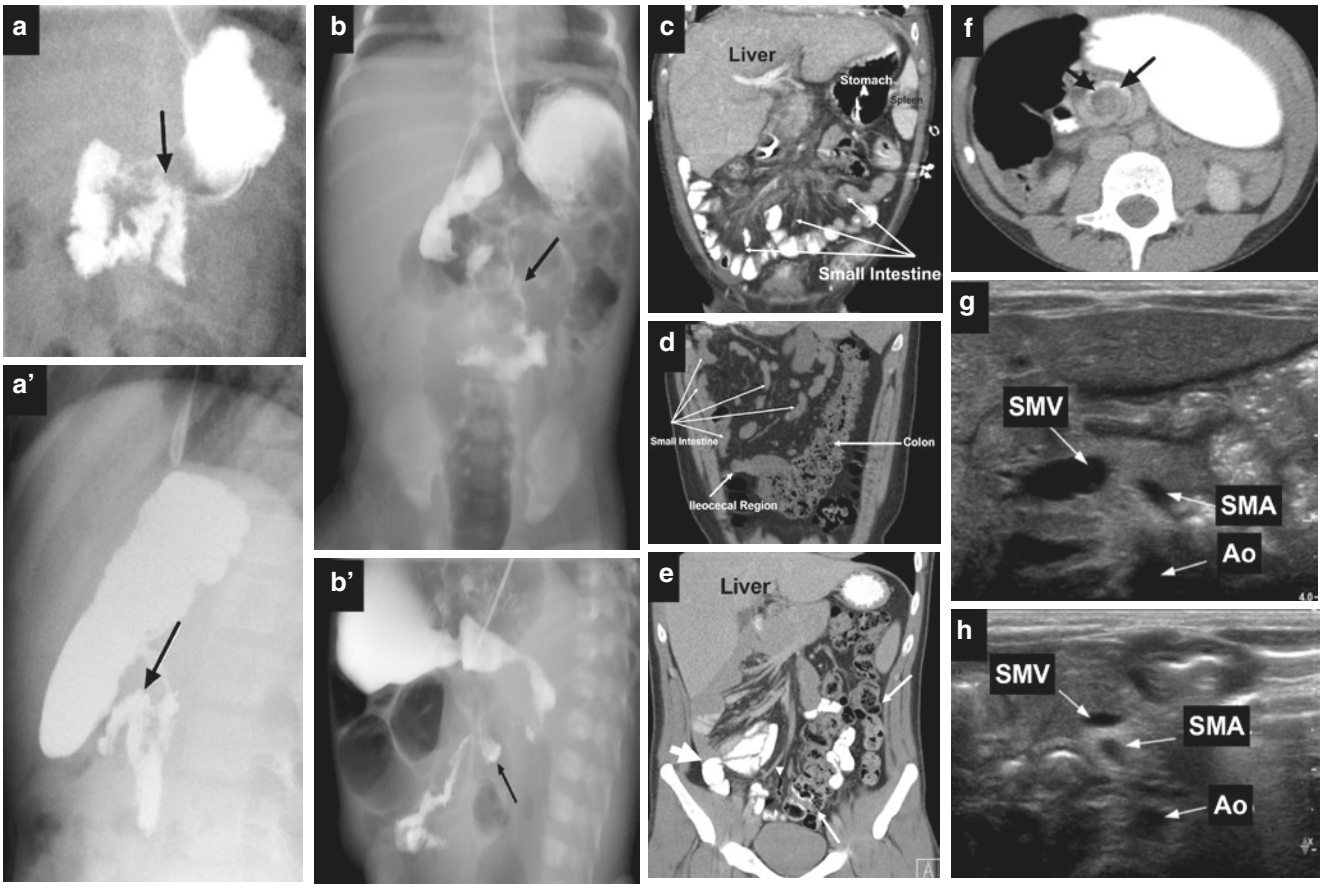

Fig. 55.10 Frontal (**a**) and lateral (**a**') views during fluoroscopic upper GI examination demonstrate normal position of the duodenojejunal junction (arrow) in the retroperitoneum, to the left of the spine, and as high as the level of the pylorus. Frontal (**b**) and lateral (**b**') views from fluoroscopic upper GI in a 2-week-old patient with malrotation and midgut volvulus demonstrate abnormally anterior and low position of the duodenojejunal junction (black arrow) with abnormal "corkscrew" configuration of the duodenum. (**c**–**e**) Coronal view of computed tomography (CT) scan: Normal abdominal CT (**c**) demonstrated the small bowel is located throughout the center of the abdomen, arising from a broad mesentery. (**d**) A 21-year-old with left atrial isomerism and malrotation, abdominal CT demonstrated intestinal malrotation with the entire of the small bowel is on the right side of the abdomen and the colon is all found on the left side of the abdomen. CT image (**e**) performed for trauma demonstrates incidental malrotation in a 19-year-old male, with small bowel (thick white arrow) completely located in the right hemiabdomen and colon (thin white arrow) located in the left hemiabdomen. The appendix is midline (white arrowhead). Axial CT performed with enteric contrast, but no IV contrast (**f**) in a 6-year-old male, demonstrates malrotation with midgut volvulus. A whirlpool of enteric contrast-containing duodenum can be seen in the upper abdomen (arrowheads). (**g**, **h**) Abdominal ultrasound: (**g**) Normal relationship of the SMV and the SMA – the SMV is to the right of the SMA. (**h**) The SMV is directly anterior to the SMA (arrow), in a child with malrotation. Ao aorta, SMA superior mesenteric artery, SMV superior mesenteric vein. (7G and H, By permission from Ref. [28])

(Figs. 55.9b2, and 55.3). In patients with intestinal malrotation, it is typical that the entire small bowel is on the right side of the abdomen and that the entire colon is located on the left side of the abdomen (Figs. 55.9b, and 55.10d, e).

55.2.1 Clinical Presentation

The diagnosis of malrotation is usually made in the neonate or young infant, with up to 50% of symptomatic patients presenting in the first week and more than 60% before the end of the first month [43]. The pathologic effects of intestinal malrotation stem from excessive mobility, compression or kinking of the gut and can result in midgut volvulus and a predisposition to torsion [43]. Volvulus occurs in 60–70% of infants with intestinal malrotation with 15% of patients developing strangulation [42]. The most common symptom of intestinal malrotation is bilious emesis with or without abdominal distention in newborns. If acute midgut volvulus develops, hematemesis, hematochezia (a sign of bowel ischemia), and abdominal guarding may occur in addition to the bilious emesis and abdominal distention. Patients with persistent symptoms of malrotation with volvulus may develop intestinal ischemia, intestinal necrosis, peritonitis, septicemia, and shock. Intestinal malrotation has been reported in 1.4% of

neonates with congenital heart disease from the Society of Thoracic Surgeons congenital heart surgery database [44], and in 2.8–4.1% of all patients with all the congenital heart diseases [45]. The incidence of congenital heart diseases with intestinal malrotation is significantly higher than the observed incidence of 1:500–1:3500 living births [46]. Malrotation is frequently observed in patients with heterotaxy with an incidence of 60–83% in patients who underwent screening [47, 48].

55.2.2 Diagnosis

Early diagnosis is of the utmost importance to avoid bowel necrosis associated with volvulus. The priority for the clinician is to recognize the child who is at risk for malrotation, based on the history and physical findings. Abdominal radiographs may reveal a gasless abdomen or dilated intestinal loops, indicating some degree of obstruction. An upper gastrointestinal (UGI) series is the gold standard for radiographic diagnosis of malrotation and volvulus. Normal rotation is present if the duodenal C-loop crosses the midline and places the duodenojejunal junction to the left of the spine at a level greater than or equal to the pylorus. If the contrast ends abruptly or tapers in a corkscrew pattern (Fig. 55.10a, b), the differential diagnosis should include midgut volvulus [28]. Abnormalities in the orientation of the SMA and superior mesenteric vein (SMV) on ultrasonography (US) or computed tomography (CT) in patients with malrotation and have suggested that this sign may be an alternative way to establish the diagnosis (Fig. 55.10g, h) [28, 49]. Normal position of the SMA is on the left of the abdomen and SMV is on the right (Fig. 55.7g). If the SMV is left or is posterior to the SMA on cross-sectional imaging, malrotation should be suspected (Fig. 55.10h). The detection of malrotation, with or without volvulus using computed tomography (CT) is common in clinical practice. The "whirlpool sign" or a whorled pattern at abdominal ultrasound and CT is highly diagnostic of midgut volvulus (Fig. 55.10f). It is a result of wrapping of branches of the SMV, mesenteric fat, intestine, and branches of the SMA, around the SMA [28, 49] (Fig. 55.10h). The whorl pattern may be associated with internal hernia, adhesion or may be seen after surgery because of disruption of the normal relationships of vessels and bowel loops. Therefore, the "whirlpool sign" is not a specific finding of midgut volvulus [49, 50]. Normal abdominal CT demonstrates that the small bowel is located throughout the center of the abdomen (Fig. 55.10c), arising from a broad mesentery that has a second fixed point in the right lower quadrant. In intestinal malrotation, the duodenum is not retroperitoneal and has no point of fixation resulting in the typical radiological pictures of the inability to visualize the third part of the duodenum across the midline from right to left and the entirety of the small bowel on the right side of the abdomen with the colon on the left side of the abdomen (Fig. 55.10d, e).

55.2.3 Treatment

55.2.3.1 Preoperative Management

The diagnosis of intestinal malrotation requires prompt surgical consultation. The patient immediately must be assessed for the presence of midgut volvulus, and the resultant intestinal ischemia. Failure to act in a timely manner, could lead to loss of the entire midgut, which includes all bowel from the distal duodenum to the proximal two-thirds of the transverse colon. If midgut volvulus is present, or strongly suspected, an emergent laparotomy must be performed. A nasogastric tube should be placed to decompress the stomach. Volume resuscitation should be initiated in preparation for operative intervention.

55.2.3.2 Surgical Management

The Ladd procedure remains the mainstay of surgical treatment for malrotation [51]. The abdomen is opened with a transverse upper abdominal incision. All the bowel is eviscerated from the abdomen and inspected for ischemia and volvulus of the mesenteric root. If volvulus is identified, this can be corrected with counterclockwise rotation of the bowel at the mesenteric root. Once the bowel has been eviscerated, it is further inspected for viability. When there are no concerns for intestinal ischemia and necrosis, the operation proceeds with a division of the adhesive bands ("Ladd's bands") that originate from the cecum, crossover the duodenum and ultimately adhere to the right lateral abdominal wall. The bands are a source of duodenal obstruction if not properly divided. Adhesions in the mesentery at its root are then taken down, effectively widening the root of the mesentery, and thereby decreasing the risk of subsequent volvulus. Finally, an appendectomy is performed.

If bowel viability is a concern in the setting of volvulus, a temporary silo will be placed with a planned second-look operation the following day. Questionably, viable bowel may recover within the first 24 hours. All obviously necrotic bowel must be resected. If the entire midgut is necrotic, the only sustainable option for subsequent nutrition and intestinal rehabilitation will often be parental nutrition bridging to intestinal transplant.

A laparoscopic approach to the Ladd procedure has been shown to be a safe and effective technique in patients with

malrotation without volvulus. It can be performed with operative times equivalent to standard open techniques and is associated with a shorter time to full enteral feeds and length of hospital stay [52]. There is a high incidence of patients with heterotaxy associated with intestinal malrotation [45], and the outcomes following cardiac surgery for patients with heterotaxy are not affected by the presence of malrotation with a low incidence of volvulus (7%) [46]. It is still controversial to perform prophylactic Ladd procedures in asymptomatic heterotaxy patients with malrotation. A prophylactic Ladd procedure is associated with lower morbidity and mortality compared with emergency surgery [45]; however, a prophylactic Ladd procedure incurs a high mortality (50%) and morbidity in patients with a single-ventricle physiology associated with shunt thrombosis, especially after initial cardiac palliation (stage I palliation) [46, 53]. In patients with critical congenital heart diseases, the timing of abdominal surgery should be carefully considered, and delayed surgical intervention for malrotation without volvulus may be reasonable [54].

55.2.3.3 Post-op Management

There are several complications of malrotation, especially if midgut volvulus occurs. Patients suffering from midgut volvulus with intestinal loss often have a delay recovery of bowel motility and function. Postoperatively, patients require bowel rest and nasogastric decompression until the return of bowel function. It is recommended to obtain central venous access and provide parenteral nutrition in patient with volvulus and expected delay of bowel function. If a significant portion of the ischemic bowel is excised, they are at high risk of intestinal failure and may require long-term parental nutrition. Patients with intestinal failure are at risk for central line complications including sepsis, liver failure, and death.

55.3 Protein-Losing Enteropathy

Protein-losing enteropathy (PLE) is characterized by a severe loss of proteins into the intestinal tract. PLE is diagnosed based on the presence of low serum albumin/total protein, enteric loss of α-1-antitrypsin in addition to symptoms of persistent or intermittent edema, diarrhea, and ascites [55]. PLE has been associated with cardiac and extracardiac disease states. PLE occurs in a variety of clinical settings (as constrictive pericarditis, congestive heart failure, and cardiomyopathy) and is commonly seen in patients after the Fontan procedure, with a frequency of approximately 3–18% [56]. PLE can develop anywhere from weeks to many years after the Fontan procedure; the median time interval between the Fontan operation and the diagnosis of PLE is 2.7 years [57]. The 5-year survival after the initial diagnosis of PLE in patients after Fontan procedure was reported to be as low as 50% in the 1990s [57], and the outcome has improved, with increased survival to 88% and 72% at 5- and 10-years, respectively [58]. In 1984, Ernest Starling reported that elevated central venous pressure results in liver congestion and a subsequent increase in liver lymphatic flow [59]. Dori et al. demonstrated leakage of protein-rich lymph into the duodenum through an abnormal focal hepatoduodenal lymphatic connection through liver lymphangiography in patients with PLE [60]. This finding suggests that increased liver lymphatic flow results in distention of the hepatoduodenal lymphatic connections and intestinal lacteals, which subsequently leads to lymph leakage into the intestine lumen [60]. The hallmark of PLE is a failure to maintain an intact intestinal epithelium. An abnormal leakage of serum proteins into the intestinal lumen causes the physical abnormalities and serologic/hemodynamic derangements. Multiple factors have been associated with PLE including a low cardiac output state, venous hypertension, an abnormal response to pro-inflammatory mediators, and severe infection or sepsis. Elevated venous pressures and inflammatory mediators such as interferon-gamma and tumor necrosis factor-alpha predispose the intestinal epithelial cells to leaking protein into the lumen.

55.3.1 Clinical Presentation

There is a wide range of clinical signs and symptoms that vary in degree from mild to severe. In some cases, PLE can be transient, when a correctable hemodynamic abnormality is noted or associated with an infection, with a reported 19% of appropriate surgical procedures causing relief of PLE [56]. A high level of clinical suspicion of PLE in patients with Fontan physiology is critical, because many patients remain asymptomatic during the early stages of the disease. Common symptoms of PLE include chronic diarrhea, peripheral edema, gastrointestinal discomfort, protuberant abdomen, poor enteral tolerance, and effusions within the pleural, peritoneal, and pericardial spaces. Hypoproteinemia, due to the enteric loss of protein that exceeds the normal rate of 1–2% of the plasma pool, leads to peripheral edema, ascites, clotting abnormalities, or recurrent infection. Conditions that cause lymphatic obstruction, such as constrictive pericarditis and post-Fontan states, have been shown to be associated with lymphopenia and loss of immunoglobulins, while inflammatory states do not have these types of features. Lymphopenia, which develops in response to lymphatic obstruction and because of the "leaky" intestinal epithelium, lends itself to potential immune dysfunction. Patients with PLE also have an abnormal coagulation profile, making them more suscep-

tible to thrombotic formation. The procoagulant state is probably secondary to deficiency of protein C, protein S, factor V, and factor VII. Fat malabsorption can also occur due to dilation and rupture of intestinal lacteals, leading to deficiencies of vitamin A, D, E, and K, and presents clinically as noninfectious diarrhea and malabsorption.

55.3.2 Diagnosis

The diagnosis of PLE is made by a clinical history of a Fontan operation or other predisposing conditions and noting the signs and symptoms. Demonstration of elevated stool α1- antitrypsin is the gold standard for diagnosis of PLE. Patients with PLE have elevated stool α1- antitrypsin clearance values >50 ml/24 hours on a 24-hour stool collection or a single spot fecal α1- antitrypsin concentration > 100 mg/ml [55]. α1- antitrypsin is an endogenous protein not present in the diet and has a molecular weight similar to that of albumin. It is neither actively secreted, absorbed, nor digested, and these properties that make it an ideal marker for evaluating protein loss. In addition, liver function tests, including serum protein and albumin concentrations, are informative. Itkin et al. reported using liver lymphangiography to access the liver lymphatic system and demonstrated liver lymph leakages as an etiology of PLE in 8 patients with elevated central venous pressure and congenital heart diseases [60].

55.3.3 Treatment

Patients with PLE may be admitted to the intensive care unit due to a low cardiac output state, arrhythmias, over-whelming sepsis, and/or edema secondary to low oncotic pressure and severe hydro-electrolyte imbalances. ICU management should be tailored to manage the cardiac complications, with careful consideration for the extracardiac manifestations of diseases, such as sepsis, electrolyte abnormalities, hypoproteinemia, and thrombosis. With the improving understanding of the lymphatic circulation in the Fontan population, alternative approaches such as lymphatic embolization to decreased liver lymphatic leakage [60] and "decompression of thoracic duct" [61] have emerged.

55.3.3.1 Cardiac-Directed Therapies

Cardiac-directed therapies include (1) treating congestive heart failure; (2) surgery or catheter-based techniques for relief of Fontan obstruction and valve regurgitation; and (3) treating arrhythmias with cardioversion, ablation therapy, medications, or AICD and/or a pacemaker [56]. All patients who are admitted to the intensive care unit with PLE must have an extensive investigation of their hemodynamics [57]. An echocardiogram and cardiac catheterization must be performed to assess ventricular function, cardiac output, atrioventricular, or semilunar valve regurgitation, Fontan baffle or conduit, pulmonary arteries, patency of the fenestration, and aortopulmonary or venous collaterals. Diuretics are helpful for reducing symptoms associated with fluid overload and edema. Arrhythmias must be treated aggressively; some patients may need atrial pacing to improve the cardiac output of the Fontan circulation associated with sick sinus. If the fenestration is closed, some patients may benefit from reopening it. Distortion of the pulmonary arteries must be treated. Mertens et al. reported that 5 of the 8 (62.5%) of patients with PLE had temporary or long-term symptomatic improvement after a successful procedure to relieve the obstruction within the systemic venous to pulmonary arterial pathway [56]. Pulmonary vasodilators including inhaled nitric oxide [62], sildenafil, and bosentan have been shown to ameliorate PLE in patients with elevated pulmonary arterial resistance. A golden rule is that the caregivers must eliminate any anatomic, hemodynamic, and the electrophysiological abnormalities in the Fontan circuit [56, 58]. In 2013, Hraska reported 2 patients with a failing Fontan physiology and PLE who were successfully treated with "decompression of the thoracic duct" to lower pressure levels of the common atrium by diverting the innominate vein directly to the common atrium [61]. Nevertheless, even an optimal surgical Fontan circulation may develop PLE. From the hemodynamic point of view, the venous/Fontan pressure is always above the physiologic value. Heart transplantation is the final option for a failing Fontan. The immediate postoperative care of patients after heart transplantation and PLE is challenging. These patients are malnourished and may develop third space syndrome associated with hypoproteinemia. However, PLE was observed to be resolved in all patients with a failing Fontan circulation and PLE who survived longer than 30 days after heart transplantation [63].

55.3.3.2 Intestinal Directed Therapies

Loss of heparan sulfate and syndecan-1 (the predominant heparan proteoglycan) from the basolateral surface of the intestinal epithelium in combination with elevated inflammatory mediators and high venous pressure are the main triggering factors for developing PLE. There are two main pharmacological strategies to stabilize intestinal cell membranes directed at reducing intestinal inflammation and protein losses: heparin [64, 65] and steroids [66].

Steroids stabilize the intestinal capillary and lymphatic cell membranes, treating the possible inflammatory component of PLE. Budesonide, an enteric-specific steroid, has been used to treat PLE in patients with preserved hepatic function [56]. There have been several reports of using steroids to treat PLE after a Fontan operation in adults and children. The studies have shown different degrees of success with steroid therapy in patients with PLE [66]. The response ranges from no response, to an almost complete disappearance of all symptoms of PLE, to frequent episodes of relapse. Side effects of steroids, which include Cushing's syndrome, hypertension, and immunosuppression, are significant limiting factors for the long-term use of these drugs.

It has been hypothesized that unfractionated heparin works because it is lipophilic and has a strong negative ionic charge [64, 65]. Both properties are important in maintaining the intestinal mucosal integrity. The negative ionic charge is of paramount importance in avoiding loss of proteins across the intestinal barrier. It appears that high-molecular-weight heparin reduces the effect of inflammatory cytokines (interferon-ϒ and tumor necrosis factor-α) in inducing a protein leak from intestinal epithelial cells. Inhibition or reduction of this effect depends on the molecular size of the heparin. Another mechanism to explain the potential benefit of heparin in PLE is that heparin might decrease chronic microemboli in the mesenteric circulation, in the setting of higher vascular resistance and increased pressures. Unfractionated high-molecular-weight or low-molecular-weight heparin may have some beneficial effects in patients with PLE after Fontan operations [64, 65]. Like steroids, heparin has significant side effects such as undesirable anticoagulation, heparin-induced thrombocytopenia with thrombosis, and decreased bone mineral density, seen with chronic exposure. The side effects appear to be decreased with the low-molecular-weight heparin, but this should be weighed in combination with the potentially reduced efficiency.

Recently, liver lymphatic lymphangiography and embolization were reported to improve albumin levels and relief of symptoms of PLE [60].

Hypoproteinemia

Nutritional management is a mainstay of therapy in patients suffering from PLE. While enteral therapy is recommended, the severity of the underlying disease may preclude that route. The low-fat (<25% of calories from fat) diet should be rich in proteins (≥2 g/kg/day) and medium-chain triglycerides (MCTs) [58]. MCTs, while not shown to decrease inflammation, are favorable because they are not absorbed via the lymphatic systemic but are absorbed directly into the bloodstream. Intravenous protein supplementation can be accomplished with 25% albumin and/or parental nutrition, with the understanding that there is ongoing intestinal protein loss.

55.3.3.3 Extracardiac Directed Therapies

Sepsis/Fluid and electrolytes

Patients with PLE have lymphopenia and hypogammaglobulinemia, which increase the risk for bacterial, fungal, and viral infections. Appropriate fluid resuscitation and broad-spectrum antibiotics to cover bacterial and fungal infections should be initiated in the setting of a suspected infection [67]. These patients may require more fluid and colloids due to loss of oncotic pressure than those patients with sepsis without PLE. A central venous catheter is helpful to monitor the central venous/Fontan pressure, to facilitate fluid replacement, and to monitor fluid administration. Diuretics should be carefully administered once the septic syndrome improves. Hyponatremia, hypokalemia, and hypomagnesemia may not be rare.

Other Extracardiac conditions

Extracardiac conditions that may have associated with hemodynamic conditions – including anemia, thyroid dysfunction (hypothyroidism or hyperthyroidism), and sleep apnea (elevated CO_2 level and pulmonary vascular resistance) – should be optimized.

In summary, multiple factors associated with PLE include a combination of a low cardiac output state, high venous pressure, increased mesenteric vascular resistance, and an abnormal response of the intestinal epithelial cells to inflammatory cytokines. The resultant abnormal protein loss appears to be facilitated by the loss of heparin sulfate and syndecan-1 on the intestinal epithelial cell. Clinical symptoms of edema and ascites result from a pro-inflammatory state in conjunction with hypoproteinemia. Therapeutic strategies related to a preexisting cardiac condition include investigation and treatment of abnormalities in the Fontan circuit, liver lymphatic lymphangiography and embolization, high protein diet, high MCT diet, and intravenous protein supplementation with albumin 25% or parental nutrition. Corticosteroids and heparin remain valuable therapies. Finally, heart transplantation has been shown to reverse the effect of PLE in pediatric patients.

55.4 Nasogastric (NG) Tube Syndrome

Forty-four percent of neonates with congenital heart diseases undergoing cardiac surgery are discharged with a feeding tube, ranging from 6% to 80% across different centers as reported by the PC4 database [36]. Upper airway obstruction related to mechanical irritation and compression-related ischemia from a nasogastric tube is called "nasogastric tube syndrome" (Fig. 55.11) [69]. NG tube syndrome is a rare

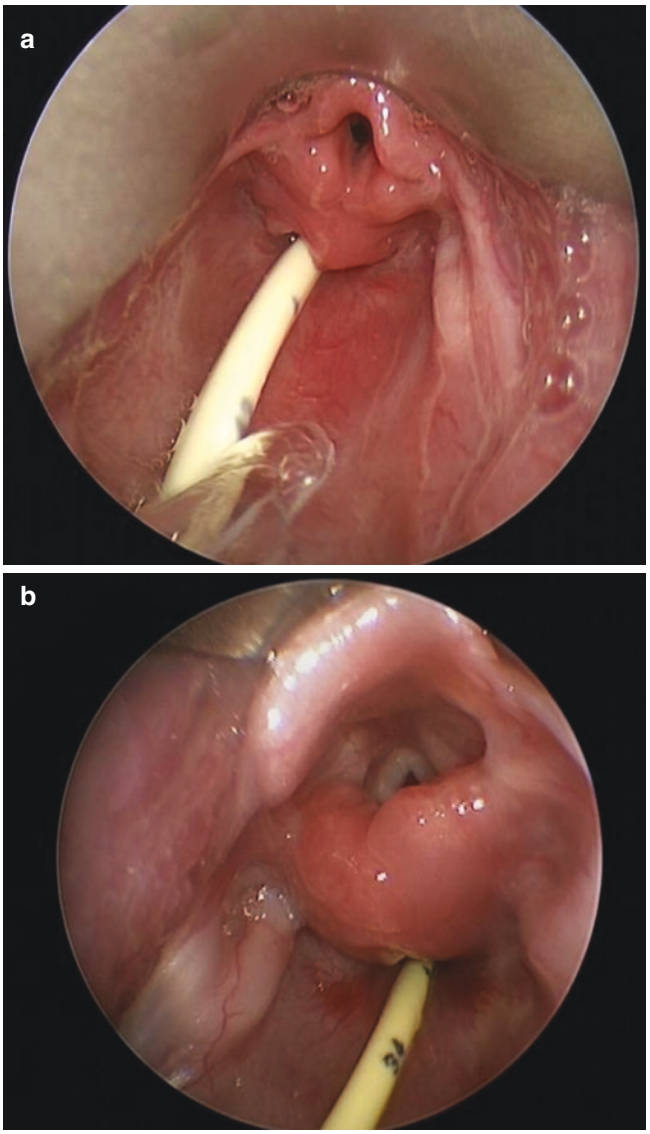

Fig. 55.11 Endoscopic view of nasogastric tube syndrome. (**a**) Patient 1, endoscopic view prior to NG tube removal. Note the significant postcricoid edema and granulation. (**b**) Patient 2, endoscopic view prior to NG tube removal. Note the significant postcricoid edema and granulation. (By permission from Ref. [68])

condition associated with respiratory distress and stridor that are temporally related to NG tube placement. In contrast to reported cases in adult populations, infants develop postcricoid edema, inflammation, and mucosal damage without developing impaired vocal cord mobility [68]. A meta-analysis demonstrated a range of NG tube onset from 12 hours after NG tube placement to 2 weeks after NG tube removal [70]. The symptoms of respiratory distress, stridor and postcricoid inflammation, were observed to resolve quicker (2 ± 1 days) than those in the adult population (1–2 weeks) [68]. Management of NG tube syndrome includes removal of the NG tube and medical treatment with steroids, antibiotics, and anti-reflux medications [68] as well as tracheostomy in some reports [71].

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Chapter 56
Growth Failure and Feeding Difficulties: Guidelines for Enteral and Parenteral Nutrition

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Abstract Nutrition support is a fundamental aspect of care for critically ill pediatric cardiac patients, with known effects on morbidity, wound healing, infection, and length of hospitalization. Provision of adequate nutrition support presents several unique challenges in the pediatric cardiac population. Pediatric patients hospitalized with congenital heart disease are usually born at normal weight but rapidly develop malnutrition (undernutrition). In fact, nearly half of children admitted for cardiac surgery are malnourished. Risk factors for preoperative growth failure in these patients include; the underlying cardiac physiology, the presence or absence of congestive heart failure, anorexia, poor oral feeding coordination, gastrointestinal abnormalities or dysfunction, and the presence or absence of genetic disease. Infants with single ventricle physiology are at particular risk for malnutrition, which is known to increase their risk for interstage mortality. Many of these children experience malabsorption due to decreased cardiac output, hypoxia, elevated right-sided cardiac pressure, and subsequent gastrointestinal dysfunction. Infants and children undergoing cardiac surgery may go on to develop further deterioration of their nutrition status due to postoperative fluid restrictions, interruptions to feeding for procedures, feeding intolerance, and delays initiating enteral nutrition due to provider concern for gastrointestinal complications of early postoperative enteral nutrition, such as necrotizing enterocolitis. Acute malnutrition that develops postoperatively further increases the risk of poor outcomes after surgical repair or palliation of congenital heart disease. Interstage monitoring programs for children with single ventricle physiology focus on screening for malnutrition and assessment of nutrition status, enteral nutrition interventions targeted to maintain normal growth, dietician care, and family engagement. Interstage monitoring programs are associated with improved malnutrition indices and with improved outcomes, including improved survival.

The preferred method of nutrition delivery for critically ill children is via *the enteral route*. Infants with cardiovascular disease and preexisting growth failure remain at high risk of further nutritional status deterioration during ICU hospitalization, however, and may also benefit from guideline-recommended early preoperative parenteral nutrition (PN) [1–25].

Expert consensus guidelines recommend early postoperative provision of PN for infants with single ventricle physiology because of their high nutritional risk, with enteral nutrition begun as soon as considered safe [17, 25]. Published recommendations for advancement of postoperative enteral feeds exist and emphasize close monitoring for feeding tolerance and for complications of enteral feeding [25]. There is little evidence to support the impact of early PN on patient outcome in cardiac patients, but most operative patients fail meet calorie goals via the enteral route during the first postoperative week due to multiple risk factors [10]. Large variation exists between centers with regard to postoperative enteral nutrition practices for children with cardiac disease, so further study of early initiation of enteral nutrition is necessary [26]. The advantages to early enteral feeding in the cardiac neonate include beneficial effects on gut motility, gut maturation, establishment of a normal microbiota, and on the development of normal immunity.

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Patient-specific conditions that necessitate PN include chronic diarrhea, inflammatory bowel disease, short gut syndrome, intestinal failure, neonatal necrotizing enterocolitis, chylothorax, persistent vomiting, surgical gastrointestinal conditions that have a prolonged postoperative recovery, and malabsorption syndromes. There are also signs of malnutrition that are independent of a disease process, which necessitate the commencement of PN. If a patient demonstrates inability to maintain normal weight gain, weight loss of more than 10%, a body weight that is less than 70% of ideal weight, inability to take enteral feeds for more than 5 days, and/or a serum albumin less than 3.5 g/dl, PN may be indicated. Certain patients may have special situations that warrant therapy with parenteral formulations specifically designed for trauma, hepatic failure, or renal failure.

PN is an important factor in ensuring that patients maintain appropriate macro- and micronutrient nutritional requirements when sufficient enteral nutrition cannot be safely delivered. PN should be used in a structured manner with an awareness of the risks and potential complications. It is imperative to estimate the total energy expenditure in order to accurately calculate the patient's caloric need prior to prescribing PN, to avoid both under- and over-nutrition [27]. This estimate allows the patient's baseline to be established, nutritional goals to be set, nutritional deficiencies to be noted, and changes in the patient's status to be monitored. Components of a nutritional assessment should include: clinical evaluation, dietician consult, anthropometric evaluation for age (weight, height, body mass index, mid-upper arm circumference, triceps skin fold thickness, and head circumference if under 2 years of age), and laboratory studies [28]. Serum albumin is measured to assess visceral protein status. Triglycerides and essential fatty acids are measured to assess lipid metabolism.

The benefits of PN must be carefully balanced with risks of infectious complications, such that enteral nutrition is optimized whenever possible to minimize reliance upon PN in the perioperative setting [29, 30]. As patients recover from surgery, PN is often continued and enteral nutrition is begun when determined to be safe, and advanced with close monitoring for feeding intolerance or gastrointestinal complications. In the setting of a functional gastrointestinal tract, patients are routinely discharged from the hospital on some type of enteral feeding by either the oral, nasogastric, nasoduodenal, or gastrostomy route [26, 31]. Implementation of cooperative quality improvement processes for inpatient and interstage phases of care improve patient nutritional status, and are associated with improved outcomes in high-risk patients [21, 22]. Essential elements of successful enteral nutrition programs include nutrition status screening, oral and enteral feeding readiness assessments, dietician assessments, and standardized approaches and indications for oral feeding, tube feeding, and gastrostomy [22]. Standardization of nutrition practices, rather than the route of enteral nutrition itself, is associated with improved outcomes, so enteral nutrition route is currently best determined by regional comfort and experience [31].

56.1 Elements of Parenteral Nutrition

The components of PN that comprise adequate nutrition include protein, carbohydrates, fat, vitamins, and minerals. The goal is to provide adequate calories to meet energy needs, sufficient protein to prevent loss of lean body mass, and electrolytes, vitamins, and minerals to fulfill the patient's daily requirements. Daily requirements for electrolytes, vitamins, and minerals may be altered in the perioperative care of these patients. Requirements for micronutrients are not well studied in children with congenital heart disease. General recommendations for initial calorie goals from PN are to reduce estimated enteral calorie needs by 10%, as the thermogenesis from enteral feeds does not occur with PN.

Protein provides the patient both essential and nonessential amino acids. The essential amino acids include leucine, isoleucine, valine, methionine, lysine, phenylalanine, tryptophan, threonine, and histadine. Tyrosine, cysteine, taurine, and glycine are considered essential for premature and newborn infants. There are special formulations, such as Trophamine®, available for this patient population. Calories derived from protein are usually not included in PN calculations because in children, the amino acids should be utilized for growth. Protein has a caloric density of 4 kcal/g. One gram of protein is equivalent to 0.16 g of nitrogen or 6.25 g of protein is equal to 1 g of nitrogen. To ensure maximum energy utilization of the supplied nonprotein calories, the calorie-to-nitrogen ratio should be at least 150 nonprotein calories per gram of nitrogen. The recommended daily amino acid intake depends on age. Premature infants require 3 g/kg/day of amino acids. Term infants need 2.5–3 g/kg/day, and children of 1–12 years need 1.5–2 g/kg/day. Protein requirements for children of more than 12 years range from 0.75 to 1.5 g/kg/day [32, 33].

Carbohydrates compose approximately 45–55% of the total caloric intake in a normal diet. Dextrose is the component that provides approximately 60–75% of the nonprotein calories in PN solutions. Dextrose monohydrate, as used in PN solutions, has a caloric density of 3.4 kcal/g. While providing additional calories through elevated dextrose content, close monitoring of glucose infusion rates (mg/kg/min) is important to prevent hyperglycemia. Usually, the rate may begin at 5–6 mg/kg/min with gradual increases by 2 mg/kg/min/day to reduce the risk of hyperglycemia. The maximum glucose infusion rate varies by age. Pre-term infants may tolerate an infusion rate up to 18 mg/kg/min, while a toddler should be limited to an infusion rate below 14 mg/kg/min. The glucose infusion rate in mg/kg/min may be calculated using the formula below:

$$\frac{\left[\text{Total volume of dextrose infusion} \times 0.01\right] \times \text{dextrose concentration} \times 1000}{\text{Child's weight}\left(\text{kg}\right) \times 1440\,\text{minutes}}$$

The maximum concentration of dextrose that may be infused through a peripheral line is 12.5%. Solutions with osmolarities greater than 900 mOsm/L may cause inflammation and sclerosis of peripheral veins. If infused peripherally, these solutions with dextrose concentrations greater than 12.5% are very irritating and will cause tissue damage, if extravasation occurs. Central venous catheters are typically used for administration due to this limitation of dextrose infusion concentrations in peripheral venous lines. These catheters may be temporary internal jugular, subclavian, right atrial or femoral vein catheters, tunneled Broviac or Hickman catheters, implantable ports, or peripherally inserted central catheters (PICC).

Fat is also a crucial element to nutritional support of the critically ill patient. Lipid emulsions provide additional calories and prevent essential fatty acid deficiency by providing fundamental fatty acids such as linoleic and linolenic acids. Approximately, 25–40% of calories are delivered as fat. Infants are started on with 0.5–1 g/kg/day of lipids and advanced to a maximum of 3 g/kg/day. A 20% lipid emulsion is typically utilized, as opposed to a 10% emulsion, due to its lower phospholipid to triglyceride ratio, which provides improved fat clearance [34]. Most lipid emulsions in current use are soy-based with egg yolk phospholipids. Currently, new sources of intravenous fat are being investigated in the United States, such as an omega-3-based solution, which in preliminary studies has shown to decrease cholestasis in patients on chronic PN. In addition, omega-3-rich lipid emulsions may have beneficial effects on immune function [35].

56.2 Risks and Complications

For many patients, PN is necessary for growth and healing. Clinicians must remember that there are risks associated with this method of nutritional support. Several risks exist with the placement of central venous catheters for PN infusions: the patient receives anesthesia for the line placement, and during placement of these catheters, subclavian artery or carotid artery puncture, hemothorax, pneumothorax, brachial plexus injury, or cardiac tamponade may occur [36, 37]. Subclavian vein thrombosis may occur at the tip of the catheter, the tip of the catheter may break, or the line may puncture through the lumen of the vessel, causing the contents to infuse into the pleural space or mediastinum. Despite sterile technique employed in the insertion, catheter-related sepsis is also a risk. The most common pathogens are *Staphylococcus epidermidis* and *Staphylococcus aureus*. PN dependence is also associated with increased risk for surgical site infections [30].

One of the major complications is parenteral nutrition-associated liver disease (PNALD). This broad term can be divided into cholestasis, steatosis, and gallbladder sludge or cholelithiasis. Cholestasis and gallbladder sludge are most common in infants and children. Premature infants may have an even worse outcome due to their still immature liver. Gallbladder sludge may be a result of decreased cholecystokinin (CCK) production from lack of enteral stimulation. Steatosis, due to increased fat synthesis, may be seen in pathologic examination of the liver. This is considered to be the result of the infusion of excessive carbohydrate calories, which exceed the patient's energy demand or expenditure and highlights the need for personalized energy prescriptions [38]. Due to these potential complications, close monitoring of liver function tests are required.

Other possible complications are nutritional deficiencies such as electrolyte imbalances, hypoglycemia, hyperglycemia, essential fatty acid deficiency, or vitamin and/or trace mineral deficiencies. Recent studies have demonstrated that excessive glucose infusions have been noted to increase carbon dioxide (CO_2) and therefore require increased ventilatory support [39, 40]. It is imperative to maintain a balance of dextrose and fat of approximately 60–75% of calories from carbohydrates and 25–40% of calories from fat. This is used to promote growth while preventing essential fatty acid deficiency.

The risk of these complications may be minimized with attention to the individual patient and their needs along with close monitoring. Due to the dynamic status of an intensive care patient, the measured resting energy expenditure or estimated total energy expenditure and required caloric demand must be reassessed daily. A daily nutritional assessment as described above, including clinical evaluation, anthropometric evaluation, and laboratory evaluation, must also be constantly reevaluated. Electrolytes should be monitored daily and as needed until stable. Liver functions tests such as aminotransferases, alkaline phosphatase, gamma glutamyl transpeptidase (gGTP), and conjugated and unconjugated serum bilirubin levels should be followed. Gallbladder sludge and cholelithiasis may be visible on ultrasound. If a patient is receiving PN for an extended period of time (typically defined as greater than 2–3 weeks) vitamin and trace mineral levels, such as selenium, carnitine, manganese, zinc, and copper levels should be obtained. Essential fatty acid panels and triene and tetraene ratios may also be drawn to detect essential fatty acid deficiency and ensure an adequate balance of nonprotein calories to fat.

56.2.1 Initiation of Enteral Feeds

Initiation of enteral feeds is based on the overall assessment of the patient. Patients should demonstrate hemodynamic stability with sufficient urine output and perfusion to suggest adequate splanchnic perfusion, and preferably be off or rapidly weaning from epinephrine and/or norepinephrine. Previous convention was to avoid enteral nutrition for patients on epinephrine or norepinephrine infusions, but data suggest that patients do not experience complications from enteral nutrition when on vasoactive infusions if perfusion is preserved [41]. An individualized approach with an assessment of overall perfusion may be a superior approach to assess readiness for enteral feeds [25]. Dopamine in doses less than 5 μg/kg/min does not affect blood flow to the GI tract, and thus feedings can be initiated while the patient is weaning off dopamine.

Preoperative enteral feeding in single ventricle patients remains controversial, with small studies reporting safe use of either ad libitum oral feeding or partial tube feeding [26, 42, 43]. There is large between center variability in practice for preoperative enteral feeding in single ventricle neonates [26, 42]. Factors reported to influence provider decisions to feed enterally include the presence of ductal-dependent cardiac lesion, treatment with PGE, adequacy of systemic cardiac output, lactic acidemia, and the presence of a umbilical artery catheter. Patients are closely monitored for feeding intolerance, and complications of enteral feeding (such as nectorizing enterocolitis).

On otherwise stable patients, oral or enteral feeds can be initiated within 24–48 h of admission to the cardiac ICU. Evidence does not support that presence of an umbilical artery or venous catheter precludes trophic enteral feeding and enteral feeding with umbilical lines in place is common practice in the neonatal intensive care unit, so these patients may be initiated on enteral nutrition [44]. Most awake patients will tolerate oral feeds, and while some infants may have oral aversion or poor oromotor coordination, they often have improvement of oromotor skills with regular speech therapy and a combination of infant directed PO and gavage (nasogastric) feeds. In infants incapable of tolerating oral feeds a nasogastric or nasoduodenal tube is easily placed blindly at the bedside or under fluoroscopic guidance. A combination of oral and nasogastric feeds, or nasogastric or nasoduodenal feeds alone is preferred to continued PN to meet calorie and protein goals in infants with a functional gastrointestinal tract. Consultation with a speech therapist is essential to successful oral feeding in these patients. In some infants with congenital heart lesions prior to surgical correction, the work of sucking and swallowing may exceed their respiratory and cardiac reserves, and they benefit from nasogastric or nasoduodenal feeding as well.

The Feeding Work Group of the National Pediatric Cardiology Quality Improvement Collaborative performed a literature review and assessment of best nutrition practices from 57 centers participating in the collaborative in order to provide nutritional recommendations and levels of evidence for those caring for infants with single ventricle physiology [25]. Their recommendations for postoperative feeding include an enteral nutrition advancement guideline and can be applied to patients with other cardiac physiology. Guideline recommendations include: nasogastric feeding with or without oral attempts begun at 20 mL/kg/day given every 3 h, and advanced to a total volume of 120–140 mL/kg/day. Breast milk is recommended as first line, followed by donor milk and then standard infant formula. Advancement is by 20 mL/kg/day, divided into the every 3 h bolus feeds. An alternative option is for initial continuous feeds at 1 mL/kg/h, advanced by 1 mL/kg/day every 4–6 h. Recommendations include increasing caloric density of formula once goal volume is achieved, if necessary to achieve goal calories. Feeding intolerance is monitored in the guideline as feeds are advanced, with feeds held from 1 to 4 h if feeding intolerance is present [25]. Intent is to achieve a goal of 20–30 g/day of weight gain. Oral nutrition is begun as 1–2 attempts per day and advanced according to patient tolerance and readiness for enteral feeding. Feeding tubes are removed once a patient is tolerating 50–75% of goal calories orally for 48 h. If patients fail to advance on oral feeds, evaluation for poor cardiac output, vocal cord injury, gastroesophageal reflux disease (GERD), delayed gastric emptying, malrotation, and pyloric stenosis are necessary. Speech therapy consultants assess patients for feeding mechanics, and need for change in formula consistency or type of bottle/nipple.

Gastrointestinal signs of feeding intolerance include abdominal distention, emesis, diarrhea, guaiac positive stool, and abdominal pain. Patients are monitored for signs and symptoms of necrotizing enterocolitis. In addition to these usual signs and symptoms of feeding intolerance in general ICU patients, patients with underlying cardiovascular dysfunction may manifest feeding intolerance as a symptom of insufficient cardiac output. They may also develop cardiopulmonary signs and symptoms as a result of feeding intolerance such as tachypnea, tachycardia, drop in NIRS or mixed venous O_2 saturation, or a new lactic acidosis. If a patient develops signs of feeding intolerance, reduction in the volume or caloric content of feedings may be required. Occasionally, patients cannot tolerate enteral nutrition at full volumes. In these cases, an attempt should be made to provide so-called "trophic" feeds at 2 ml/h or less; the provision of minimal enteral feeds is thought to prevent the breakdown of intestinal mucosa and bacterial translocation, despite being inadequate for full nutritional support [45]. Slow advancement toward goal feeds is usually possible but may require interentions to improve systemic cardiac output.

56.2.2 Estimation of Caloric Needs

Nutritional support for critically ill children ultimately aims to provide sufficient energy, and substrate to support healing and growth. To that end, energy requirements of children with congenital heart disease have been explored in multiple studies. However, a consistent picture of caloric requirements before corrective surgery, during the immediate postoperative period and during long-term recovery has yet to emerge, as most studies involve a small number of patients with a variety of cardiac lesions and preexisting conditions [46, 47]. Traditional process recommends increasing the predicted basal metabolic rate (Table 56.1; [48]) by a stress correction factor of 10–30%. However, several studies have demonstrated that in critically ill, mechanically ventilated children, the actual energy expenditure measured by indirect calorimetry is lower than that predicted by stress-related correction of the resting energy expenditure [49, 50]. Furthermore, immediately after surgical correction of a congenital heart lesion, the energy requirements are at or below the predicted resting energy expenditure in most children [51, 52], although metabolism shifts toward fat oxidation and gluconeogenesis [52]. Despite recognized trends or predictors of shifts in energy needs, energy requirements vary substantially between patients and in a single patient over time, and equations used to determine energy needs perform poorly when applied to an individual. Even patients with similar preoperative physiology vary widely in their caloric needs, and the physician exam and vital signs do not accurately identify patients as hypermetabolic or hypometabolic [27].

Repeated indirect calorimetry measurements to accurately determine energy needs during CICU hospitalization are recommended [24, 27]. Given the potential impact of adequate calorie delivery on patient outcome, the goal is to establish a targeted, personalized nutrition prescription that meets, but does not exceed, calorie needs. Indirect calorimetry presents challenges with regard to cost, availability, and needed expertise, in addition to inherent limitations of the technology. If indirect calorimetry is not available either the World Health Organization equations or the Schofield weight for height or weight equations can be used without a stress factor modification during ICU hospitalization [24]. Due to preexisting malnutrition or growth failure [51], catch-up nutrition may be beneficial perioperatively. Long-term goals should be established in consultation with a registered dietician with experience in children with cardiovascular disease. Caloric requirements and energy source utilization return to baseline within several days of corrective surgery in most children with an uncomplicated postoperative course and may be similar to infants without congenital heart disease [46, 51].

Once mechanical ventilation is discontinued, accurate prediction of caloric needs becomes less feasible, since muscle activity and work of breathing increase with spontaneous breathing. A realistic goal is to target caloric intake toward the predicted basal metabolic rate and then monitor subsequent weight gain. The World Health Organization publishes updated estimates of energy expenditure in infants, children, and adolescents (Table 56.1).

Table 56.1 World Health Organization: equations to predict energy expenditure

Infants birth–12 months
TEE (kcal/kg/day) = (−99.4 + 88.6 × W)/W
Children and adolescents
Boys: TEE (kcal/kg/day) = (310.2 + 63.3 × W − 0.263 × W2)/W
Girls: TEE (kcal/kg/day) = (263.4 + 65.3 × W − 0.454 × W2)/W

Adapted from Food and Agriculture Organization of the United Nations [48]
W weight in kilograms

56.2.3 Factors Complicating Enteral Feedings in Cardiac Patients

56.2.3.1 Gastroesophageal Reflux Disease (GERD)

GERD is quite common in cardiac ICU patients and may present a significant obstacle to initiation of enteral feeds. Although, all infants have gastroesophageal reflux (GER) to some extent, a number of clinical signs manifest the pathological nature of GERD in cardiac patients. Vomiting of oral or nasogastric (NG) feeds, occasionally associated with transient hypoxemia noted on pulse oximetry, represents a warning sign that reflux is significant enough to result in aspiration. Back or neck arching associated with feeds is another strong indicator of clinically significant GER. Arching is often severe enough to resemble opisthotonic-like posture. Less frequently, stridor and/or mild respiratory distress with retractions are observed when reflux occurs frequently enough to irritate the posterior pharynx and the upper airway.

Evaluation of GERD consists of a multistep approach and varies by institution. The simplest method relies on the therapeutic trial of anti-reflux medications described below. Resolution of symptoms within days to weeks justifies continued use of pharmacotherapy. The gold standard for diagnosis of GERD relies on continuous measurement of esophageal pH using a probe. Detection of acidic pH above the lower esophageal sphincter provides the diagnosis. This technique is rarely used since patients in the cardiac ICU often have indwelling esophageal atrial leads or NG/nasoduodenal (ND) tubes.

Radiologically, definitive diagnosis is made preferably with a nuclear medicine "milk" gastric scan using Technecium-99 labeled sulfur colloid added to regular milk-based formula. During the milk scan, radioactive contrast is instilled into the stomach via an NG tube, the tube is withdrawn, eliminating a potential artifact of a foreign body impairing the function of the lower esophageal sphincter, and the contrast is then imaged in cinematographic fashion over the course of 1–2 h. Data provided by the scan are frequency of regurgitation into the esophagus and the esophageal level reached by the regurgitated material. Additionally, the time constant for elimination of contrast from the stomach into the duodenum is obtained, which allows for independent evaluation of gastric motility. Normal motility results in elimination of approximately 50–60% of the contrast from the stomach within 1 h. Reduced motility has been associated with increased frequency and severity of GER in the pediatric population.

An upper GI series is another radiologic tool for evaluation of GER. During this study, a radio-opaque contrast is instilled into the stomach via an NG tube, the tube remains in place, and the contrast is then imaged using static radiographic images at 10–15 min intervals. Although often used to diagnose GERD, an upper GI series tends to be inferior to the milk scan in sensitivity and specificity. Available data suggest that almost everyone has some degree of reflux observed on upper GI, partly related to the presence of a foreign body passing through the lower esophageal sphincter. Additionally, since the images are obtained at a much lower frequency during an upper GI series than during the milk scan, the ability to detect infrequent reflux events and to assess their severity is quite limited.

Treatment of GERD relies primarily on inhibition of acid production in the stomach with an occasional added emphasis on enhancing gastric motility. Nonpharmacological interventions include elevation of head of the bed, maintaining the patient in an upright posture for 30 min after feeding, and smaller, more frequent feeds. Histamine receptor type-2 antagonists such as ranitidine or famotidine are inexpensive and readily available. Ranitidine can be used at doses as high as 3 mg/kg/dose orally 3 times daily whereas famotidine is usually dosed at 0.5 mg/kg/dose orally or intravenously every 12–24 h. Famotidine dosing requires adjustment when renal impairment is present.

Proton pump inhibitors (PPIs) such as pantoprazole, lansoprazole, or omeprazole generate profound acid suppression in the stomach. Pantoprazole is given intravenously at a dose of 0.5–1 mg/kg as a single daily dose. Lansoprazole is given orally at doses of 7.5, 15, and 30 mg for children weighing less than 10 kg, 10–30, and greater than 30 kg, respectively. Lansoprazole possesses an additional advantage for the pediatric population in that it is available as an orally disintegrating, pleasant-tasting tablet that may also be dissolved in water and administered through a feeding tube. Omeprazole is also available as an oral formulation; the dose is 10 mg daily for children weighing less than 20 kg, and 20 mg daily for children greater than 20 kg in weight.

Pro-motility agents such as metoclopramide and erythromycin ethylsuccinate have become second-line agents in the treatment of GERD. Metoclopramide is given intravenously or orally at a dose of 0.1–0.2 mg/kg/dose every 6 h. It is also occasionally used for several days to facilitate progress of a feeding tube from the stomach through the pylorus into the duodenum. Rarely, extrapyramidal side effects can occur within 24–48 h of administration of metoclopramide; unwanted cardiac complications include blood pressure instability, supraventricular tachycardia, and A-V dissociation. Neurologic side effects of metoclopramide have been well characterized. It should also be noted that metoclopramide has been implicated in bone marrow suppression, which is important in the setting of transplantation.

Erythromycin ethylsuccinate is effective at improving gastric motility in doses of 10 mg/kg/dose every 8 h. Oral administration route is strongly preferred as intravenous administration of erythromycin has been associated with fatal cardiac complications. Additionally, administration of erythromycin to neonates 0–2 weeks of age for greater than 14 days in duration increases the risk of hypertrophic pyloric stenosis ten-fold. Thus, H_2-receptor antagonists and PPI agents remain the mainstay of GERD treatment in children. If patients still have feeding intolerance suggestive of GERD, despite nonpharmacologic and pharmacologic treatments, nasojejunal feeds can be considered.

56.2.3.2 Chylothorax

Postoperative chylothorax occurs in approximately 0.5–5% of children after open heart surgery [53, 54] and is associated with prolonged ICU stay [55]. The majority of cases are related to surgical manipulation of the thoracic duct or intraoperative traumatic injury. Rarely, superior vena caval thrombosis or elevated SVC pressures underlie the etiology of chylous effusion. Symptomatically, patients are likely to become tachypneic and tachycardic with a corresponding free-flowing effusion on chest radiography or ultrasonography. If the child has been fed a diet containing long-chain fatty acids, the effusion will likely contain elevated triglyceride levels (>1.2 mMol/L). In children who have been fasting, the fluid may appear serosanguinous – the diagnosis is then made when feedings are initiated. Conservative treatment requires switching to enteral nutrition based on a formula enriched with medium-chain-triglyceride oils (e.g., Portagen®) [56]. Alternatively, a low-fat diet may be used if patient is taking food by mouth. Fat reduction of human

breastmilk and replacement with MCT's has been evaluated as a dietary treatment for breastfed infants with chylothorax in a small study but requires further investigation [57]. An effusion occupying greater than 20–30% of the hemithorax requires chest tube-mediated drainage. If chylothorax persists despite these measures for longer than 7–10 days, the treatment progresses to enteral rest and PN. These measures will lead to resolution of the chylous effusion in 80–90% of the cases [56]. The remaining 10–20% of patients with a chylothorax may require treatment with octreotide starting at 10 μg/kg/day as a continuous infusion or in divided doses and titrating up to 40 μg/kg/day [58, 59]. In remarkably recalcitrant cases, surgical interventions such as thoracic duct repair or ligation, pleurodesis, or pleuroperitoneal shunting may be necessary.

56.2.3.3 Laryngopharyngeal Dysfunction and Aspiration

Swallowing difficulties and airway abnormalities are quite common in children with heart disease and present a significant obstacle to successful oral feeds and timely discharge from the hospital. Incidence of swallowing dysfunction after cardiac surgery in children has been reported at about 4% [60]. However, the nature of the procedure significantly impacts the probability of postoperative swallowing dysfunction. For instance, incidence of laryngopharyngeal dysfunction after Norwood procedure can reach almost 50% [61]. Diagnosis of laryngopharyngeal dysfunction is made with a modified barium swallow or a salivogram, which shows abnormal passage of the food bolus through the oropharynx or frank aspiration of the material past the vocal cords. Bedside consultation by a trained speech pathologist is essential to evaluating the respiratory effort during feeding and oral-motor mechanics. Clinically, significant difficulty is evident when stridor, choking, coughing, and/or oxygen desaturation develop during oral feeding. Interventions may include positional change during feedings, modifications of the nipple/bottle, and limiting food textures to those that demonstrated no evidence of aspiration on the modified barium swallow [62]. In the most refractory cases, a gastrostomy tube may be required to provide adequate enteral nutrition.

The incidence of airway abnormalities in children with congenital heart disease is also approximately 3%, with laryngeal paralysis and subglottic stenosis comprising the majority of diagnoses [63]. Diagnosis requires direct laryngoscopy and bronchoscopy by an otolaryngologist familiar with pediatric airway problems. Most common presentation is intolerance of feeds or failure of extubation [64]. Surgical intervention may be required in up to 40% of children with a defined airway abnormality [63].

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Chapter 57
Hematological Aspects: Anticoagulation, Heparin-Induced Thrombocytopenia, and Plasma Exchange

Peter H. Shaw

Abstract Patients in the cardiac intensive care unit (CICU) are at risk for thromboses due to their cardiac anatomy or because of iatrogenic procedures (e.g., cardiac bypass; catheterization). There are several anticoagulants used in the care of pediatric cardiac patients, each with unique mechanisms of action, methods of monitoring, and most have antidotes for rapid correction of anticoagulation.

57.1 Anticoagulation

Cardiac ICU patients are at risk for thromboses due to their cardiac anatomy or because of iatrogenic procedures (e.g., cardiac bypass; catheterization). There are several anticoagulants used in the care of pediatric cardiac patients, each with unique mechanisms of action, methods of monitoring, and most have antidotes for rapid correction of anticoagulation.

57.1.1 Indications

All of the indications for anticoagulation are too extensive to include in this chapter. The most comprehensive evidence-based overview is in "Antithrombotic Therapy in Neonates and Children" from the ninth ACCP conference on antithrombotic and thrombolytic therapy from 2012 [1].

57.1.2 Medications and Monitoring

57.1.2.1 Heparin

Heparin is an anticoagulant, which works by binding to antithrombin III, amplifying 1000-fold its ability to inactivate clotting factors II, VII, IX, X, XI, and XII. It prevents new clots and the extension of existing clots while allowing the body's own clot lysis mechanisms to work. It is administered subcutaneously (SQ) or intravenously (IV). It has a biologic half-life ($T_{½}$) of approximately 1 h.

Heparin effect is monitored by the partial thromboplastin time (PTT).

If long-term anticoagulation is required, particularly in the outpatient setting, heparin is often used to commence anticoagulation therapy until the oral anticoagulant coumadin is therapeutic. An alternative to coumadin for long-term outpatient anticoagulation is low molecular weight heparin (LMWH).

Dosing and Monitoring

At the start of anticoagulation with heparin, the patient should be bolused with a dose of 75 units/kg IV over 10 min and then started on a continuous infusion at the following doses:

- Age ≤ 1 year: 28 units/kg/h
- Age > 1 year: 20 units/kg/h

Four hours after initiating heparin, check the first PTT. The goal is 60–85 s and should be adjusted as follows:

PTT (s)	Bolus (units/kg)	Hold (minutes)	Rate change (units/kg/h)	Repeat PTT (h)
<50	50	0	Increase 10%	4
50–59	0	0	Increase 10%	4
60–85	0	0	No change	24
86–95	0	0	Decrease 10%	4
96–120	0	30	Decrease 10%	4
>120	0	60	Decrease 15%	4

Adapted from Monagle et al. [2]
Once PTT is therapeutic, check a CBC, PT, and PTT daily

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Correction of Anticoagulation

If a patient is bleeding while on heparin and the PTT is supratherapeutic, the heparin should be stopped and *protamine sulfate* should be given immediately. Protamine neutralizes heparin within 5 min, but can cause hypotension, bronchoconstriction, and pulmonary hypertension from histamine release. Hypersensitivity reactions to protamine sulfate occur in patients with reactions to fish or those with previous exposure to protamine therapy or protamine-containing insulin. To minimize these side effects, it should be given very slowly, IV in doses *not to exceed 50 mg* in any 10-min period. Infusion rate of 10mg/ml solution should not exceed 5 mg/min. The dose is based on the amount of heparin administered within 2 h as follows:

Time since last heparin dose (minutes)	Protamine dose per 100 units heparin received (mg)
<30	1
30–60	0.5–0.75
60–120	0.375–0.5
>120	0.25–0.375

Adapted from Monagle et al. [2]
Obtain a PTT 15 min after protamine sulfate dose given

Side Effects

Short-term side effects of heparin include bleeding and heparin-induced thrombocytopenia (HIT). HIT will be discussed more extensively in the following section. Long-term side effects include alopecia and osteoporosis.

57.1.2.2 Low Molecular Weight Heparin

The pharmacokinetics of low molecular weight heparin (LMWH) is more predictable than unfractionated heparin. LMWH targets anti-factor Xa activity rather than anti-thrombin (IIa) activity, so the anti-Xa level is monitored instead of the PTT.

Correction of Anticoagulation

If a patient has bleeding complications while on LMWH, the drug should be promptly stopped. Protamine sulfate has not been shown to completely correct the anticoagulant effects of LMWH.

Side Effect

Short-term side effects include bleeding and HIT, although the rate of HIT is lower than with unfractionated heparin [3, 4]. HIT will be discussed more in the following section. Other side effects include mild local reactions, pain, and bruising at the injection site. Late side effects include alopecia and osteoporosis.

57.1.2.3 Vitamin K Antagonists (Coumadin, Warfarin)

Coumadin is an oral anticoagulant that inhibits the synthesis of active forms of the vitamin K-dependent clotting factors, II, VII, IX, and X, as well as regulatory factor proteins C, S, and Z.

Dosing and Monitoring

Coumadin loading dose on the first day of therapy is 0.2 mg/kg enterally as a single dose. If the patient has liver dysfunction, dosing would start at 0.1 mg/kg. Maximum dose can be 10 mg (5 mg for patients with liver disease).

Coumadin is monitored by the INR (international normalizing ratio). The goal in most instances is 2–3, but for patients with mechanical valves, the goal INR is 2.5–3.5.

Please follow the table below for loading doses and adjustments:

Correction of Anticoagulation

The main antidote for coumadin is vitamin K, but fresh frozen plasma (FFP) is also used. Here are the guidelines:

Patient Is Not Bleeding

If the patient is restarted on coumadin in the near future, treat with phytonadione (vitamin K1) at a dose of 0.5–2 mg IV or SQ. If the patient is not restarted on coumadin in the near future, treat with phytonadione (vitamin K1) at a dose of 2–5 mg IV or SQ.

Patient Has Bleeding That Is Not Life-Threatening

Treat with phytonadione (vitamin K1) at a dose of 0.5–2 mg SQ or IV and give FFP at 20 ml/kg IV.

Patient Has Bleeding That Is Life-Threatening

Treat with phytonadione (vitamin K1) at a dose of 5 mg IV over 10–20 min and give FFP at 50 ml/kg IV.

Elective Reversal of Coumadin

If the INR is less than 1.5, no reversal is needed for most surgery. For neurosurgery, it is ideal for the INR to be 1.

When there is a *high risk* of thrombosis:

- Hold coumadin 3 days before surgery.
- Twenty-four hours before surgery, initiate heparin therapy as an infusion without a bolus.
- Stop IV heparin 6 h before surgery and check PTT 3 h before surgery—it should be normal.
- If INR remains >1.5, 12 h before surgery, give 0.5 mg of phytonadione (vitamin K1) SQ and recheck INR 6 h later.
- Once cleared by surgeons, heparin IV is restarted at the earliest of 8 h postoperatively at the previous rate. Once therapeutic for 24 h, restart oral coumadin. Once INR is therapeutic stop heparin.

When there is a *low risk* of thrombosis:

- Hold coumadin 3 days before surgery.
- Check INR the day before surgery. If INR is more than 1.5, give 0.5 mg of phytonadione (vitamin K1) SQ and recheck INR 6 h later.
- Once cleared by surgeons, restart oral coumadin if patient can take enterally medications on post-op day one.

Guidelines adapted from Monagle et al. [2].

Side Effects

Short-term side effects of coumadin include bleeding and necrosis. Bleeding can manifest as hemoptysis, excessive bruising, bleeding from mucosal surfaces, or hematuria or hematochezia. The risk of bleeding is greater if the INR is supratherapeutic.

A rare complication of coumadin is necrosis, which can occur shortly after starting therapy in patients with protein C deficiency and is clinically identical to purpura fulminans. This risk is decreased if the patient is therapeutic on heparin. Osteoporosis is a risk of long-term coumadin use.

Drug Interactions

In addition to oral vitamin K intake, there are many drugs that affect the metabolism of coumadin and can adversely affect the INR (please consult your hospital's formulary or pediatric dosing references). It is important to review all medications a patient is taking concurrently with coumadin, as stopping or starting medications can affect the INR.

57.1.2.4 Direct Thrombin Inhibitors

The use of direct thrombin inhibitors (DTIs) is now used almost exclusively in the management of HIT in children.

The most commonly used one is *argatroban*.

Conversion to an Oral Anticoagulant

Coumadin (warfarin) may be introduced when platelet count starts increasing, but DTI should be continued until platelet count normalizes. After 4–5 days of coumadin, if platelet count is normal and PT is therapeutic, stop DTI for a few hours and recheck INR. If it is between 2 and 3, it is safe to discontinue DTI.

Correction of Anticoagulation

There is no antidote or reversal agent for argatroban. Half-life of argatroban is short at 39–51 min

Side Effects

The most common side effect of DTIs is bleeding.

57.2 Heparin-Induced Thrombocytopenia

57.2.1 Description and Pathophysiology

Heparin-induced thromocytopenia (HIT) occurs when autoantibodies form against platelet factor 4 (PF4), neutrophil-activating peptide 2 (NAP-2), and interleukin 8 (IL-8). This causes platelet aggregation and consumption of coagulation factors which can lead to both thrombosis and bleeding.

HIT can occur shortly after heparin is given (even in IV fluids) but usually occurs 5–15 days after the initiation of heparin. It is important to substitute for heparin when HIT is suspected or confirmed. Even when HIT's only manifestation is thrombocytopenia and heparin is stopped, risk of thrombosis in subsequent 30 days approaches 50% unless alternative anticoagulant is used.

57.2.2 Diagnosis

HIT can be diagnosed by the detection of the PF4 antiplatelet antibody in the patient's blood by one of two assays: washed platelet activation assays and commercial enzyme immunoassays (EIAs).

A negative test generally rules out HIT. However, because weak antibodies can also be detected (especially by EIA), a positive test does not necessarily confirm HIT. There may be false-positive results and low diagnostic specificity, because HIT antibodies can be detected by EIA in about 50% of patients 1 week after cardiac surgery.

57.2.3 Management

If there is no risk for thrombosis, discontinue heparin and the platelet count is normalized. If there is risk for thrombosis or a thrombosis is being treated, follow guidelines above for using DTIs.

57.3 Antifibrinolysis

57.3.1 Aminocaproic Acid

Extracorporeal membrane oxygenation (ECMO) as part of cardiopulmonary bypass is associated with potentially catastrophic bleeding complications because of the aggressive anticogaultion that is required to keep the circuits open and the fibrinolysis that can occur. When aminocaprioc acid, an antifibrinolytic, is used prophylactically for patients on ECMO/cardiopulmonary bypass, it has been found to decrease the overall bleeding, transfusion requirements, intracranial hemorrhage in atrisk neonates [5, 6] and surgical site bleeding [7].

57.3.1.1 Dosing and Monitoring

- *Children*: loading dose of 100–200 mg/kg IV, followed by 100 mg/kg/dose every 6 h or by a continuous infusion of 30 mg/kg/h (maximum 30 g/day)
- *Adults*: 4–5 g IV over the first hour followed by a continuous infusion of 1–1.25 g/h for 8 h or until bleeding ceases.

  Dose should be reduced to 25% in case of renal failure.

57.3.1.2 Side Effects

Side effects include hypotension, bradycardia, arrhythmia, headache, seizures, rash, hyperkalemia, nausea, vomiting, decreased platelet function, agranulocytosis, leukopenia, myopathy, acute rhabdomyolysis, glaucoma, deafness, renal failure, dyspnea, and pulmonary embolism. It is contraindicated in hypersensitivity to the drug, disseminated intravascular coagulation, and ongoing intravascular clotting process.

57.3.2 Aprotinin

Aprotinin and tranexemic acid are used to prevent hemorrhage after cardiopulmonary bypass interventions and liver transplantation. They are also widely used throughout the world for post-CPBP patients, particularly in the case of reoperation and in neonates and in those with preexisting coagulopathies. In the USA in 2008, aprotinin was removed from the market based on a number of reports regarding adverse effects in the adult population. It is currently available in some countries on compassionate use basis. Studies have compared its efficacy and safety to that of tranexemic acid and the latter drug was found it to be effective [7–10].

57.3.2.1 Dosing and Monitoring

- *Infants and children*: Test dose of 0.1 mg/kg IV (maximum 1.4 mg); *body surface less than 1.16 m*^{2}: loading dose of 240 mg/m^2 IV, 240 mg/m^2 into the pump priming, then 50 mg/m^2/h as a continuous infusion IV during the surgery; *body surface greater than 1.16 m*^{2}: loading dose of 280 mg/m^2 IV, 280 mg/m^2 into the pump priming, then 70 mg/m^2/h as a continuous infusion IV during the surgery.
- *Adults*: Test dose of 1 ml (1.4 mg) IV, followed by a loading dose of two million KIU (280 mg) IV, two million KIU (280 mg) into the pump priming, and 2,50,000 KIU/h (35 mg/h) continuous infusion IV during the surgery.

In Europe and in Australia, aprotinin is also used in the postoperative period at 1000–4000 KIU/kg/h IV.

57.3.2.2 Side Effects

Side effects include anaphylaxis, arrhythmia, heart failure, myocardial infarct, cerebrovascular events, chest pain, hypotension, pericardial effusion, pulmonary hypertension, fever, seizures, dizziness, hyperglycemia, hypokalemia, acidosis, nausea, vomiting, constipation, diarrhea, gastrointestinal hemorrhage, hemolysis, anemia, thrombosis, liver insult, phlebitis, arthralgia, renal failure, bronchoconstriction, pulmonary edema, and apnea. It is contraindicated in hypersensitivity to the drug and previous exposure within a 12-month period.

57.3.3 Tranexamic Acid

This drug is used off-label after CPBP as a prophylaxis against hemorrhage and to reduce postoperative bleeding.

57.3.3.1 Dosing and Monitoring

Loading dose is 100 mg/kg diluted in 20 ml of 0.9% NaCl over 15 min, followed by a continuous infusion of 10 mg/kg/h IV.

57.3.3.2 Side Effects

Side effects include nausea, diarrhea, vomiting, hypotension, and thrombosis. It is contraindicated in hypersensitivity to the drug, subarachnoid hemorrhage, or active intravascular clotting process.

57.4 Fibrinolytics

57.4.1 r-TPA

r-TPA (Alteplase®) may be used in case of acute ischemic stroke, pulmonary embolism, acute myocardial ischemia or infarct, and systemic thrombosis and also used to treat occluded central venous or arterial indwelling catheters.

57.4.1.1 Dosing and Monitoring

- *Systemic thrombosis*: 0.1 mg/kg/h IV for 6 h; monitor bleeding and fibrinogen levels (keep above 100 mg/dl). If persistent thrombosis, increase dose by 0.1 mg/kg/h every 6 h to a maximum of 0.5 mg/kg/h.
- *Venous thrombosis*: 0.06 mg/kg/h in neonates and 0.03 mg/kg/h in older children, IV.
- *Central venous catheters*: instill 110% of the internal lumen volume into the occluded catheter and let it dwell for 30 min. Recommended concentration is 1 mg/ml, maximum 2 mg in 2 ml in patients between 10 and 30 kg, and 2 mg in 2 ml in patients above 30 kg. If the catheter is functional, aspirate 5 ml of blood out to remove the residual drug and clot, and then flush with normal saline. If the catheter remains occluded, let it dwell for a total of 2 h and repeat the above. If it remains occluded, a second dose can be administered.

57.4.1.2 Side Effects

Side effects include gastrointestinal or genitourinary hemorrhage, ecchymosis, nausea, vomiting, fever, retroperitoneal hemorrhage, gingival hemorrhage, epistaxis, intracranial hemorrhage, hemopericardium, and arrhythmias (reperfusion). It is contraindicated in hypersensitivity to the drug, active internal bleeding, cerebrovascular hemorrhagic event, intracranial neoplasm, aortic dissection, arteriovenous malformation or aneurysm, bleeding diathesis, severe hepatic or renal disease, hemostatic defects, and severe uncontrolled hypertension.

57.5 Plasma Exchange

Plasma exchange (also known as plasmapheresis) is the removal, treatment, and return of plasma into a patient's circulation. During plasmapheresis, blood is taken out of the body through a needle or catheter. The plasma is then removed from the blood by a cell separator. This can be accomplished in any one of the following three ways:

- *Discontinuous flow centrifugation* – One venous catheter line is required. Typically, a 300-ml aliquot of blood is removed at a time and centrifuged to separate plasma from blood cells. The blood cells are returned to patient while the plasma is treated.
- *Continuous flow centrifugation* – Two venous lines are used. This method requires less blood volume to be out of the body at any one time as it is able to continuously spin out plasma.
- *Plasma filtration* – Two venous lines are used. The plasma is filtered using a standard hemodialysis equipment. This continuous process requires less than 100 ml of blood to be outside the body at one time.

In plasma exchange, the removed plasma is discarded and the patient receives replaced donor plasma. Heparin is used to prevent the line and circuit from thrombosing.

57.5.1 Indications

Plasma exchange may be used in the cardiac ICU setting if the patient develops a coagulopathy, such as DIC (disseminated intravascular coagulation) or autoimmune hemolytic anemia (either IgM or IgG-mediated). In ABO-incompatible solid organ transplantation, the recipient may develop IgM antibodies against the donor ABO blood type. Plasma exchange can be used to remove these isohemagglutinins.

57.5.2 Utilization and Monitoring

Plasma exchange works by both removing pro-coagulant and hemorrhagic factors as well as antibodies from the blood and replacing the patient's clotting factors with FFP. This blood product contains clotting factors II, V, VII, VIII, IX, X, XI, and XIII. It also contains fibrinogen and von Willebrand factor. Cryoprecipitate contains higher concentrations of the latter two factors and may be used to supplement FFP.

57.5.2.1 Monitoring

The PTT as well as fibrinogen need to be monitored at least twice per day while the patient is undergoing plasma exchange. The heparin should be adjusted to keep the PTT between 60 and 85 s. The fibrinogen level should ideally be kept above 150 to minimize the risk of bleeding. Cryoprecipitate (1 bag per 10 kg of body weight) can be used to replace fibrinogen.

57.5.2.2 Side Effects

While the patient is undergoing plasma exchange, there is the risk of both bleeding and clotting. Careful monitoring as stated above can minimize these risks. There may also be hypotension from fluid shifts, so the rate of fluid exchange has to be monitored closely.

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Chapter 58
Acute Kidney Injury and Renal Replacement Therapy

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Abstract Acute kidney injury (AKI) is a common complication of children with heart disease in the intensive care unit. Patients with AKI are at an increased risk for morbidity and mortality independent of severity of illness. Given that there is currently no direct pharmacologic intervention for the treatment of AKI, prevention and minimizing further renal injury is crucial. General medical measures in the management of AKI include:

(a) Avoidance of nephrotoxic medications
(b) Diuretic use
(c) Renal Replacement Therapy

The following chapter will review the diagnostic and management considerations of the pediatric cardiac patient with AKI. The use of renal replacement therapy including modalities such as continuous renal replacement therapy (CRRT), peritoneal dialysis, sustained low-efficiency dialysis, as well as newer options for CRRT in smaller patients will be discussed.

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58.1 Acute Kidney Injury

58.1.1 Definition and Epidemiology

Small increases in serum creatinine of 0.3 mg/dl have been shown to be a risk factor for an increase for morbidity and mortality in both pediatric and adult hospitalized patients [1, 2]. AKI occurs in 30–60% of children after cardiac surgery [3]. The Kidney Disease Improving Global Outcomes (KDIGO) classification for AKI was introduced in 2012 (Table 58.1) [4]. The KDIGO criteria for AKI differ mainly from the previously proposed pediatric Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (pRIFLE) criteria in that the degree of creatinine change is used as a diagnostic tool and a pediatric-specific statement defining Stage 3 is included. The KDIGO has been validated in the pediatric critical care population [5, 6].

58.1.2 Etiology

Often times the etiology of AKI in patients in pediatric cardiac intensive care patients is multifactorial. Factors shown to be associated with an increased risk of AKI in

Table 58.1 The Kidney Disease Improving Global Outcomes (KDIGO) classification for AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline or ≥ 0.3 mg/dl increase	<0.5 ml/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	three times baseline or increase in serum creatinine to ≥ 4 mg/dl or initiation of renal replacement therapy or in patients <18 years of age a decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥24 h or anuria for ≥12 h

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children undergoing operative repair of congenital heart disease include young age, a Risk Adjustment in Congenital Heart Surgery (RACHS-1) category ≥ 4, longer cardiopulmonary bypass time, nephrotoxic medication exposure, low body weight, previous cardiac surgical procedures, and univentricular anatomy [7, 8]. Additionally, renal vasoconstriction secondary to low cardiac output syndrome is a known contributor to AKI in the pediatric cardiac population. Fluid overload and resulting renal congestion have been implicated in AKI in multiple intensive care unit (ICU) patient groups, including patients after cardiac surgery [9].

58.1.3 Clinical Manifestations

Laboratory parameters can be useful in the evaluation of patients with AKI. Obtaining a urinalysis to evaluate for leukocytes, nitrites, and a urine culture can be used to evaluate for infection. Urine microscopy may reveal muddy brown or granular casts in patients with acute tubular necrosis. Obtaining urine chemistries, specifically urine sodium, creatinine, and urea, can be helpful in distinguishing prerenal from intrinsic causes of AKI. Generally, patients with a low fractional excretion of sodium (<1%) and of urea (<35%) are thought to have a prerenal etiology for AKI. Monitoring closely for electrolyte abnormities including hyponatremia and hyperkalemia should be done. If not already completed, a renal ultrasound should routinely be done in children with cardiac disease and an elevated serum creatinine in order to evaluate for any genitourinary abnormalities.

58.2 Nephrotoxic Medications

Medication-associated AKI is recognized as a common etiology for AKI in the pediatric cardiac population. In particular, the use of ibuprofen and indomethacin in the management of a patent ductus arteriosus has been implicated in the development of AKI. Additionally, exposure to radiocontrast agents, antibiotics, antifungals, and antivirals can lead to the development of AKI. Angiotensin-converting enzyme (ACE) inhibitors are commonly used in the postoperative pediatric cardiac surgery population and have been associated with AKI [10]. Nephrotoxicity may oftentimes be synergistic, given the frequent use of multiple coinciding nephrotoxic medications in the pediatric cardiac population [11].

58.3 Fluid Overload and Diuretic Use

The prevention and treatment of fluid overload can be challenging in children with heart disease. The negative consequences of fluid overload have been demonstrated in the pediatric critical care population [12]. The expansion of the interstitial space and increase venous pressure can lead to tissue edema and organ dysfunction. In intensive care patients, the development of intra-abdominal hypertension, typically defined as a sustained intra-abdominal pressure ≥ 12 mmHg, has been shown to be an independent predictor of morbidity and mortality [13]. Thabet et al. conducted a multivariate analysis of risk factors for death in general pediatric ICU patients admitted over 24 h and requiring a bladder catheterization [14]. Intra-abdominal hypertension was found to be an independent risk factor for ICU morality. Fluid congestion and elevated venous pressures can result in decreased renal blood flow and glomerular filtration rate (GFR) [15]. Numerous investigations have shown a significant association of fluid overload and AKI [16]. Also of concern is that fluid overload can lead to falsely low creatinine values and, therefore, missed diagnoses of AKI. Studies in both critically ill adults and children have demonstrated that the dilution of serum creatinine by fluid accumulation may result in an underestimation of the severity of AKI [17, 18]. Therefore, it is important to evaluate patients for fluid overload. A formula commonly used to assess fluid status by percent fluid overload is: fluid input (liters) − fluid output (liters)/weight (kg) × 100 [19].

Loop diuretics, notably furosemide, are the most potent diuretics used for fluid removal. When using loop diuretics, it is important to monitor for hypocalcemia, hypokalemia, and hypomagnesemia. Continuous infusions of furosemide can be used to achieve a more predicable increase in urine output and less hemodynamic instability [20]. Coadministration of thiazide diuretics may increase the efficacy of loop diuretics.

58.4 Renal Replacement Therapy

Given that medical interventions such as fluid restriction and diuretic use are oftentimes ineffective in preventing and treating renal replacement therapy, the use of renal replacement therapy is becoming increasingly more common in pediatric cardiac intensive care patients. The types of renal replacement therapy used in the care of pediatric cardiac intensive care patients include continuous renal replacement therapy (CRRT), peritoneal dialysis (PD), acute intermittent hemodialysis, and sustained low-efficiency dialysis (SLED).

58.5 Continuous Renal Replacement Therapy

58.5.1 Background

CRRT when used early and intensively in the course of renal failure, it has the potential to substantially aid in the care of patients with severe AKI. Hemofiltration was first described in the late 1970s as a means of removing extracellular fluid from patients with edema refractory to diuretics [21]. Continuous hemofiltration, combined with the administration of an appropriate fluid, is now recognized as a form of renal replacement therapy in AKI.

58.5.2 Basic Principles of CRRT

Table 58.2 includes the common terms and definitions used when referring to CRRT. Hemofiltration and hemodialysis are similar in a few aspects. Both techniques require access to the circulation so that blood can pass through an extracorporeal circuit that includes either a dialyzer or a hemofilter. The mechanism by which the composition of the blood is modified differs between the two.

Table 58.2 Terms and definitions

Dialysis	The separation of electrolytes and low molecular weight solutes from the blood across a semipermeable membrane
Clearance	The ability of a filter to remove metabolic waste products from the blood. Occurs by diffusion, filtration, and convection
Diffusion	Passive movement of solutes through a semipermeable membrane from an area of higher to lower concentration
Ultrafiltration (convective transport)	The movement of water along with small solute across a semipermeable membrane
Osmotic ultrafiltration	Passive movement of water from an area of lower concentration (blood) to an area of higher concentration (dialysate fluid). The common osmotic agent used is dextrose. The greater the difference in concentration between the two "compartments" the greater the fluid removal. Plasma proteins increase the plasma oncotic pressure and oppose fluid removal from osmotic ultrafiltration
Hydrostatic ultrafiltration	The movement of water along with small solutes from the blood to the dialysate, via a hydrostatic pressure gradient between the two compartments
Hemofiltration fluid	Sometimes referred to as "dialysate" or "bath"
Effluent	Fluid collected from the hemofilter that includes dialysate and fluid removed from the patient
Predilution fluid	Replacement fluid that enters the circuit before the filter
Postdilution fluid	Replacement fluid that enters the circuit after the filter
Countercurrent flow	Hemofiltration fluid flows through the filter in the opposite direction as the blood. This provides increased clearance

During *dialysis*, blood flows along one side of a semipermeable membrane as a crystalloid solution is pumped along the other side of the membrane to the blood flow. Through the process of diffusion, molecules cross the membrane where the dialysis fluid is designed to produce as near normalization of the plasma as possible. This is affected by having the sodium concentration of the dialysis fluid physiologic, whereas the potassium concentration is variable and can be less than that of normal plasma to establish a gradient from the plasma to the fluid that promotes the removal of potassium ions from the patient's blood. Urea, creatinine, and phosphate substances that are to be removed completely are not found in the dialysis fluid. The removal of salt and water is accomplished by the creation of a transmembrane pressure gradient; the pressure being lower in the dialysis fluid compartment. In accordance with the laws of diffusion, the larger the molecule the slower is its rate of movement across the membrane. Urea, a small molecule, is cleared efficiently, whereas creatinine and phosphorus are larger molecules that are cleared less well (Fig. 58.1).

In contrast to dialysis, *hemofiltration* works by having blood under pressure pass down one side of a highly permeable membrane, which allows both water and substances of high molecular weight to pass across the membrane by convective flow (passive movement of solute across a membrane along with water). This is what occurs in glomerular filtration. In contrast to hemodialysis, hemofiltration allows large molecules such as urea, creatinine, and phosphate to clear at similar rates (Fig. 58.2). Profound hypophosphatemia can easily develop unless the patient's phosphate intake is supplemented or replaced via IV fluids. Larger molecules such as heparin, insulin, myoglobin, and vancomycin, cleared in only negligible amounts during dialysis, are cleared more efficiently by hemofiltration.

Current technology cannot reproduce the complex function of the kidney where glomerular filtration is selectively reabsorbed by the renal tubules. During hemofiltration, the filtrate is discarded and the patient receives replacement fluid. This replacement fluid is a solution where the major crystalloid components of the plasma are at physiologic levels, yet phosphate is not in the replacement fluid. Fluid balance for the patient is determined by adjusting the rates of hemofiltration production and the replacement fluid. For example, if there is no need for the removal of fluid from the patient, the rate at which the replacement fluid is given is matched exactly with the rate of production of hemofiltrate minus any continuous fluids that the patient is receiving. Generally, fluid removal is desired as patients with renal failure have total body fluid overload or the clinical need to

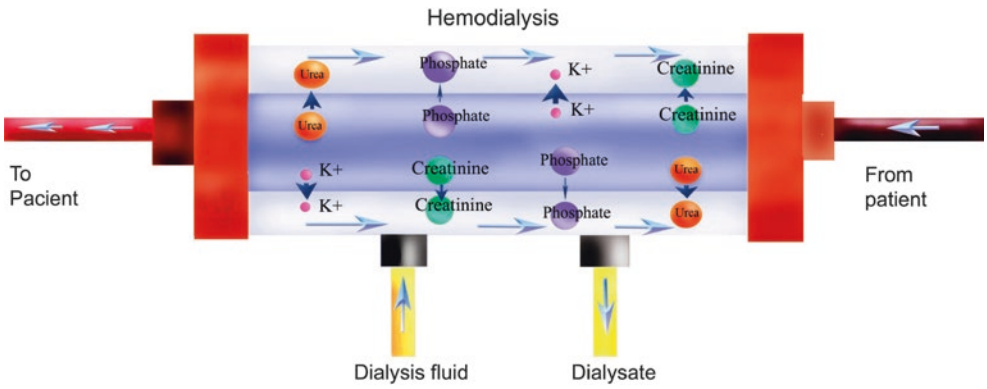

Fig. 58.1 Hemodialysis. The arrows that cross the membrane indicate the direction of movement of each solute through the membrane. The relative size of the arrows indicates the net amounts of the solute transferred. Other arrows indicate the direction of flow

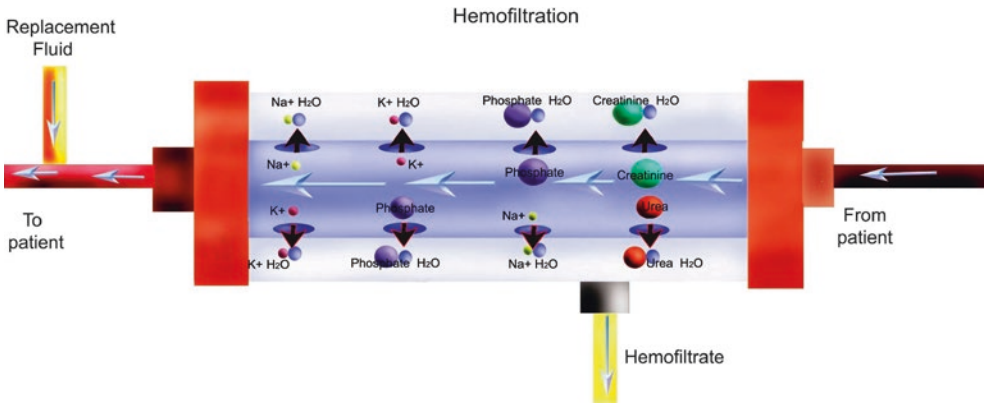

Fig. 58.2 Hemofiltration. The arrows that cross the membrane indicate the direction of movement of each solute through the membrane. The relative size of the arrows indicates the net amounts of the solute transferred. Other arrows indicate the direction of flow

administer fluids to a patient with oliguria. This is accomplished by replacing less fluid through the infusion of replacement fluid than is removed by hemofiltration.

Hemofiltration leads to an increase in the concentration of red cells and plasma protein in the blood. This increases the viscosity of the blood and induces a high colloid oncotic pressure at the distal end of the hemofilter. Therefore, *the filtration rate should be no more than 30% of the blood flow rate*. The continuous nature of hemofiltration is the most important contribution to the treatment of patients with AKI in intensive care units, where most have multisystem organ dysfunction. The majority of these patients has a negative nitrogen balance and are in dire need of appropriate nutrition. This task becomes difficult when fluid restriction is necessary in the treatment of respiratory distress syndrome and renal failure. CRRT allows for both appropriate fluid removal and supplying the much needed nutrition.

58.5.2.1 Continuous Venovenous Hemofiltration with Dialysis (CVVHD)

This configuration adds dialysis to the CVVH system whereby both convective and diffusive clearance are achieved. Higher clearance rates of small solutes are achieved at any given blood flow by this modification. Acute hyperkalemia or hyperammonemia is one important indication for this configuration where additional clearance might be needed immediately at the inception of CRRT. This configuration can also be referred to as continuous venovenous hemodialysis with filtration.

58.5.2.2 Slow Continuous Ultrafiltration (SCUF)

This configuration is similar to CVVH except that there is no use of hemofiltration replacement fluid. Fluid removal is by hydrostatic ultrafiltration. *The fluid removal rate should not exceed 30% of the blood flow rate*. This configuration is selected when the only goal is to remove excess body fluid.

58.5.3 Indications for CRRT

1. Patients who meet the criteria for hemodialysis or PD are hemodynamically deranged or have experienced abdominal trauma or surgery.
2. Patients with oliguric or anuric renal failure frequently require administration of intravascular volume expanders such as salt poor albumin, packed red blood cells, fresh frozen plasma, and medications.

3. Patients with oliguric or anuric renal failure can be improved of their nutritional status by increasing fluid administration of total parenteral nutrition (TPN), intralipids, or nasogastric (NG) feedings.
4. Patients with oliguric or anuric renal failure also have hepatic failure. CVVH may remove various toxins and small molecules. It has been well documented that CVVH may improve overall survival of these patients.
5. Metabolic derangements where the production of noxious metabolic products is continuous. Hemodialysis is frequently insufficient in such cases because of its intermittent nature, for example, hyperammonemia and hyperkalemia.
6. In certain cases of drug intoxication, the filters used for CVVH have larger pores than conventional hemodialysis filters; thus drug removal may be enhanced. The continuous nature of CVVH and the high rate of daily ultrafiltration that is obtained make this therapy very useful.
7. Removal of fluid in volume overloaded patients who are resistant to diuretic therapy or with AKI.

58.5.4 Contraindications

There are no absolute contraindications for the use of CVVH except for life-threatening bleeding, if one only uses systemic heparinization in the management of CVVH. The use of the citrate anticoagulation protocol is considered in this situation. In addition, one should not initiate renal replacement therapy while the patient is hypotensive. This can be ameliorated by ensuring adequate intravascular volume, a normal ionized serum calcium level, and the use of vasopressor agents.

58.5.5 Nutrition and CRRT

Hemofiltration prescriptions will result in significant amino acid depletion across the hemofilter membrane. In the nondialytic setting of AKI, the standard recommendation for protein requirements is in the range of 1.5 g/kg/day. In patients on hemofiltration, protein administration may be in the range of 3–4 g/kg/day to maintain positive nitrogen balance. Since dialysate solutions are deficient in phosphorus unless added by pharmacy, hypophosphatemia will occur, requiring that additional phosphorus be added to TPN. There is also loss of glutamine, an amino acid needed for protein production, regulation of signaling, trafficking of proteins, and sustaining immune function. It is essential to provide glutamine supplementation to all critically ill patients, and in particular, those who sustain losses through hemofiltration.

As mentioned earlier, the use of CRRT adds the benefit of optimizing nutrition during critical illness, since one has to be less concerned with restricting fluid intake. Fluid balance is now more easily controlled.

58.5.6 Vascular Access for CRRT

Vascular access for CRRT is decided upon by the size of the patient, the decision for what blood flows are needed, and the type of anticoagulation. Blood flow rates (BFR) through the hemofilter need to be maintained in the range of 3–5 mL/kg/min. This will translate into blood flows of 10–70 mL/min in patients <15 kg, 50–100 mL/min in patients 15–30 kg and 100–250 mL/min in patients >30 kg. Dialysate or replacement fluid becomes saturated with solute at the prescribed rate of 2 L/h/1.73 m^2. Therefore, higher BFRs have little effect upon solute clearance, and efforts to increase BFR increase the resistance in the circuit. Triple lumen access is helpful in patients where sites are limited and in those were citrate anticoagulation is being used, since a calcium infusion is needed to prevent hypocalcemia as a result of the chelating properties from citrate. Table 58.3 gives the suggested catheter sizes and sites of insertion for patient weight.

58.5.7 Machinery for CRRT

Industry-sponsored machinery (PRISMAFLEX, Gambro, Lakewood, CO; BM-25, Baxter, Deerfield, IL; NxStage

Table 58.3 Suggested catheter type and size for hemofiltration

Patient size	Catheter size (product name)	Insertion site
Neonate	Single lumen 5.0 Fr (COOK) (need two catheters)	Femoral artery or vein
	Dual lumen 7.0 Fr (COOK, MEDCOMP)	
	Check flow introducer sheath 4.0 Fr (COOK)	Internal jugular, subclavian, or femoral vein
3–6 kg	Dual lumen 7.0 Fr (COOK, MEDCOMP)	
	Triple lumen 7.0 Fr (MEDCOMP, ARROW)	Internal jugular, subclavian, or femoral vein
6–15 kg	Dual lumen 7Fr, 8.0 Fr (KENDALL, ARROW, VAS–CATH)	Internal jugular, subclavian, or femoral vein
15–30 kg	Dual lumen 8.0Fr, 9.0 Fr (MEDCOMP, VAS–CATH)	Internal jugular, subclavian, or femoral vein
>30 kg	Dual lumen 10.0, 11.5 Fr, 12 Fr (ARROW, KENDALL, VAS–CATH)	Internal jugular, subclavian, or femoral vein

System, NxStage Medical, Lawrence, MA; B. Braun Diapact, Bethlehem, PA) offers a variety of BFRs, warming systems, accurate ultrafiltration controllers, venous and arterial pressure monitor, and blood leak detectors. These systems allow for local prescriptions of hemofiltration including CVVH and CVVHD.

One could use adaptive machinery that includes a blood pump segment with an air leak detector. Unfortunately, adaptive machinery does not include the ability to regulate ultrafiltration and thermic controls and increases nursing time and overall expense of performing CRRT.

58.5.8 Membranes

The choice of a hemofilter membrane for CRRT depends on the machine, the need for convective or diffusive clearance, and the size of the patient. The Baxter, Braun, and the Fresenius machines allow for individual choice of the hemofilter membrane. The AN-69 hemofilter might be a better choice than polysulfone membranes for patients with sepsis. However, one problem that occurs with the AN-69 membrane is a bradykinin reaction when it interacts with acidotic plasma [22]. This problem can be avoided by using a priming solution of PLASMA–LYTE A (pH 7.4) with the addition of 20 mEq/L sodium bicarbonate and by ensuring a normal serum ionized calcium level before placing the patient on the circuit [23]. Table 58.4 gives a summary of some of the available pediatric hemofilters and their properties. For venovenous hemofiltration, a larger circuit volume may be required depending on the volume of the blood lines.

58.5.9 Solutions

1. A variety of solutions can be used for CRRT. The decision to use replacement fluid is based on the overall solute and ultrafiltration clearance requirements of the patient as well as the local standard of care. The generally accepted rate of replacement and dialysate solutions for CRRT is 2 L/1.73 m^2/h, though adequate metabolic control and clearance can be achieved with lower rates. Studies have shown that both lactate and bicarbonate-based solutions result in the same degree of clearance, but plasma lactate levels can be higher in patients on lactate-based solutions. This, obviously, raises the question in a critically ill patient as to whether the lactate is from the solution or from end organ malperfusion. In addition, patients with hepatic failure may not be able to metabolize lactate into CO_2 and hence, bicarbonate, exacerbating the lactic acidosis. Therefore, many programs have transitioned to using bicarbonate-based solutions. The first FDA-approved bicarbonate-based solution for CRRT became available in 2000 (Normocarb®, Dialysis Solution Incorporated, Richmond Hills, ON, Canada). This permitted programs to maintain a bicarbonate-based dialysis solution with less expense and risk of pharmacy error. Normocarb® and Accusol 30 2K 0Ca are also calcium-free, allowing the use of citrate anticoagulation instead of heparin. A list of commercially available solutions used for CRRT is given in Table 58.5. These solutions can be used in a diffusive or a convective mode.

Table 58.4 Choices for pediatric hemofilters and their properties

Hemofilter (manufacturer)	Properties/surface area	Priming volume
AMICON(Baxter)	Polysulfone/0.07 m^2	15 mL
PAN (Asahi)	Polyacrylonitrile	
0.3	0.3 m^2	33 mL
0.6	0.6 m^2	63 mL
1.0	1.0 m^2	78 mL
PRISMAFLEX (Gambro)		
M60	AN-69/0.6 m^2	93 mL
M100	AN-69/0.9 m^2	152 mL
HF1000	Polysulfone/1.16 m^2	128 mL

Table 58.5 Commercially available solutions for CRRT

Electrolytes mEq/L	Normocarb	PrismaSATE	Accusol	NxStage
Na	140	140	140	140
K	0	0, 2 or 4	0, 2 or 4	0, 2 or 4
Cl	105	108–120.5	109.5–116.3	109–113
HCO_3	35	22 or 32	30 or 35	35
Lactate	0	3	0	0
Ca	0	0, 2.5 or 3.5	2.8 or 3.5	3.0
Mg	1.5	1.0 or 1.5	1 or 1.5	1.0
Dextrose g/L	0	0 or 0.11	0 or 0.11	0.1

58.5.10 Anticoagulation

Anticoagulation is needed to maintain the patency of an extracorporeal circuit. Before making the decision to provide systemic anticoagulation for CRRT, one should determine whether the patient needs it. Many patients with multisystem organ dysfunction have an underlying disease that results in systemic anticoagulation (e.g., septic shock with disseminated intravascular coagulation (DIC)).

One should consider not using anticoagulation if a patient has any one of the following:

(a) Prothrombin time and international normalized ratio (PT-INR) more than 2.5, activated partial thromboplastin time (aPTT) more than 60 s
(b) Platelet count less than 60,000

(c) Active bleeding
(d) Patient is in the first 24 h postoperative

In these patients, vascular access with a large catheter and using a high blood flow rate through the circuit could be sufficient to maintain hemofiltration without systemic anticoagulation.

Traditionally, *heparin* has been the mainstay of anticoagulation for CRRT. The use of heparin loading between 10 and 30 units/kg as a bolus and then 10–20 units/kg/h maintains an activated clotting time (ACT) of 180–240 s or a PTT of 60–80 s is usually adequate for most patients. Heparin provides systemic anticoagulation and bleeding is the obvious risk of systemic heparinization. *Citrate* anticoagulation can be used as an alternative to heparinization and provides regional anticoagulation [24]. Citrate is infused post-patient (ACD-A solution) but before the hemofilter, to bind the calcium that is in the hemofiltration circuit. When calcium is bound with citrate, the blood loses its ability to coagulate and keeps the circuit patent. In order to prevent citrate toxicity in the patient, calcium then is infused independent of the circuit and back to the patient to maintain a physiologic ionized calcium level of 1.1–1.4 mmol/L. The overall result is hemofiltration system anticoagulation without patient anticoagulation. Citrate anticoagulation requires a calcium-free dialysis bath to prevent any potential binding of calcium and any potential risk of coagulation in the hemofiltration system. Two primary side effects with the use of citrate are metabolic alkalosis and "citrate loc." Since citrate is metabolized through the Krebs cycle, 1 mmol of citrate produces 3 mmols serum bicarbonate from the production of CO_2 by cellular respiration. This can be remedied by reducing the amount of bicarbonate in the replacement fluid and adding the difference with normal saline. "citrate loc" is when citrate delivery exceeds citrate clearance. Citrate is metabolized and cleared in the liver and the hemofilter membrane. "Citrate loc" is seen clinically as rising total serum calcium and dropping serum ionized calcium. This gap is due to citrate being bound to the calcium. This can be remedied by holding the citrate dose for a period of time (usually 30 min) and then resuming at a lower infusion rate.

In patients with heparin-induced thrombocytopenia, *argatroban* can be used as an alternative agent for anticoagulation in CRRT. Argatroban is a direct thrombin inhibitor [25]. During therapy aPTT levels should be monitored closely.

The synthetic derivative of *prostacyclin*, epoprostenol, can be used for anticoagulation while on CRRT [26–28]. Prostacyclin inhibits platelet aggregation and adhesion. The usual dose of prostacyclin for anticoagulation with CRRT is 2–8 ng/kg/min administered prefilter. Its main drawback is the risk of hypotension; however, the vasodilator half-life is 2 min.

58.5.11 Writing the Prescription for CRRT

In many programs CRRT is ensured by a multidisciplinary team including intensivists and nephrologists. CRRT can potentially affect all organ systems, so it is important to provide the patient with continuous monitoring recognizing that CRRT is a dynamic process. Ideally, this should include continuous monitoring of at least ECG, pulse oximetry, and arterial and central venous pressures. The physician in charge of CRRT must perform a series of calculations *before* writing the prescription and implementing CRRT. These calculations are found in Table 58.6 and will oblige the physician to carefully manage the patient's fluid balance, electrolytes, and nutrition.

Table 58.6 CRRT calculation sheet

1. Determine the patient's body surface area (BSA) using a nomogram or calculate using the Mosteller formula:
   BSA (m^2) = ([height (cm) × weight (kg)]/3600)$^{1/2}$
   Answer: _____ m^2
2. Calculate patient insensible fluid losses.
   For patients who are breathing humidified gas or who are being mechanically ventilated:
   Insensible loss per hour (mL) = (300 mL/m^2/24 h × BSA)/24 h
   For patients who are breathing room air:
   Insensible loss per hour (mL) = (400 mL/m^2/24 h × BSA)/24 h
   Answer: _____ mL/h
3. Calculate blood flow rate through hemofilter (start at 3–5 mL/kg/min)
   Blood flow rate (mL/min) = patient weight (kg) × __ mL/kg/min
   Answer: ____ mL/min (minimum 30 mL/min)
4. Calculate countercurrent flow dialysate rate – *only if dialysis is used*
   Countercurrent flow dialysate rate (mL/h) = 2000 mL/1.73 m^2/h
   Countercurrent flow dialysate rate (mL/h) = (2000 mL × BSA)/1.73 m^2
   Answer: ____ mL/h countercurrent dialysate
5. Calculate filter replacement fluid
   Filter replacement fluid rate (mL/h) = 2000 mL/1.73 m^2/h
   Filter replacement fluid rate (mL/h) = (2000 mL × BSA)/1.73 m^2
   Answer: _____ mL/h (minimum 100 mL/h) filter replacement fluid
6. Calculation of electrolyte losses
   Calculate clearance in liters/24 h using filter replacement.
   Clearance (L/24 h) = [filter replacement fluid (mL/h) × 24 h]/1000 mL/L
   Answer: _____ liters clearance/24 h
   Potassium loss (mEq)
   Potassium loss (mEq) = liters clearance/24 h × [serum K^+ (mEq/L) – replacement fluid K^+ concentration (mEq/L)]
   Answer: ____ mEq potassium loss/24 h
   Phosphorus loss (mmol)
   There is no accurate formula for calculating 24-h phosphate losses through CRRT. However, when one assumes a clearance of 2 L/1.73 m^2/h, an acceptable guideline for initiation of sodium phosphate replacement would be 1 mmol/kg/day.
   Answer: ____ mmol phosphorus loss/24 h

(continued)

Table 58.6 (continued)

The daily losses for potassium (mEq) and phosphorus (mol) must be added to the 24 h maintenance prescription for these two elements (in either parenteral nutrition or maintenance fluids) to avoid hypokalemia and hypophosphatemia.
7. CRRT anticoagulation
For CRRT using heparin anticoagulation
If ACT is <165 s, give heparin IV bolus (15–20 units/kg)
Answer: ____ units heparin load
Begin heparin continuous infusion 5–15 units/kg/h to maintain ACT range 150–200 s
Answer: ____ units/h
For CRRT using citrate anticoagulation
ACD-A infusion rate (mL/h) = blood flow rate through hemofilter × 1.5
Answer: ____ mL/h ACD-A (initial rate)
Calcium chloride infusion (10 mg/mL in 0.9% NaCl) = ACD-A rate × 0.3
Answer: ____ mL/h (initial rate)

Important: Can use the example citrate and calcium chloride titration scales in Fig. 58.3 to guide your therapy during the course of CRRT when using citrate anticoagulation

58.6 CRRT Physician Orders

Orders should not be written until all of the calculations from Table 58.6 above have been completed. Net hourly balance should be determined which reflects the difference between the total hourly fluid intake (all IV fluids, additional volume expanders and transfusions, calculated insensible loss, and filter replacement fluid), and total hourly fluid output (ultrafiltration, drains (pleural, mediastinal, gastric, peritoneal, cerebrospinal fluid (CSF)), and urine) from the perspective of the patient and not the circuit! In the authors' experience, net hourly balance should be kept at zero for at least the first 2 h as the patient is adjusting to CRRT. The ultrafiltration rate should be reassessed frequently (Fig. 58.3).

58.7 Nursing Considerations

A team approach is germane to the success of a CRRT program. Caregivers involved in the team should receive special training in the pathophysiology of renal failure, fluid and electrolyte balance, extracorporeal circuits, anticoagulation, aseptic technique and infection control, modes of CRRT and their indications, and setting up/troubleshooting the circuit. It is imperative that physicians, nurses, and technicians who are involved in the CRRT team be educated together through a training module that includes company product in-services, patient scenarios, and setting up the equipment for CRRT. The authors suggest that the CRRT team successfully complete the educational module through testing and complete competency checks on a regular basis to stay current.

58.8 Neonatal CRRT

There are numerous challenges that occur when presented with a neonate requiring CRRT. In particular, obtaining adequately sized venous access in order to achieve appropriate blood flow rates can be difficult. Typically, CRRT in neonates requires the use of a CRRT machine designed for older children and adults. The CRRT machines that are available for use in the United States are approved by the Federal Drug Administration for patients greater than 25 kg and are used off-label for smaller patients. In order to mitigate the risks of hypotension and anemia, blood priming of the circuit is needed when the extracorporeal circuit is more than 10% of a patient's blood volume [29]. As a result, CRRT in smaller patients requires the frequent exposure to blood products. Several new machines are in development that will address the needs of neonates with cardiac disease requiring CRRT. The Cardio-Renal Pediatric Dialysis Emergency Machine (CARPEDIEM) has an extracorporeal volume of 27 ml. The machine is not yet readily available in the United States, but the potential for future routine use is encouraging. Ronco and colleagues describe the first successful trial of the machine on a 3-day-old neonate using a 4 French hemodialysis catheter [30]. Also not yet available in the United States, the Newcastle infant dialysis and ultrafiltration system (NIDUS) can provide CRRT to patients weighing between 800 g and 8 kg using a single lumen vascular access catheter [31]. Askenazi et al. report the use of the Aquadex FlexFlow System (Gambro) for CRRT in infants [32]. The Aquadex circuit was originally designed for ultrafiltration in adults with congestive heart failure. Although the machine does allow for countercurrent dialysis, ultrafiltration can occur with an extracorporeal volume of 33 ml [32].

58.9 Acute Intermittent Hemodialysis

Acute intermittent hemodialysis provides clearance mainly by diffusion and the removal of fluid by ultrafiltration. The dialysis prescription is determined based on a patient's fluid status, metabolic needs, and hemodynamic stability. An advantage of acute intermittent hemodialysis is that it provides the form of renal replacement therapy with the most rapid solute clearance potential. Therefore, it is desirable for the treatment of conditions such as acute ingestions, hyperammonemia, and fluid overload. The shorter duration of an intermittent hemodialysis treatment provides time off of the extracorporeal circuit, allowing opportunities for physical rehabilitation and travel to diagnostic studies. The rapid volume shots that can occur with intermittent hemodialysis may not be tolerated in patients with hemodynamic instability, making CRRT or PD a more preferred method of renal replacement therapy.

Determine the initial Anti-coagulant Citrate Dextrose Formula A and initial Calcium Chloride rates:

Anti-coagulant Citrate Dextrose Formula A Rate (Will be 1.5x the Prismaflex Blood Flow Rate)

Initiation: _____ X 1.5 = _____ml/hour
Blood Flow Rate Citrate Rate

Calcium Chloride Rate (Will be 30% of the Anti-coagulant Citrate Dextrose Formula A rate)

Initiation: _____ X 0.3 = _____ml/hour
Citrate (ml/hour) CaCl Rate

Obtain the initial ionized Calcium values after 30 minutes of therapy:

Circuit (postfilter) ionized Calcium drawn from Prismaflex return line sample port
Patient (systemic) ionized Calcium drawn from patient's arterial line or central line.

Collect subsequent ionized calcium samples from the circuit and the patient at 30 minute intervals until the circuit and patient ionized calcium levels are within the defined **No Adjustment** range. As noted below.

Once the circuit and the patient ionized calcium levels are within the **No Adjustment** range, obtain subsequent samples every hour.

CITRATE INFUSION TITRATION

Circuit Ionized Calcium (mMol/L)	Citrate Titration Scale
<20 kg Patient	
<0.25	Decrease by 4 ml/hr
0.25–0.39	**No Adjustment**
0.4–0.5	Increase rate by 4 ml/hr
>0.5	Increase rate by 8 ml/hr
≥ 20 kg Patient	
<0.25	Decrease rate by 8 ml/hr
0.25–0.39	**No Adjustment**
0.4–0.5	Increase rate by 8 ml/hr
>0.5	Increase rate by 16 ml/hr

CALCIUM INFUSION TITRATION

Patient Ionized Calcium (mMol/L)	Calcium Chloride Titration Scale (NS 1000 ml + Calcium Chloride 10,000 mg)
<20 kg Patient	
>1.4	Decrease by 4 ml/hr
1.0–1.4	**No Adjustment**
0.9–<0.1	Increase rate by 4 ml/hr
<0.9	Increase rate by 8 ml/hr
≥ 20 kg Patient	
>1.4	Decrease rate by 8 ml/hr
1.0–1.4	**No Adjustment**
0.9–<0.1	Increase rate by 8 ml/hr
<0.9	Increase rate by 16 ml/hr

Fig. 58.3 Example initiation and titration scale for anticoagulation with citrate in CRRT

58.10 Sustained Low-Efficiency Dialysis (SLED)

SLED, sometimes termed Prolonged Intermittent Renal Replacement Therapy (PIRRT), refers to any hemodialysis treatment performed with a conventional dialysis machine over a longer period of time than with a traditional intermittent dialysis treatment. Solute and fluid removal is slower than with conventional hemodialysis, but is faster than with conventional CRRT. An advantage of the use of SLED is that it allows for planned times off of dialysis without impacting the dialysis dose. Typically heparin is used for anticoagulation with a lower heparin requirement when compared to CRRT. SLED necessitates the use of a dialysis machine with flexible options for lower dialysate flow rates. Several meta-analyses including adult patient populations have compared SLED to CRRT and have shown no difference in mortality [33]. There is very limited published pediatric experience with the use of SLED. Lee and colleagues report their experience with SLED in 14 critically ill children [34]. They describe a decrease in inflammatory markers, good hemodynamic stability, improvement in fluid overload, and pH and electrolyte imbalance in a total of 60 pediatric sessions [34].

58.11 Peritoneal Dialysis (PD)

58.11.1 Background

PD has been a mainstay of renal replacement therapy for infants and children with renal failure for over 50 years. While hemofiltration and hemodialysis have largely supplanted PD for the management of AKI and the treatment fluid overload, it continues to play an important role and has certain advantages to therapies, which require vascular access.

58.11.2 Advantages

PD has distinct advantages over other renal replacement therapies. PD catheters are relatively easy to insert and can be placed in virtually any sized child. It is a widely available therapy that is inexpensive and does not require specially trained personal or sophisticated dialysis equipment. Unlike other therapies, PD does not require anticoagulation or anticoagulation monitoring. PD can be used as both a continuous and intermittent therapy, large amounts of volume can be removed without inducing hemodynamic instability and it can provide superior clearance to intermittent hemodialysis. Additives such as antibiotics, insulin, and potassium can also be administered in the peritoneal fluid and therapeutic blood levels can be obtained. PD also provides nutrition to the patients as the dextrose in the dialysate solution is absorbed across the peritoneum.

58.11.3 Disadvantages

The primary disadvantage of PD is its lesser efficiency than vascular therapies and unpredictability of the amount of clearance and fluid removal. The volume of fluid that can be removed is not comparable to that of hemodialysis or hemofiltration and precise quantity of fluid removal cannot be achieved. Another disadvantage is that commercial peritoneal dialysate solutions are lactate based. PD removes bicarbonate from the patient and exchanges it for lactate. PD can worsen lactic acidosis in the critically ill patient who cannot convert lactate to CO_2 and bicarbonate.

58.11.4 Principles of PD

PD is performed via a single lumen catheter that is placed in the peritoneal membrane (Fig. 58.4). A dialysate solution is then instilled into the peritoneum. Solute and fluid removal primarily occurs via diffusion. The peritoneum is a semipermeable membrane to both large and small molecules. Uremic toxins, potassium, phosphorous, and proteins move across the peritoneal membrane over a concentration gradient into the peritoneal fluids. The greater the volume infused into the peritoneum and the more frequent the fluid is exchanged, the greater is the clearance. Dialysate solutions contain varying degrees of dextrose which makes it hyperosmolar in relationship to the plasma. Water diffuses across the peritoneum over a concentration gradient which results in osmotic ultrafiltration. Unlike hemofiltration, osmotic ultrafiltrate is slightly hypotonic in relation to the plasma, and hypernatremia can develop with rapid fluid removal.

58.11.5 Indications

PD is a useful modality in infants following surgical repair of congenital heart disease. A PD catheter is placed at the time of surgery, and PD is instituted if oliguria, fluid overload, or electrolyte disorders develop. Dialysis can be initiated immediately postoperative, if needed. PD is also a good choice for cardiac patients where:

(a) CRRT is not available
(b) Vascular access is limited
(c) Anticoagulation is contraindicated

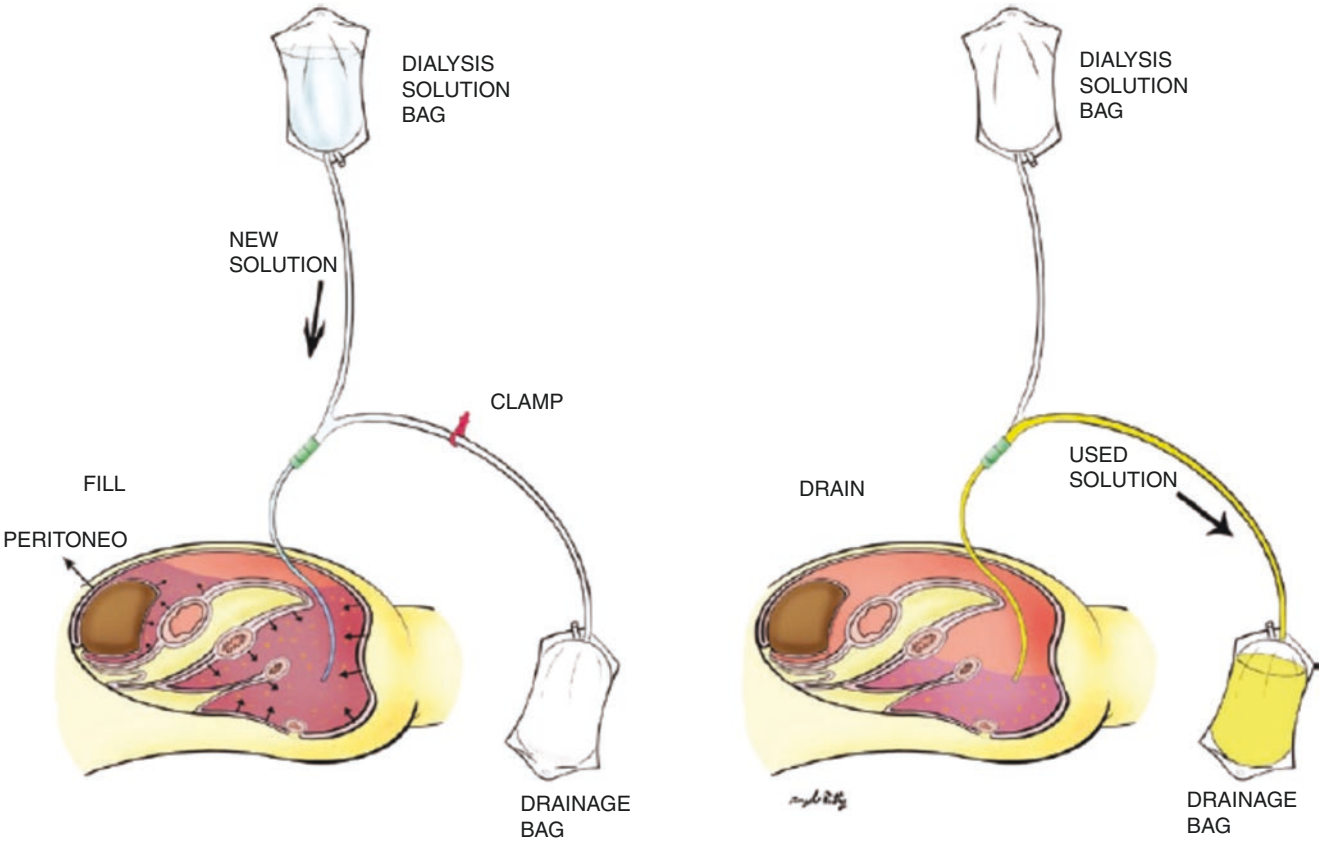

Fig. 58.4 Manual PD using a Y set

(d) Prolonged dialysis may be required due to acute tubular necrosis- or diuretic- resistant edema due to severe heart failure

58.11.6 Contraindications

The primary contraindication to PD is recent abdominal surgery, abdominal drains, or abdominal wall defects. PD is also contraindicated if there is a communication between the abdominal cavity and the thorax. PD will not be successful if there are extensive abdominal adhesions or peritoneal membrane failure. PD can be instituted safely within 2 weeks following most major abdominal surgeries. Gastrostomy tubes, ileostomies, colostomies, and vesicostomies are not contraindications to PD. A ventriculoperitoneal shunt (VP shunt) is a relative contraindication to PD.

58.11.7 Access

PD catheters come in three sizes. An infant catheter is used in patients <3 kg, a pediatric catheter in children up to 5 years of age, and an adult catheter in children >5 years of age. Pediatric and adult catheters have the same internal diameter but differ in the length of the catheter.

Dialysis catheters can be cuffed or uncuffed, straight, or coiled. An uncuffed acute PD should not be placed for more than 72 h. A Tenckhoff single-cuffed acute dialysis catheter is most often used in children. If chronic dialysis is a possibility, a double-cuffed catheter should be placed.

58.11.8 Apparatuses for Dialysis

Acute PD is easy to initiate and can be done manually. All that is needed is a "Y set" that connects to the PD tubing (Fig. 58.4). One end of the Y connects to the dialysate solution and the other end to a drain bag. Manual PD can be initiated with this set up. For infants, a special manual dialysate set called "Dialy-Nate®" is available. This is a closed system with a buretrol to administer small volumes of dialysis and multiple connectors for dialysate bags. Many centers will use an automated PD machine called a "cycler" for acute PD in children. This machine performs continuous cycled PD (CCPD). Some cyclers can be used in infants because they can deliver a dwell volume as low as 60 mL.

58.11.9 Dialysis Prescription

There are various components for writing a PD prescription: (a) dialysate +/− additives, (b) dialysate dwell volume, and (c) dwell time and number of exchanges.

58.11.10 Dialysate

Dialysate solutions have the same electrolyte composition (Table 58.7), but vary in the dextrose concentration. The dialysate type is referred to by the dextrose concentration as 1.5, 2.5, or 4.25%. These concentrations may slightly vary within countries. The standard dialysate used to initiate acute PD is 1.5%. Dialysate concentrations can be increased if fluid removal is not adequate with a 1.5% dialysate. When initiating acute PD, 200 units/l of heparin is usually added to the dialysate to prevent the development of fibrin. Heparin does not result in systemic anticoagulation as it does not cross the peritoneum. If hypokalemia develops, 2–4 mEq/L of potassium chloride can be added to the dialysate.

58.11.11 Dwell Volume

Acute PD is usually initiated at a low dwell volume of 10 mL/kg. A low volume is used to prevent leakage of fluid around the catheter from increased intraperitoneal pressure. The dwell volume is then progressively increased to as much as 40–50 mL/kg. A dwell volume of 30–40 mL/kg can safely be reached within 10–14 days of catheter insertion.

58.11.12 Dwell Time

A standard dwell time for acute PD is every hour. If dialysis is initiated within 24 h of catheter insertion, the dwell time can be decreased to 20–30 min to prevent leakage from around the catheter. More rapid dwell times are also useful for aggressive fluid removal or in the case of hyperkalemia. Continuous dialysis is used for optimal fluid removal. Intermittent dialysis with hourly exchanges for 8–10 h/day is usually sufficient when a dwell volume of 40–50 mL/kg is achieved.

Table 58.7 PD solution composition

Dextrose	1.5, 2.5, and 4.25%
Sodium	132 mEq/L
Chloride	98 mEq/L
Calcium	3.5 mEq/L
Magnesium	0.5 mEq/L
Lactate	40 mEq/L

58.11.13 Complications

There are a variety of complications that can occur with acute PD. The most common complications of acute PD are a dialysate leaking around the catheter exit site and infections.

A dialysate leak can be best avoided by:

(a) Waiting 1 or 2 days after catheter placement to initiate dialysis
(b) Using a cuffed dialysis catheter
(c) Using a low dwell volume of 10 mL/kg with rapid exchanges.

PD should be temporarily interrupted and the dwell volume decreased if a dialysate leak develops. Fibrin glue can be placed to the exit site.

Peritonitis and a peritoneal catheter exit site infection are the other common complications. The diagnostic criteria for peritonitis are a cloudy dialysate with a white blood cell count >100/μL and >50% neutrophils. Peritonitis is not a reason to discontinue dialysis and can be treated by adding antibiotics to the dialysate.

Problems with filling and draining can occur with dialysis. This can be either due to poor positioning of the catheter, fibrin obstruction of the catheter, constipation, or omentum wrapped around the catheter. Experienced dialysis personnel should be consulted if any complications arise.

58.12 Conclusion

AKI continues to be a significant factor contributing to the morbidity and mortality of critically ill children with and without heart disease. The Prospective Pediatric CRRT Registry was established in 2001 and is made of 13 pediatric centers in the United States. The data obtained from the registry has provided important information regarding the epidemiology and technical aspects of CRRT in critically ill children [35]. The recent AKI literature has explored the association of AKI with specific potentially nephrotoxic medications along with the use of biomarkers for predicting AKI. The reader is encouraged to review the current literature on the topic of AKI in infants and children and CRRT [36–39].

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Chapter 59
Neurological Complications: Intracranial Bleeding, Stroke, and Seizures

Robyn A. Filipink and Michael J. Painter

Abstract Infants with congenital heart disease are at risk for multiple neurodevelopmental impairments. The three major neurological complications, hemorrhage, stroke, and seizures are critical in the medical management of this special population. Detection and treatment of these sequelae will affect prognosis and promote more favorable outcomes.

Within the first 12 months of life, approximately one-third to one-half of the 30,000–40,000 infants born in the United States each year with congenital heart disease (CHD) will undergo cardiac surgery [1, 2]. This large infant group is an accessible population for detailed assessment of medical and surgical techniques as well as outcome measurements. Over 60 years ago, before the advent of cardiopulmonary bypass which allowed for open heart surgery, survival was the goal not often realized for these patients. Each decade has heralded surgical and medical advances that have decreased mortality. Intraoperative strategies favor low-flow bypass over deep hypothermic circulatory arrest and acid–base management prefers the acidotic pH-stat approach to the alkalotic alpha-stat strategy. In recent years, there has been a shift in emphasis to neurological morbidity.

There is an emerging consensus that complex CHD is associated with neurodevelopmental impairments including cognition, academic achievement, social and communication skills, fine and gross motor skills, executive functioning, visual perception, and attention [3]. As neurological outcomes have become more important, cardiac intensive care unit (CICU) care is increasingly including the neurologist to help detect, manage, and offer prognosis for neurological complications. A full appreciation of the unique vulnerability of the cerebral vasculature and brain anatomy, along with understanding the major neurological complications of CHD, will guide comprehensive care for this special pediatric population.

A useful division to understand risk and neurological complications is the partition of the medical course into the preoperative, perioperative, and postoperative periods. Before entering the operating room, the CHD patient has accumulated risk starting from the prenatal period. Their genetic predisposition to central nervous system (CNS) problems may include brain dysgenesis and malformations. Infants with CHD have a higher incidence of cranial ultrasound abnormalities [4], and newer magnetic resonance imaging techniques are clarifying the nature of brain abnormalities seen prior to corrective cardiac surgery [5]. Hypoplastic left heart syndrome (HLHS) is a common heart defect, and a retrospective investigation of this population found that 29% had minor or major CNS anomalies [6]. These included microcephaly, immature cortical mantle formations, holoprosencephaly, and agenesis of the corpus callosum [6]. Other common CHD carry neurologic abnormalities in varying ranges: tetralogy of Fallot 5–10%, truncus arteriosus 4–10%, and coarctation of the aorta 4–9% [6]. The combination of coarctation of the aorta and ventricular septal defect has a 70% incidence of brain lesions among full-term infants [4]. These CNS anomalies may cause seizures and abnormal cerebral blood flow leading to intracranial hemorrhage and vaso-occlusive insults. The specific cardiac defect may also predispose the patient to hemodynamic shock, hypoxemia, and acidosis in the newborn period. If the cardiac disease is serious, the patient may suffer cardiac arrest, further contributing to hypoxic–ischemic injury.

The perioperative time continues to carry risk of cardiac and systemic collapse. Chronic hypoxia has become less of a concern as early cardiac repair decreases this exposure. However, the immature cerebral vasculature and parenchyma are vulnerable to injury from surgical intervention. Fragile vasculature has difficulty compensating for the metabolic

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and circulatory changes which occur during cardiac bypass. Low or absent cerebral blood flow during bypass leads to global hypoperfusion, likely the main cause of hypoxic–ischemic and reperfusion injury. Risk is also present during the core cooling and rewarming phases of deep hypothermic cardiac surgery. Complications include focal ischemia from embolic and thrombotic insults and hemorrhage from bypass-induced coagulation disturbances.

In the postoperative period, the CHD patient faces cardiopulmonary dysfunction, hemodynamic instability, and continued cerebral vaso-dysregulation. Effects from surgery may become apparent as they were masked by paralytics and sedation. Cerebral insults occurring in the pre- and perioperative periods may lead to seizures during the recovery time. Hemorrhage and vaso-occlusive insults continue to be complications.

The major neurological sequelae present throughout the three important risk time periods are stroke, hemorrhage, and seizure. It is important to recognize these acute neurological issues and, when possible, exercise primary and secondary prevention to avoid long-term complications. This chapter reviews these three neurological manifestations of neurological injury facing pediatric cardiac patients and discusses the prevalence, physical signs and symptoms, and work-up strategies and treatment.

59.1 Hemorrhage

The intrinsic circulatory disturbances associated with congenital cardiac disease can predispose the brain to hemorrhage. This injury can occur anytime during the continuum of care, but age is a major risk factor. Sites of hemorrhage vary as full-term infants are more likely to have intraparenchymal and subdural hemorrhage, while premature neonates more commonly have intraventricular, intracerebellar, and subarachnoid hemorrhages [7]. The immature germinal matrix is especially predisposed to injury because of its structural and physiologic vulnerability. CHD neonates are susceptible to hemodynamic instability, and up to 24% may develop hemorrhage [8]. Surgery compounds risk as patients are exposed to changes in blood pressure, cerebral blood flow, and anticoagulation. One-third of neonates who underwent surgery with varying cardiac disease had new parenchymal hemorrhage diagnosed by MRI [9].

Additional risk factors include delivery complications, maternal coagulopathy, evolution of ischemic lesions, and infection. Identifying specific cardiac patients who carry a greater risk for hemorrhage is an important tool. These populations are HLHS [10] and coarctation of the aorta, the latter of which has an associated increase in intracranial aneurysms and hypertension [7, 11].

Symptoms of hemorrhage are wide ranging, depending on the mental status of the cardiac patient as sedation and paralytics needed for stabilization can mask neurological deficits. Physical signs include weakness, pupillary changes with increased intracranial pressure, acute vital sign changes, and clinical seizures. In contrast, some hemorrhages can remain clinically silent. An MRI study comparing pre- and postoperative asymptomatic intracranial hemorrhages in full-term CHD neonates revealed that 43% had extension of hemorrhage, 26% had decreased hemorrhage, and 30% remained unchanged [12]. Sites of hemorrhage were the choroid plexus, subdural space, intraparenchymal, and occipital horn [12].

One should have a low threshold to evaluate for intracranial hemorrhage (Fig. 59.1). The most widely used modality is cranial ultrasound (US). Portability with availability at the bedside makes this modality most useful in patients who are unstable and unable to be moved from the intensive care unit. Computerized tomography (CT) is the next technique employed for patients who may be transported, as it gives better spatial resolution and requires short scanning time. MRI is the best modality for dating hemorrhage and differentiating primary hemorrhage from transformed hemorrhagic infarct. Limitations on MRI include contraindication for ferromagnetic devices (e.g., pacemakers and valves) and patient transport issues [13]. Other criteria for performing preoperative cranial US include birth weight less than 1500 g, hemodynamic compromise sufficient to cause metabolic acidosis, coagulation disturbance, and certain cardiac lesions such as hypoplastic left heart syndrome and coarctation of the aorta [1].

Complications from hemorrhage include seizure, as blood itself represents an irritant, stroke involving stasis of blood flow, and long-term neurological disability. The postmortem neuropathology of 405 pediatric cardiac patients who underwent transplantation revealed extraparencymal hemorrhage in 31% with obstructive cardiac lesions and 16% of the total population with varied cardiac defects [14].

Management of hemorrhage employs serial imaging to survey extension. In the acute setting, transfusion and fresh frozen plasma may be used, if not contraindicated by cardiac vulnerability. Some patients may be on aspirin therapy which increases the risk of bleeding and must be taken into account. The coagulable state of the patient can be precarious when balancing cardiac disease and risk of bleeding with possible serious neurological sequelae. An important issue that arises once a patient is found to have an intraventricular–periventricular hemorrhage preoperatively is the timing of surgery. The main concern is to avoid extension of injury. Small subependymal hemorrhages should not delay surgery [1]. However, intraventricular or intraparenchymal hemorrhages may call for waiting at least a week before cardiopulmonary bypass can be performed [13].

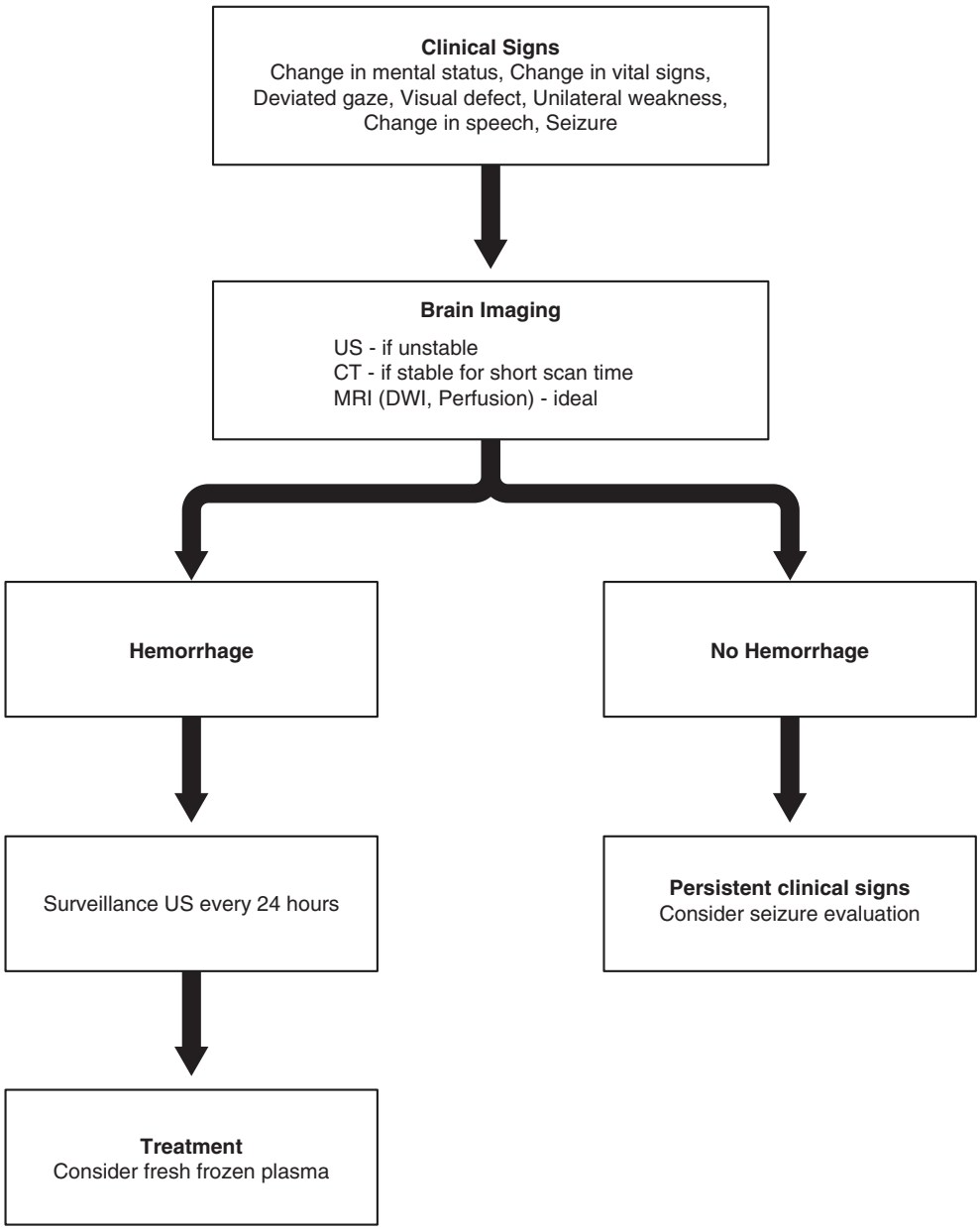

Fig. 59.1 Hemorrhage evaluation in CHD infants

59.2 Stroke

Congenital heart disease is the leading known risk factor for childhood stroke. Estimates of the incidence of stroke per 100,000 children range from 2.5 [15] to 13 [16], including both ischemic and hemorrhagic strokes. At least 20% are associated with CHD [15, 17–19]. In young patients with CHD, the risk of stroke is nearly 11 times higher than in the general population [20]. Realizing the high incidence of stroke allows for risk stratification based on age, specific cardiac disease, presence of thrombotic or embolic sources, inherent or acquired hypercoagulable states, and vascular anatomy.

An ischemic event specific to neonates is periventricular leukomalacia (PVL). This manifests as necrosis in the white matter surrounding the lateral ventricles and involves injury to immature oligodendrocytes. Vascular immaturity combined with hemodynamic instability from cardiac defects and surgery plays an important role. In general, preterm infants are at greater risk for PVL. The association between cerebral blood flow and the occurrence of PVL was examined preoperatively in 25 term infants with a variety of congenital heart defects. Decreased baseline cerebral blood flow was associated with PVL, which was present in 28% of this cohort [2]. In a study of full-term CHD infants, MRI uncovered 16% with PVL before surgery and 48% with new PVL in the postoperative period [9]. Another study found PVL through MRI in more than 50% of neonates after cardiac surgery [21]. These studies underscore the susceptible time for CHD patients.

HLHS patients are a particularly vulnerable group. An association of up to 25% has been reported between HLHS patients and the occurrence of PVL [10]. Among those who undergo Fontan operations, there is a 2.6% [22] to 8.8% [23] prevalence of stroke, and the risk may extend up to 15 years [24]. Additionally, postmortem evaluation after cardiac transplantation revealed that infarct was the primary central nervous system pathology in HLHS patients [25].

Embolic sources require cardiac anatomy that allows for passage into the cerebral circulation. Endogenous sources include intracardiac and systemic emboli, such as deep vein thrombosis and pulmonary emboli. Emboli may be induced by stasis, altered vascular pressure, surface interactions, and circulation induced by cardiopulmonary bypass, deep hypothermic circulatory arrest, and immobilization. Septic emboli can occur in up to 50% of patients with infective endocarditis [25–27] and show a predilection for the middle cerebral artery territory [28]. Exogenous emboli are related to surgery and include synthetic debris, air, platelet, and fat. Thrombotic insults can involve both the arterial and venous systems and are related to possible systemic inflammatory vascular changes and increased central venous syndrome, respectively [1]. The role of prosthetic materials in altering blood flow pathways is another contributor to embolus and thrombosis formation. Hypercoagulable states secondary to cardiac disease [29–31] and additional coagulation pathway abnormalities contribute to stroke. Lutterman et al. highlighted the association between moyamoya syndrome, a chronic cerebrovascular disease of progressive stenosis and eventual occlusion of the internal carotid arteries, and congenital heart disease [32]. Additional risks for stroke include venous thrombosis [33], intracranial aneurysms, and large vessel dissection [34].

The signs and symptoms of stroke are similar to those of hemorrhage (Fig. 59.2). Focal signs are related to the anatomy in the infarct area and can include motor and sensory deficits, alterations in consciousness, acute changes in vital signs, language disturbance, or visual field defects. Seizures can also be a cardinal sign of cerebral dysfunction. Age is a factor that can help guide the evaluation of a patient with suspected stroke. Infants often present with focal seizures [17, 35, 36], whereas older children more readily show language, motor, and visual deficits. As mentioned earlier, physical signs can easily be disguised by medication and recovery state.

Brain imaging reveals the presence of infarct, areas and extent of involvement, and hemorrhagic components. Cranial US is limited by low spatial resolution and the inability to detect acute and evolving ischemic areas, but may be the only modality available for a patient in critical condition. CT detects the presence of blood, but subtle findings in acute stroke such as loss of gray–white matter differentiation may not be detected until 6 h after infarction has occurred [37]. MRI using diffusion-weighted imaging (DWI) is superior in detecting cerebral ischemia [38] within 30 min from onset [38]. Magnetic resonance angiography (MRA) visualizes intra- and extracranial vasculature to detect occlusion, dissection, and vascular anomalies. Alternatively, computed tomography angiography (CTA) and conventional angiography may give better visualization of vascular anatomy, but have the added risk of radiation exposure. Conventional angiography allows for vascular intervention, but is also limited by the stability of the patient to undergo anesthesia and the procedure. Techniques to assess perfusion aim to determine if there is reversible ischemia and salvageable brain tissue. These include xenon-enhanced CT, CT perfusion, MR perfusion, and diffusion imaging. Each has its own advantages and disadvantages, but tolerability of scanning time is the main limiting factor for patients in the CICU.

Stroke complications include seizure, progression to hemorrhage, and apparent and subtle long-term neurological deficits. The interplay between these major complications is exemplified by the relationship of some antiepileptic medications and anticoagulants used to prevent primary or further strokes. For example, warfarin's effectiveness can be decreased by phenobarbital, a widely used antiseizure medication.

Unfortunately, in contrast to adults, there is minimal epidemiological evidence and no acute intervention studies on children to guide treatment. Acute therapy for adults ranges from revascularizing ischemic areas with thrombolytics either remotely by intravenous administration or directly by intra-arterial administration or invasive neurosurgical intervention such as vascular stents or angioplasty. The first national estimate of the use of thrombolytic therapy for ischemic stroke in children reported that less than 2% of children received this treatment [39]. None of the patients receiving thrombolytics had CHD, and practically, thrombolytics are rarely, if ever, given to this high-risk population. This highlights the need for further investigation into acute stroke interventions for pediatric CHD patients.

Primary preventative care aims to provide prophylactic treatment, while secondary prevention aims to stop hemorrhagic conversion of the infarcted area or avoid future strokes. Indications for primary prophylaxis include prosthetic heart valves, dilated cardiomyopathy, intracardiac thrombus, and prolonged immobility. Therapies include antiplatelet medications such as aspirin and plavix and anticoagulation medications such as warfarin and low-molecular-weight heparin. Hemorrhage is the primary side effect. Decisions require careful assessment of risk and benefit. Although the precise risk for children with CHD is unknown, adult studies again serve as guides and offer information on surgical timing. Large infarcts in adults, involving a cerebral lobe or more than 30% of a hemisphere, have greater risk for hemorrhage

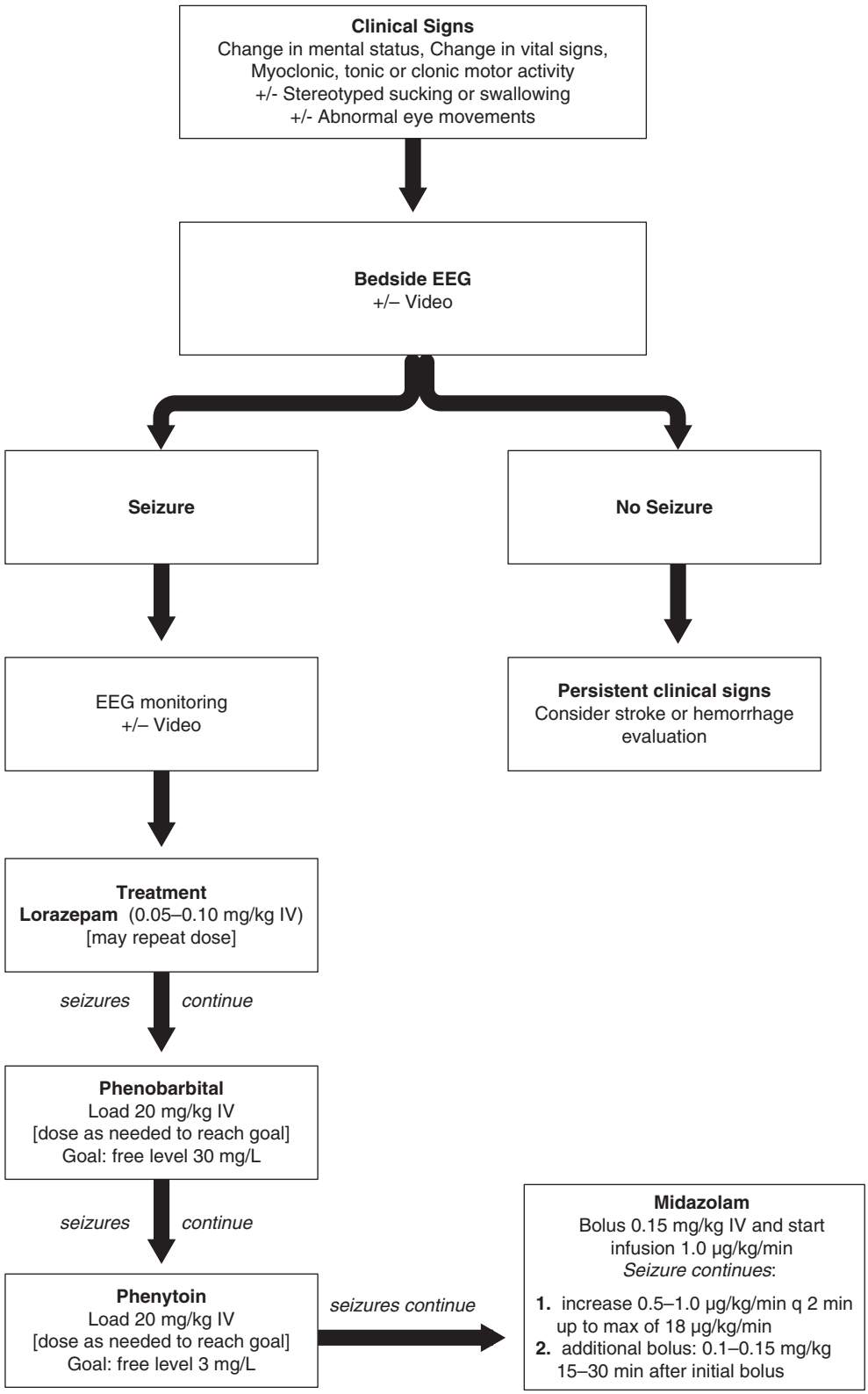

Fig. 59.2 Stroke evaluation in CHD infants

[40–42]. Within the first 48 h, 70% of adult strokes evolve to hemorrhagic transformation [41]. This data helps formulate a logical stepwise approach to stroke in the CICU.

59.3 Seizure

Seizures are common manifestations of neurological dysfunction in CHD patients. The neonatal period is the time of highest seizure incidence [43–45]. Even before cardiac surgery, patients may have seizures that reflect their underlying brain dysgenesis. Seizures are also a common complication after surgery. Incidence varies depending on the mode of seizures identification. One study that looked at perioperative electrical seizures, background pattern of amplitude-integrated EEG (aEEG), and 2-year neurodevelopmental outcome reported that 3/4 of the 30% that had seizures did not have a clinical correlate [46]. Electrographic seizures, detected by video-EEG monitoring for 48 h postoperatively, occurred in 11.5% of CHD infants, and none had clinically visible seizures [47]. In contrast, another study noted a seizure incidence of 1.2% for CHD infants after surgery, and these seizures were diagnosed clinically [48].

A risk factor for increased seizures in infants is the duration of deep hypothermic circulatory arrest (DHCA). DHCA duration of more than 40 min significantly increases incidence of electrographic seizures [49]. Hemorrhage and stroke predispose a patient to seizure. Cyclosporin toxicity is another etiology which is particular to CHD patients on immunosuppressants [49]. As discussed earlier, moyamoya syndrome should be considered when the presentation includes both stroke and seizure [32].

Identification of seizures in the newborn period can be very difficult to detect clinically (Fig. 59.3). Physical signs can include behaviors and movements that are very different

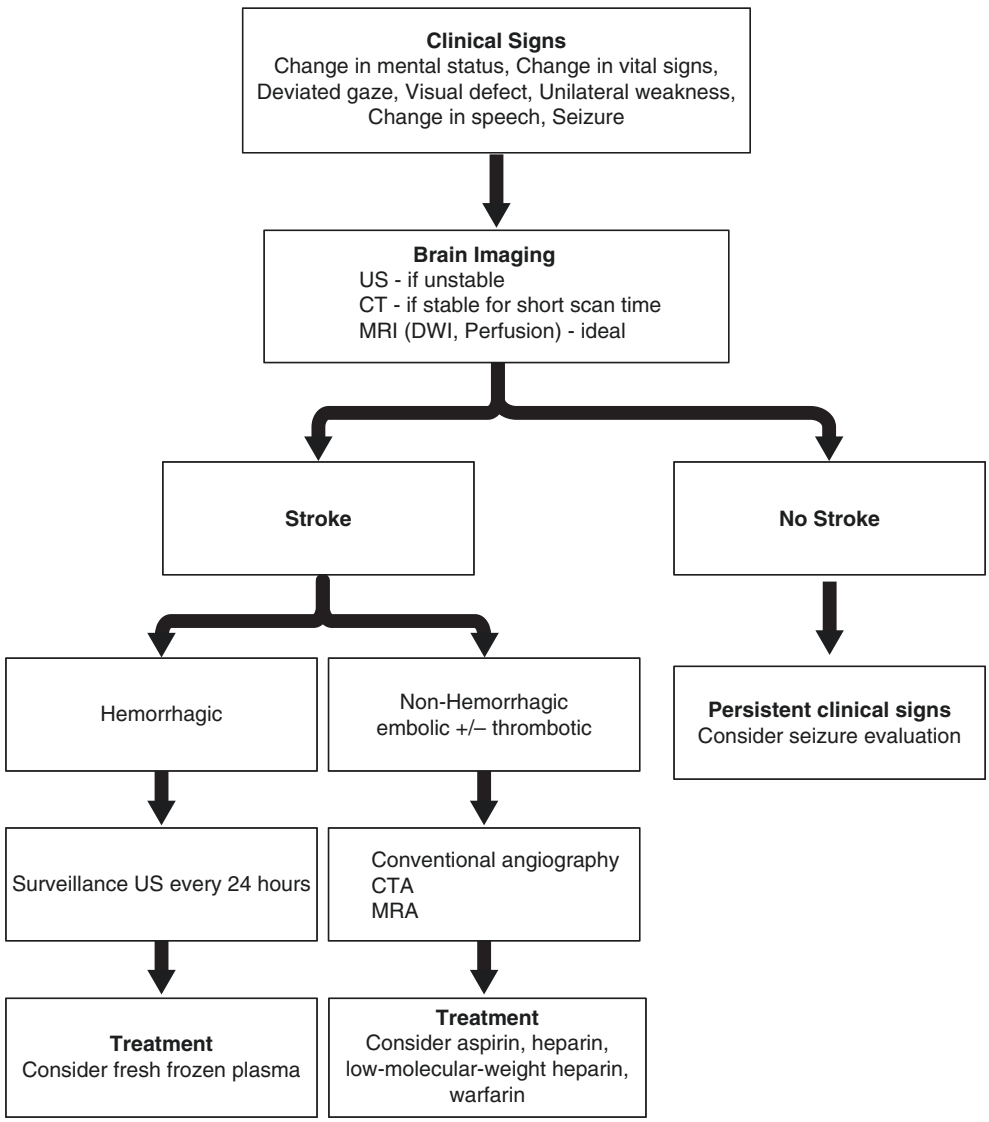

Fig. 59.3 Seizure evaluation in CHD infants

from the typical tonic–clonic epileptic movements of older children. Episodic autonomic changes may be the only sign of a seizure [50–52]. Clinical signs of focal seizure can vary from rhythmic shaking of an extremity, twitching of one side of the face or eye deviation, to subtle change in mental status. Generalized seizures may present as whole-body rhythmic shaking with loss of consciousness. As mentioned earlier, however, electrographic seizures may not have a clinical correlate. Therefore, a low threshold of clinical suspicion is needed for evaluation of seizures.

EEG is the definitive test to detect seizures and quantify their frequency. EEG is performed at the bedside where a trained technician can apply electrodes and run a recording even on unstable patients. Video-EEG helps determine if clinically suspicious movements, behaviors, or autonomic changes are a sign of seizure activity. Abnormal EEG background is a strong predictor for concomitant and subsequent seizures in the following 24 h [53]. Burst suppression patterns, which are a markedly abnormal background, are highly indicative of chronic static encephalopathy [54]. Median recovery to a continuous background occurred at 6 h and sleep–wake cycling at 21 h; however, increased risk of early mortality and poor neurodevelopment was associated with delayed recovery in aEEG background [46]. Epileptogenic discharges, such as excessive sharp waves, can indicate a lowered seizure threshold. Therefore, the EEG is a valuable tool to identify seizures and help predict future seizure risk as well as, to some extent, neurological outcome.

The underlying cause for seizures determines prognosis. Infants with brain dysgenesis have a high chance of developing epilepsy, but there are other associated risk factors. A retrospective review of childhood stroke reported that 49.3% of patients developed at least one seizure and 28.8% developed recurrent seizures [35]. Stroke occurring in the newborn period carries the lowest risk for epilepsy [55]. Additional information has emerged from studies following congenital cardiac patients. West syndrome, defined by the combination of infantile spasms, hypsarrhythmia, and developmental delay, has been reported in a small group of CHD after surgery [56].

The importance of this manifestation of cerebral disturbance is underscored by a study which associated poorer cognitive outcome with seizures. It revealed that preoperative seizures in a group of children with HLHS predicted lower full-scale IQ [57]. In survivors of corrective surgery for D-transposition of the great arteries, perioperative seizures were associated with poor neurodevelopmental outcome at 1 [58] and 4 [59] years after surgery. Conversely, recent outcome data on a group of 178 neonates and infants after cardiac surgery showed that the occurrence of seizures was not predictive of worse development at 1 year of age [60].

Acute treatment for seizures is related to the underlying cause. Correcting electrolyte abnormalities and identifying toxic medication levels are important steps in the approach to the seizing child. The commonly used medication algorithm outlined by du Plessis [13] first employs lorazepam at an infusion dose of 0.05–0.1 mg/kg and the dose may be repeated twice if needed. If seizures continue, phenobarbital is loaded at a dose of 20 mg/kg to a maximum of 40 mg/kg. Higher doses may be required, but blood levels will help determine appropriate dosing (goal level 40 mg/L). Administration of phenobarbital leads to a 50% or more reduction in less than half of infants experiencing seizures [47]. Phenytoin is the next step for continued seizures. The loading dose is 20 mg/kg, with repeat dosing if necessary. Both phenobarbital and phenytoin have been reported to be equally, but incompletely, effective in controlling seizures in less than half of neonates. Their combined use led to a slight improvement in seizure control in 57–62% of neonates [61]. It is important to note that non-neonatal status epilepticus algorithms will also include levetiracetam and valproic acid as addition second-line medications.

Prolonged seizure activity unresponsive to these medications may be treated with an infusion of IV midazolam. Favorable response to midazolam in this situation has been reported using an IV bolus of 0.15 mg/kg, followed by continuous infusion (1 μg/kg/min) increasing by 0.5–1 μg/kg/min every 2 min until a favorable response or a maximum of 18 μg/kg/min. A second bolus of 0.10–0.15 mg/kg may be administered 15–30 min later if seizure activity continues [62]. As many patients will not go on to develop epilepsy, the duration of antiepileptic medications must be considered for each patient based on etiology for seizures, brain imaging, and timing of seizures to other events such as stroke. After this approach, the likelihood of seizure recurrence can dictate management and, in most cases, medication can be weaned within 2–6 months. Patients who continue to have seizures or have increased predisposition to epilepsy (abnormal EEG, brain malformation, or insult) will be transitioned to more appropriate daily antiepileptic medication.

59.4 Conclusion

Three interconnected neurological complications encountered in the pediatric CICU are hemorrhage, stroke, and seizure. As risk follows a patient throughout their hospitalization, and beyond, the physician must be ever vigilant. By employing the discussed detection, surveillance, prevention, and treatment strategies, one can effectively treat the pediatric patient with congenital cardiac disease and promote an improved neurological outcome.

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Chapter 60
Infections in the Cardiac Intensive Care Unit

Timothy Onarecker and Marian G. Michaels

Abstract Children in the cardiac intensive care unit (CICU) are at a high risk of infections. This may be due to underlying immunodeficiency and iatrogenic alterations in the immune system or due to invasive procedures. Some patients are admitted to the CICU primarily due to an infection, while others develop secondary infections once they are in the CICU setting. This chapter reviews the types of infections that can occur in the pediatric CICU to give an understanding of predisposing factors, primary and secondary infections.

60.1 Predisposing Factors

A child's immune status is a critical factor influencing the risk of infection while in the CICU setting. Age itself affects the child's immune capacity. Infants with congenital heart defects (CHD) are often admitted to the CICU shortly after birth. Their immature immune system coupled with the absence of immunizations puts them at risk of infections with consequential morbidity and mortality.

In addition, some congenital cardiac defects are associated with immunodeficiencies such as asplenia or syndromes such as Di George syndrome involving full or partial deletions of chromosome 22q11^{-}. Thymic development is variably impacted in Di George syndrome affecting the T-cell arm of the immune system; when fully absent, children are at severe risk of opportunistic infections such as transfusion or breast milk-associated cytomegalovirus (CMV) and *Pneumocystis jiroveci* pneumonia (PJP). Modern blood bank techniques with leukocyte reduction of blood products reduces the risk of transfusion-transmitted CMV but does not eliminate it fully. Lymphocytes in non-irradiated blood products, normally cleared by host immune cells, can partially engraft leading to a rare but lethal condition known as transfusion-associated graft-versus-host disease [1]. Accordingly, all newborns whose immune status is not known and those with known T-cell insufficiency should receive irradiated blood products. At the UPMC Children's Hospital of Pittsburgh, all neonates receive CMV-safe (filtered) and irradiated blood products. Those at high risk of CMV disease also have CMV-negative blood products requested. Prophylaxis against PJP can be started between 4 and 6 weeks of age with trimethoprim-sulfamethoxazole for children with immune deficiencies.

Immunizations are an important strategy to protect all children particularly those with underlying splenic dysfunction as seen with many congenital heart disease syndromes and those who require transplantation. Hepatitis B vaccine can be given at birth followed by second and third doses at 1 and 6 months of age. Other routine neonatal vaccinations should be given on an accelerated schedule starting at 6 weeks of age. This is particularly important for heart transplant candidates, as they may not respond adequately to vaccines after they receive antirejection immunosuppressive agents [2]. Palivizumab to protect against severe respiratory syncytial virus (RSV) is discussed specifically under RSV.

The nutritional status of patients with CHD is an important aspect of a healthy immune system. Children with uncontrolled heart failure or anatomical anomalies may develop malnutrition due to impaired feeding and/or increased caloric needs, putting them at increased risk of infections [3]. Nutritional impairment also contributes to poor wound healing, increasing the likelihood of surgical-site infection.

Nosocomial infections are a significant concern for children in a CICU setting. Infants and children in the CICU often have surgical wounds and invasive catheters that interrupt the

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normal protective barriers of the body. The presence of sternal wounds, central line catheters, chest drains, and pacing wires puts these patients at risk of nosocomial bacterial and yeast infections [4]. Intubation of the trachea and ventilatory support put the patient at risk of tracheitis and ventilator-associated pneumonia. Use of bladder catheters, often necessary for accurate measurement of urine output, is also a risk of urinary tract infections.

Extracorporeal membrane oxygenation (ECMO) is required at times to provide cardiovascular or respiratory support in patients undergoing cardiac surgery or as a bridge to cardiac transplant. A retrospective review of nosocomial infections associated with ECMO over a 4-year period found increased infections in children with CHD (29/75) compared to other underlying diseases (8/66) [5]. The authors postulated that this increased risk of nosocomial infection may partly be due to longer cannulation times, increased likelihood of undergoing major procedures, or having an open sternum. Ventricular assist devices (VADs) represent another important bridge to heart transplantation in patients with end-stage heart failure. Its use in pediatric populations is becoming increasingly more common, in part due to the development of pediatric-specific devices [6]. Bacterial infection is an unfortunately frequent complication associated with the use of VADs. One study looked at 51 patients with VAD placement and found 33 infections related to the VAD, including 3 fatal infections [7].

Finally, circulating nosocomial infections that are particular to a time of year such as respiratory syncytial virus, or in a specific institution, such as vancomycin-resistant enterococci, may be additional risk factors for children requiring CICU care. While every hospital should employ good hospital infection control policies, it is clear that nosocomial infections can occur. Accordingly, it is important to know the epidemiologic risks for individual institutions.

Immunosuppressive therapy required for cardiac transplants puts patients at significant risk of infection in the CICU. Host T lymphocytes are the primary cells involved in graft rejection and, therefore, are the main target of immunosuppressive medications [8]. Many protocols exist, and most start with an induction phase of intense T-cell depletion with either anti-thymocyte globulin or interleukin-2 receptor antagonist. This is followed by maintenance therapy with a variable combination of a corticosteroid, calcineurin inhibitor (e.g., tacrolimus or cyclosporine), and an antimetabolite (e.g., mycophenolate mofetil). Suppression of T-lymphocyte activity predisposes the patient to opportunistic viral and fungal infections. These infections can be newly acquired, from the donor or reactivation of latent infection. Patients at high risk of reactivation of viral infection should be placed on appropriate antiviral prophylaxis. The incidence and mortality of opportunistic infections has improved with advances in surveillance, prophylaxis, and immunosuppressants [9].

60.2 Types of Infections

60.2.1 Surgical-Site Infections

Surgical-site infections (SSI) may occur following any surgical procedure but present a significant problem after cardiac surgery. Rates of SSI after cardiac surgery typically range from 1% to 5% but up to 18% in those with delayed sternal closure [10–12]. Infections can occur at every level of the wound site, from the skin down to the cardiac tissue and mediastinum, and occur despite prophylactic antibiotics [13]. There are numerous risk factors for SSI throughout the hospital course. The highest-risk groups are those with delayed sternal closure and those requiring re-exploration surgeries for bleeding [13, 14]. Pre- and intraoperative risks include the need for hospitalization, younger age, complexity of the procedure, duration of cardiopulmonary bypass (CPB), and incorrect timing of preoperative antibiotics [11, 15]. Postoperatively, those with cyanosis, longer mechanical ventilation, and longer CICU stay were at higher risk of SSI. When looking specifically at organ/space infections, the need for preoperative hospitalization, aortic cross-clamp greater than 85 min, and requiring at least three RBC transfusions were all independent risk factors [15].

Gram-positive organisms, particularly *S. aureus* and coagulase-negative staphylococci, are prominent causes of infection. *Pseudomonas aeruginosa* is the most frequently isolated Gram-negative organism [14, 16]. Guidelines for the prevention of SSI have been established by the Society of Thoracic Surgeons, but protocols still vary among institutions. Preoperatively, patients should receive bathing with chlorhexidine gluconate to reduce cutaneous bacterial load and nasal mupirocin for those with MRSA colonization [10]. Patients should receive cefazolin within 60 min of incision, and for those with a history of MRSA colonization, vancomycin should be given within 120 min to reduce risk of SSI [10]. For routine cardiac surgery, postoperative prophylaxis should be given no longer than 48 h [10]. No benefit has been found for duration longer than 48 h, and extended durations increase risk of resistant organisms [17]. However, patients with delayed sternal closure typically receive prophylaxis until 24 h after sternal closure due to the high risk of infection, though no studies have been performed to analyze the efficacy of this practice [18].

60.2.2 Catheter-Associated Infections

Most patients in the CICU regardless of their underlying condition will have a central venous catheter placed. Catheter-related bloodstream infections (CRBSIs) are fre-

quent complications of long-term vascular catheters. Infection may occur locally at the site of catheter insertion, along the tract of the catheter, or in the bloodstream. Clinical findings can be minimal and may only manifest as fever [19]. The main risk factor for bloodstream infection is the duration of the catheter greater than 7 days [20]. This highlights the importance of strict adherence to sterile techniques during placement, use, and dressing changes of central lines. These measures include gowning, gloves, sterile drapes, and chlorhexidine/isopropyl alcohol solutions to prepare the skin before placement [21]. Daily assessment of their need and prompt removal of catheters help to minimize the rate of infections [21]. The use of prophylactic antibiotic locks has been shown to potentially reduce the incidence of CRBSIs, but the routine use is often hampered by the frequent necessity of continuous infusions in CICU patients [22]. Guidelines recommend the use of prophylactic antibiotic locks only in patients with a history of recurrent CRBSI [21]. Data are limited regarding the management of catheter-related infections in children. Accordingly, guidelines are derived from adult data. Empiric therapy should include vancomycin and a Gram-negative agent according to the local and patient-specific antibiogram (e.g., 4th-generation cephalosporin, carbapenem, or β-lactam/β-lactamase combination) [19]. For critically ill patients and those at high risk of candidemia, empiric anti-candidal therapy, typically an echinocandin, may also be started empirically. Antimicrobials can be tailored to target specific pathogens once they are identified. Patients should receive 10–14 days of pathogen-specific systemic therapy starting from the first day of sterile cultures. Salvage of long-term catheters can be attempted, but generally should be removed in patients with severe sepsis, tunnel infections, thrombophlebitis, or if cultures remain positive >72 h. Short-term catheters should be removed for most infections aside from coagulase-negative staphylococcus. If line salvage is attempted, antibiotic lock therapy should be strongly considered and given for the duration of systemic therapy [19].

60.2.3 Urinary Tract Infections

Urinary tract infections (UTIs) are another of the most common nosocomial infections in the CICU. Incidence after cardiac surgery in children ranges from 1% to 7% of patients [4, 23, 24]. Gram-negative bacilli including *E. coli*, *Klebsiella*, *Enterobacter*, and *Pseudomonas* account for the majority of infections, and are a potential source of multidrug resistant organisms. Other organisms include *Enterococcus* and *Candida* spp [23]. Longer duration of catheterization, presence of renal and/or urinary tract anomalies, and genetic syndromes (e.g., Di George) are associated with increased risk of UTI [23]. Similar to central venous catheters, the necessity of indwelling urinary catheters should be assessed frequently, and they should be removed when possible to reduce the risk of infection.

60.2.4 Respiratory Tract Infections

Respiratory infections have a significant impact on the postoperative course of cardiac surgery patients. Similar to other hospital-acquired infections (HAI), those requiring preoperative admission, longer duration of CPB, longer duration of mechanical ventilation are at increased risk of upper and lower respiratory tract infections [24]. Higher complexity of a patient's heart disease has also been shown to have a direct relationship to risk of nosocomial pneumonia [25]. The diagnosis of respiratory infections in intubated patients is often determined by the analysis of respiratory fluid specimens and is complicated by the presence of bacterial colonization. Endotracheal tube colonization increases with prolonged intubation, and does not necessarily indicate infection. To distinguish colonization from true infection, three elements should be evaluated [26]:

1. Clinical signs and symptoms such as a change in the respiratory status and change in the color, consistency, and volume of tracheal secretions
2. The Gram stain of the secretions which should show neutrophils, as well as moderate to heavy staining of a single type of bacterium
3. Growth of moderate to heavy amount of bacteria

To ascertain the cause of pneumonia, deep suctioning or a bronchoalveolar lavage may be required.

60.2.5 Transfusion-Transmitted Infections

Patients in the CICU often receive multiple transfusions of blood products. Blood product safety has improved significantly over the past several decades largely due to the development of nucleic acid amplification testing [27]. The American Red Cross voluntary blood supply estimates HIV and HCV transmission risk of 1 in 2,000,00 per transfused unit [28]. The risk of transmission of hepatitis B has been reduced to 1 in 1,000,000 per unit. Leukoreduction techniques for packed RBC have decreased transmission of viruses such as CMV and Epstein-Barr virus (EBV) [29]. Still of concern is transmission of infections with a long incubation period such as human T-cell leukemia virus (HTLV) and Creutzfeldt-Jacob disease. Nucleic acid testing has also been developed for emerging infections such as

West Nile virus and Zika virus, which also can be transmitted with transfusions. Bacterial contamination of platelets is currently the most frequent transfusion-associated infection.

Prevention of transfusion-associated infections relies on appropriate screening of blood donors and proper techniques for collecting and storing blood products. The use of a designated donor unit can reduce some risk of infants who require repeated transfusions by avoiding exposure to multiple donors. Judicious administration of blood products may also decrease infection risk.

60.2.6 Myocarditis

Myocarditis is an important cause of morbidity and mortality in children (see specific chapter in this book), and affected children are often managed in the CICU. Viral infections, in particular, coxsackievirus B and adenovirus, have long been recognized as the most common causes of myocarditis in children [30, 31]. With advances in viral testing, other viruses such as parvovirus B19, influenza, and CMV have also been identified as causes of myocarditis [32–34]. A wide variety of other less frequently encountered infections can result in myocarditis including bacteria, fungi, rickettsia, and protozoans. Immune-mediated disease and drug hypersensitivity reactions have also been implicated in cases of myocarditis [35].

The clinical features of myocarditis range from self-limited illness with subclinical myocardial dysfunction to severe cardiac failure or even sudden death [36]. The diagnosis is often based on clinical findings, viral testing, inflammatory and cardio-selective markers, and imaging [37]. Endomyocardial biopsy (EMB) is the gold standard, providing optimal tissue for histology, culture, and PCR but is often deferred due to the risk of high-severity adverse events in patients with acute myocarditis [38]. Imaging typically includes chest X-ray, electrocardiography, transthoracic echocardiography (TTE) to detect signs of mechanical and electrical dysfunction. Cardiac magnetic resonance imaging has also emerged as a valuable noninvasive diagnostic tool [39]. It is more sensitive than TTE, and is capable of detecting subtle areas of myocardial inflammation, which can also assist in EMB [39].

Treatment involves supportive measures, which may include optimization of ventricular pre- and afterload, inotropic support, mechanical ventilation, and in severe cases mechanical devices such as ECMO or VADs. Adjunctive therapies such as intravenous immunoglobulin (IVIG) and immunosuppressants have not been proven to be of benefit. Potential benefits of IVIG to treat myocarditis have been suggested in some case series and retrospective reviews [40, 41]. Randomized controlled trials (RCTs) have shown conflicting results. A Macnamara [42] study of 62 adults found no improvement in mortality or ventricular function at 1 and 6 months. Another trial by Bhatt [43] studied efficacy of IVIG in 83 children with acute encephalitis with myocarditis, and reported improvement in ejection fraction at discharge. However, evaluation of this study by Cochrane Review determined these results to be of low quality due to high risk of bias based on the methods of study. While there may be potential benefit in select patients, there is insufficient evidence to support routine use of IVIG pending higher quality randomized studies. Data on the benefits of corticosteroids to treat myocarditis are similar. Some randomized trials have shown potential benefit in the treatment of myocarditis, but these studies have small patient numbers and low-quality methodology [44]. Use of corticosteroids has potential benefits, but routine use is not supported. Pleconaril, an antiviral agent with in vitro activity against enteroviruses, was evaluated in an RCT involving 61 children for the treatment of enteroviral sepsis and myocarditis [45]. It failed to show significant benefits, and is currently not available for this treatment.

60.3 Specific Infections

60.3.1 Viral Infections

Patients in the CICU setting are at increased risk of disease from viruses due to their underlying condition; however, several viruses deserve particular mention.

60.3.1.1 Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection (LRTI) in all children <2 years. Children with certain types of CHD are at increased risk of severe RSV infections [46]. Acquisition of RSV just prior to admission for cardiac surgery is associated with an increased rate of LRTI in the postoperative period and subsequent increased morbidity. Advances in medical care have resulted in significant reduction in mortality in this group of patients, but morbidity remains a serious concern [47]. Unlike healthy infants where RSV is rarely severe after the first 12 months of life, children with CHD continue to develop serious disease due to RSV through 2 years of age [47]. Accordingly, palivizumab prophylaxis is recommended for children <24 months of age with hemodynamically significant congenital heart disease. Transplant recipients are at increased risk of serious RSV disease if they are under 1 year of age or within the first posttransplant month [48]. Of note, children undergoing CPB should receive a dose of palivizumab after bypass even if it has transpired less than a month [49].

Treatment with antiviral medications have not shown proven benefit. Ribavirin has been used off-label to treat RSV infections. A systematic review of 12 randomized trials comparing ribavirin to placebo to treat RSV infection showed potential reduction in rates of respiratory decompensation, duration of mechanical ventilation, and duration of hospitalization [50]. However, these trials were insufficiently powered to provide definitive answers about its efficacy. Due to the lack of clear evidence of efficacy, routine use of ribavirin is not recommended, but some data would suggest that it is reasonable to consider its use for immunocompromised patients with severe LRTI [51].

60.3.1.2 Cytomegalovirus

CMV is less of a risk of CICU patients since the institution of leukoreduction of RBC transfusions, but it is one of the main causes of infection after solid organ transplantation. It can lead directly to disseminated infection as well as deleterious impact on allograft survival. Multiple factors contribute to the clinical course of infection, including the degree of immunosuppression [52]. Infection can be donor-derived, community-acquired, or reactivated latent infection. The highest risk occurs in patients who are CMV seronegative at the time of transplant and receive organs from CMV seropositive donors. Infection usually occurs 1–6 months after transplantation, although it may occur later if patients receive prophylaxis [52]. A combination of prophylaxis with ganciclovir and/or valganciclovir, preemptive therapy, and routine monitoring of quantitative CMV PCR of the blood help reduce the risk of CMV infection and CMV-related mortality [52].

60.3.1.3 Epstein-Barr Virus

Epstein-Barr virus (EBV) is a ubiquitous pathogen in the general population, causing a variety of illnesses such mononucleosis. In the CICU, its impact is primarily observed in recipients of heart or lung transplantation. EBV infection can manifest along a wide spectrum of diseases, ranging from nonspecific febrile illness to posttransplant lymphoproliferative disorder (PTLD). Primary EBV infection in the posttransplant period carries the highest risk of EBV-related disease [53]. This occurs frequently in younger children who are more often EBV-naïve prior to transplant. The risk of developing PTLD is highest during the first year following transplantation often associated with donor transmission. Routine monitoring of quantitative EBV loads allows for early detection and prompt initiation of therapeutic efforts. Reduction of immunosuppression remains the most effective means of prevention and treatment of PTLD [54]. Second-line therapy with the anti-CD20 monoclonal antibody, rituximab, has provided additional effective treatment for those who do not tolerate or respond to reduction of immunosuppression [55].

60.3.1.4 Influenza Virus

Children undergoing cardiac surgery during influenza season are at risk of community-associated infection prior to hospitalization or nosocomial acquisition [56]. In addition, influenza A infection of children with underlying CHD frequently leads to hospitalization. Depending on the severity of illness, these children may be managed in the CICU [57]. Universal vaccination is recommended for everyone over 6 months age. In times of vaccine shortage, attention should be paid to those at highest risk including children with heart disease. Likewise, family members and all health care workers should be vaccinated against influenza. While vaccination is critical before and after heart transplantation, recipients have a lower response rate compared to immunocompetent individuals [58]. Children with CHD or heart transplant who have been exposed to individuals with documented or presumed influenza should be given postexposure prophylaxis with oseltamivir due to high risk of serious infection.

60.3.2 Bacterial Infections

Nosocomial and community-acquired bacterial infections are a large burden of patient morbidity and mortality in the CICU. Specific bacterial infections were discussed previously, but general infection prevention principles are the foundation of protecting high-risk patients from infection. Attention to hand-washing, strict sterile technique for central line insertion, and removal of all catheters as soon as they are not medically needed are all measures which help to decrease this risk. Familiarizing yourself with your local, and if available, unit-based antibiogram will help guide decisions on empiric therapy. *Clostridium difficile* is a potential pathogen in the CICU setting as patients are often exposed to multiple antibiotics and nosocomial spread can occur. Finally, it is important to remember that CICU patients are always at risk of typical "general pediatric" infections such as neonatal sepsis/meningitis.

60.3.3 Fungal Infections

Candida species are the most frequent etiology of fungal infection in the CICU. A retrospective analysis of 1540 patients identified an incidence of invasive fungal infection

(IFI) in <1% of patients [59]. Despite the low incidence, they are associated with serious morbidity. Risk factors for invasive candidiasis include *Candida* colonization, recent major surgery, corticosteroids, parenteral nutrition, exposure to broad-spectrum antibiotics, presence of central venous catheters (CVCs), and immunosuppression [60, 61].

Guidelines recommend empiric antifungal therapy for children in the CICU is an echinocandin or liposomal amphotericin B [62]. Fluconazole is an acceptable alternative for less critically ill patients with no recent azole exposure or history of azole resistance. For persistent candidemia, CVC removal is recommended though this is often a limited option due to the frequent necessity of central access. In these cases, line salvage is a reasonable option. A prospective open label study by McGhee et al. [63] showed that line salvage can be accomplished adding antifungal locks in infected CVCs to the standard systemic therapy.

Recipients of heart and lung transplants are at higher risk of IFI. An analysis of data from a multi-institutional registry of pediatric heart transplant recipients showed the occurrence of IFI in 123 of 1854 patients [61]. These IFIs were caused by yeasts (66.2%), molds (15.8%), and *Pneumocystis jiroveci* (13%). Forty-nine percent of patients with an IFI died within the first 6 months of transplant. Additional risk of IFI was associated with pre-transplant invasive procedures (e.g., ECMO, VAD, mechanical ventilation). Transplant recipients are routinely placed on trimethoprim-sulfamethoxazole in the first few weeks posttransplant for *Pneumocystis* prophylaxis. For those patients at high risk of IFI, the use of prophylactic antifungals should be considered.

60.3.4 Parasitic Infections

Parasitic infections are infrequent causes of disease in CICU patients in the United States. *Toxoplasma gondii* can cause disease after heart transplantation particularly in a child who is seronegative prior to transplantation and receives an organ from a seropositive donor. The use of immunosuppressants to prevent graft rejection and the propensity of the organism to infect cardiac muscle confer a unique risk of infection in these patients [64]. Cases of fulminant toxoplasmosis infection have been well described in solid organ transplant (SOT) recipients [65, 66]. Pyrimethamine and sulfadiazine in combination are effective treatment for toxoplasmosis [67]. Trimethoprim-sulfamethoxazole can be used as prophylaxis [68].

Cryptosporidium is an intracellular protozon that causes gastroenteritis in humans. Immunosuppressed patients with cryptosporidiosis can present with life-threatening persistent diarrhea. Treatment is most commonly with nitazoxanide in addition to supportive care [69].

60.4 Prevention of Infections

Mortality and morbidity in the CICU can be impacted by reduction of infections using preventive strategies. Infection control measures for prevention of nosocomial spread of infections should be a priority. Intense monitoring of handwashing, sterile barriers as well as glove and gowning for procedures where soiling can occur should be done routinely. One study of a *Serratia marcescens* outbreak in a pediatric CICU found that the nosocomial infection rate most strongly correlated with patient census and the nursing hours to patient day ratio. The authors postulated that this increased CICU activity reflected a greater risk of breaks in aseptic techniques [70]. Accordingly, attention to hospital staffing can be important for infection control.

Optimizing the infant's immune system with routine immunizations can decrease the risk of infection for infants with underlying cardiac disease. Infants with associated asplenia or immune defects will particularly benefit from immunization against *S. pneumoniae* and *H. influenzae*. Palivizumab given monthly during the RSV season can decrease the risk of severe RSV disease in infants with hemodynamically significant CHD [71, 72].

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Chapter 61
Skin Protection

RoseMarie Faber and Erin L. Colvin

Abstract The skin is much more than an external barrier for the protection of internal organs. The skin's color, texture, and overall condition provide an accurate assessment of infants and children's health, illness, and internal organ dysfunction. Critically ill infants and children with acquired and congenital heart disease are at risk for loss of skin integrity because of significant risk factors such as hypotension, hypoperfusion, and poor nutrition. Compromised infants and children are at further risk of developing wounds that cannot heal without expertise. Disruptions in skin integrity increase the risk of developing complications including infection, sepsis, or even death. This chapter reviews physiology of the skin, the phases and factors of wound healing, risk assessment of skin impairment, and skin protection from hospital-acquired pressure injuries and surgical site infections. In addition, this chapter addresses how to promote skin integrity with the use of delayed sternal closure, extracorporeal membrane oxygenation, and ventricular assist devices in infants and children experiencing hemodynamic instability related to congenital heart disease, cardiovascular surgical repair, or heart failure.

61.1 Anatomy and Physiology

As one of the largest organs, the skin acts as a protective barrier, thermal regulator, and immune defense mediator. There are three layers to the skin—the *epidermis, dermis,* and *subcutaneous* tissue. The avascular epidermis is the outer layer of the skin that is comprised of multiple cell layers each with a separate function. Within the basal layer, stratified epithelium undergoes cellular division continuously [1]. Basal layer cells are formed by mitosis and pushed up to the surface by the remaining layers of the epidermis to undergo keratinization. Keratinization results in creating the outermost, waterproofed, and dead layer of the epidermis. Keratinization facilitates the shedding and rejuvenation of keratinocytes, which help to prevent colonization on the epidermis. Within the epidermis are specialized epidermal cells such as melanocytes which produce melanin, Langerhans cells which are the primary defense of the immune system, and Merkel's cells in which their function is unclear. Premature and term infants have at least 13% of their body weight comprised of skin, and premature infant's skin is immature [2]. In combination of immaturity and the necessity of being monitored within the intensive care unit, premature and term infants are at a greater risk for loss of skin integrity and mechanical or adhesive trauma; all of which attributes to an increased risk for dehydration and systemic toxicity related to increased absorption rate of transcutaneous chemicals.

The dermis is the highly vascular layer of skin which lies beneath the epidermis. "The dermis varies in thickness and contains the lymphatic vessels, hair follicles, sweat glands, blood vessels, nerves, etc." ([1], sic 339). The dermis is comprised of three types of tissue which are present throughout the body. Tissue types include collagen, elastic tissue, and reticular fibers. Fibroblasts and macrophages create collagen which provides mechanical strength and elasticity to the skin. The dermis' vasculature supports both the dermal and epidermal cells by aiding in thermal regulation and using sebaceous glands to secrete sebum which maintains skin hydration. Infants and children generate less sebum and have higher water content and a thinner dermis. Premature and term infants have less collagen which may lead to greater edema related to altered blood flow and perfusion to the epidermis [2].

Subcutaneous tissue serves as the skin's supporting layer because this layer is comprised of the same structures found

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in the dermis including the sweat glands. Subcutaneous tissue provides a cushion to skin trauma, regulates body temperature, and metabolizes energy. Infants and children are at risk for thermal instability because they have less subcutaneous tissue. Located within the subcutaneous tissue are sweat glands. Thermoregulation through sweat gland production is essential for life, and sweat removes acids and toxins from the body.

61.2 Phases of Wound Healing

Maintaining skin integrity in the intensive care environment is difficult related to highly invasive procedures, hypoperfusion, hypotension, poor nutrition, immobilization, medical devices, decreased sensory perception, and higher patient acuity. Wound healing, although difficult at times, is the process of repairing injured tissue through regeneration of the skin's tissue. Regeneration occurs by replacing similar tissue; however, subcutaneous tissue and muscle cannot be replaced, these areas heal by forming new connective or scar tissue to fill in the wound bed. The three phases of the cellular process involved in wound healing are inflammatory, proliferation, and remodeling [3].

The inflammatory phase functions to debride dead cells and bacteria from the wound bed and to initiate the healing process. Neutrophils, macrophages, and lymphocytes comprise the inflammatory cells. During the inflammatory phase, cellular activities occurring include vasoconstriction and vasodilation. During vasoconstriction, blood loss is prevented and clot formation begins. Vasodilation succeeds vasoconstriction, promoting prostaglandin and histamine release and increasing vascular permeability. Neutrophils removed damaged or dead cells and bacteria from the wound bed. Macrophages remove dying neutrophils to prevent them from prolonging the inflammatory process [3]. Lasting 4–6 days, the onset of the inflammatory phase may be delayed by a persistent decrease in cardiac output. Classic signs and symptoms of the inflammatory phase include redness, edema, skin which is warm or hot to touch, and discomfort.

Epithelization, angiogenesis, and granulation tissue are the primary components of the proliferative phase of wound healing. Epithelial cells move in a pattern to restore the normal layers of the epidermis. Angiogenesis allows for cell migration and capillary formation. The granulation phase and tissue deposition requires nutrients supplied by the capillaries. An unhealed wound occurs when there is a failure of the formation of granulation tissue. Healthy granulation tissue is bright, beefy red, and bleeds easily. Granulation tissue that is black, blackish red, or gray in color depicts hypoperfusion or infection.

The most important cellular process is the maturation or remodeling phase because of the occurrence of collagen synthesis. Collagen synthesis builds tensile strength and scar formation over 3 weeks to 2 years. Repetitive invasive procedures, hypoperfusion, hypotension, poor nutrition, immobilization, and medical devices can impede collagen synthesis. Collagen which forms in injured skin tissue is thinner, has a tensile strength of about 80%, and will never become as organized as undamaged skin [3].

61.3 Factors in Wound Healing

In critically ill infants and children with acquired and congenital heart disease, disturbances in tissue perfusion and nutrition can add to the complexity of wound healing. Tissue perfusion disturbances may include small vessel occlusion, embolus, or external compression. Cardiac insufficiency, inotropic infusions, large vessel disruptions, inadequate tissue perfusion, hemodynamic instability, and decreased circulatory volumes are classified as general tissue perfusion disturbances. Inadequate tissue perfusion leads to tissue hypoxia. In addition, incontinence-associated dermatitis caused by increased moisture adds to the risk of skin breakdown and delayed wound healing [4]. Frequent use of medical devices such as chest tubes, endotracheal tubes, mediastinal drains, nasogastric tubes, restraints, and urinary catheters in pre- and postoperative pediatric cardiovascular ICU patients places them at high risk for developing pressure injuries. Bedside nurses are in the perfect position to prevent pressure injuries from occurring, but often are faced with multiple nursing tasks and demands of the patient's acuity.

61.4 Validated Risk Assessment Tools and Promoting Skin Integrity

Because critically ill infants and children have an increased risk of skin impairments, the key to healthy, intact skin is knowledgeable healthcare providers. Promoting skin integrity by using evidence-based guidelines can facilitate positive patient outcomes. The Center for Medicaid and Medicare mandates all healthcare providers use guidelines for prevention and treatment of hospital-acquired pressure injuries or surgical site infections, which if not implemented, may lead to legal and financial implications for healthcare organizations. According to the National Guideline Clearinghouse (2016), a validated risk assessment tool in addition to noting intrinsic and extrinsic risk factors is performed on all patients upon entry to the intensive care unit and the assessment should be repeated on a regularly scheduled basis or when there is a significant change in the infant's or child's condition [5].

Tools which assess the risk of skin impairment help providers prioritize preventive and management strategies. A validated, pediatric risk assessment tool is *Quigley and Curley's Modified Braden Q Scale*. A study was conducted in a pediatric intensive care unit to analyze how the initial *Modified Braden Q Scale* scores relate to the risk of skin impairment [6]. Results of this study demonstrated the *Modified Braden Q Scale* was high in sensitivity among infants and children aged 3 weeks to 8 years if the infants and children did not have congenital heart disease. The Braden Q Scale performed moderately well on Infants and children up to 14 years of age with congenital heart disease [6]. The *modified Braden Q* has seven subscales which include mobility, activity, sensory perception, friction and shear, and tissue perfusion and oxygenation. Each of the modified Braden Q subscales are scored from one (*more risk*) to four (*less risk*). The minimum pressure ulcer risk assessment score which an infant or a child can receive is 7 and the maximum score is 28. Any total score obtained on a critically ill infant or child which is 16 or less for three consecutive days, places the infant or child at a greater risk for developing hospital-acquired pressure injuries. Preventive skin care measures must be implemented to optimize patient outcomes. The *modified Braden Q scale* is the only validated immobility-related pressure injury risk assessment tool for critically ill infants and children [7]. In addition to the *modified Braden Q*, there are two different risk assessment tools used by pediatric providers. One is the pediatric organ dysfunction score, which was created by using the 2005 international pediatric sepsis consensus definitions [8]. The second is the vasoactive inotropic score, which is used mainly in clinical research to measure the severity of the illness and to quantify the amount of cardiovascular support the patient receives [9].

Maintaining skin integrity is an ongoing process and is something providers take for granted until the skin becomes impaired. Promoting skin integrity by using established skin care guidelines can maximize patient outcomes. Diligent assessments of all skin care areas confirm the need for individualized plans of care. Infants and children should be bathed with a pH-balanced cleanser or using the healthcare's chlorhexidine bathing protocol. Chlorhexidine-based soaps and cloths reduce the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) [10]. Water, not emollients and moisturizers, lubricate the skin. Emollients and moisturizers are often used to describe the same topical solutions; however, emollients work by preventing water loss, and occluding the epidermis and moisturizers improve hydration [3]. Emollients and moisturizers should be applied only after bathing or cleansing the area of the skin with water. Bath oil should not be added until the end of the bath to enable hydration of the skin to occur first, and then, the hydration can be sealed into the skin with the bath oil.

To promote skin integrity in the pediatric cardiac intensive care unit, critical care nurses should minimize the impact of medical devices in such a way that the nurse alters pressure points regularly, pads persistent pressure areas, and frequently assesses the affected areas. Early initiation of nutritional support via enteral or parenteral feedings maximizes nutritional status and promotes wound healing. Albumin levels should be checked daily. Hypoalbuminemia and capillary leak are caused by acute and chronic inflammatory responses and contributes to interstitial edema which impedes fragile skin by expanding collagen fibers. Protein, calorie, and vitamin deficiencies have an adverse effect on wound healing. Adequate pressure reduction enhances capillary blood flow to the skin and underlying soft tissues. Routine assessment for hospital-acquired pressure injuries in neonatal and pediatric patients is necessary to track at-risk patients and initiate skin care preventive measures.

Providers may want to consider creating a unit-based, nurse-led skin care champion or skin care team which is responsible for weekly full assessment skin care rounds on every patient and assists bedside nurses in prioritizing pressure-related injury prevention in the pediatric cardiovascular ICU. Research supports the use of trained skin care teams or bedside critical care nurses as skin care champions to facilitate teamwork, improve reliability, and support consistent use of preventive skin care measures. Team members may be advanced practice nurses and/or bedside nurses. Some pediatric ICU skin care teams incorporate the hospital's certified Wound, Ostomy, Continence Nurse (WOCN) into the unit-based rounds. Implementing a unit-based skin care team allows bedside nurses to have a specialized and knowledgeable team to assist with full-body skin assessments, pressure-related injury prevention plans, and can make recommendations for treatment strategies should a pressure-related injury occur instead of waiting an indefinite amount of time depending on the WOCN's existing schedule to develop a treatment plan for the damaged skin [11].

61.5 Prevention of Hospital-Acquired Pressure Injuries

The development of hospital-acquired pressure injuries is a multifaceted process that, at times even with the best evidence-based preventive strategies, may not be avoided. In April 2016, the National Pressure Ulcer Advisory Panel (NPUAP) revised the terminology from pressure ulcer to pressure injury to describe pressure injuries as they relate to intact and ulcerated skin [12]. In addition to the terminology change [13], NPUAP updated the stages of pressure injuries to accurately reflect intact and ulcerated skin. In 2014, NPUAP convened to achieve consensus on intrinsic and

extrinsic risk factors associated with unavoidable pressure injury [14]. Goals of nursing care for pediatric cardiovascular ICU patients are to identify intrinsic and extrinsic risk factors to prevent the formation of a pressure-related injury. Every effort should be made to modify the risk factors; however, many risk factors of hospital-acquired pressure injuries remain nonmodifiable related to current medical and surgical treatments. Examples of nonmodifiable risk factors in the pediatric cardiovascular ICU patient include (1) administration of vasopressors which may decrease tissue perfusion; (2) treatment with extracorporeal membrane oxygenation due to low cardiac output; (3) intolerance to repositioning due to hemodynamic instability; (4) anasarca; and (5) use of medical devices [15].

The Wound, Ostomy, and Continence Nurses Society (WOCN) updated the clinical practice guideline for prevention and management of pressure injuries in 2016. The goal of the 53 different recommendations for prevention of pressure injuries is to support clinical nursing practice by developing consistent research-driven information, improve patient safety, and improve cost-effective patient outcomes [5]. Assessment, prevention, and treatment strategies are the foci of these recommendations. Risk assessment using a validated tool should be performed within 24 h of being admitted to the pediatric cardiovascular ICU, repeated at regular scheduled intervals or when there is a significant change to the patient's condition [7]. Electronic health records can be built to include the risk assessment tool. A few assessment recommendations are provided to examine intrinsic and extrinsic risk factors, inspect the skin regularly, implement early progressive mobility as soon as possible, and evaluate nutritional status. Preventive recommendations include using care strategies to minimize or reduce pressure, friction, and shear, maintain the head-of-bed elevation at or below 30°, reposition at a minimum of every 2 h, and consider prophylactic dressings to prevent pressure point ulcerations. Treatment strategy recommendations include using support surfaces such as gel cushions, multilayered foam dressings [16], mattress overlays, and integrated bed systems, elevate heels off the bed surface, provide adequate nutrition, cleanse the wound at each dressing change, and use systemic antibiotics if bacteremia, sepsis, or advancing cellulitis is present [5].

61.6 Surgical Site (Sternal Wound) Infections

Surgical site infections (SSI) contribute to 31% of all healthcare-associated infections (HAI). Following pediatric cardiothoracic surgery, the incidence of sternal wound infections is between 0.25% and 6% [17]. Associated with SSIs are mortality rates between 7% and 20%, an increase in healthcare costs and length of stay, and possible penalties or nonpayment of hospital stay for infants and children diagnosed with a HAI. With the addition of the complex physiology of congenital heart disease and the potential adverse effects associated with cardiopulmonary bypass, risk assessment and preventive measures for SSIs may be difficult. In 2017, a single-center, pediatric cardiac ICU completed a retrospective, matched case-control study, which demonstrated an association with SSIs related to potentially altered antimicrobial prophylaxis due to an increase in postoperative fluid overload and thoracostomy output and intravenous fluid boluses [17]. "Providers may consider modification of antimicrobial prophylaxis dosing or alterations in fluid management and diuresis in response to assessment of peak fluid overload and fluid volume shifts in the immediate postoperative period" ([17], sic 771).

In 2017, the U.S. Department of Health and Human Services' Centers for Disease Control (CDC) and Prevention (www.cdc.gov) updated their prevention guidelines for surgical site infections. The CDC recommends healthcare providers receive infection control training, demonstrate competency, and implement institution-specific policies and procedures [18]. To improve surgical care, hospital infection control programs should:

- Address appropriate prophylactic antibiotic use [18].
- Perform routine audits to monitor and document adherence to the infection control program to improve surgical care [18].
- Provide feedback to providers regarding his or her compliance of the policy [18].
- Perform audits on compliance to recommended infection control practices for SSI prevention [18].
- Provide feedback to providers regarding surgical infection control procedures [18].
- Monitor SSI data and use the data to guide direct prevention activities [18].
- Provide feedback on the SSI data to surgeons, cardiovascular ICU advanced practice nurses and bedside nurses, and surgical personnel [18].

Negative-pressure wound therapy (NPWT) may be considered as a current therapy for sternal wound management by promoting wound healing through a sustained negative pressure within the wound bed. Generally, the negative pressure is set from −5 to −125 mm Hg. Despite three common potentially life-threatening complications—bleeding, infection, and retained dressing material—being reported in 2009 to the Federal Drug Administration's medical device reporting system, a comprehensive assessment and analysis were completed shortly after the reports by the Emergency Care Research Institute (ECRI). ECRI determined that NPWT is a

safe alternative to traditional wound healing treatment strategies. Without any large-scale controlled trials, no direct causative connection has been associated with NPWT and these serious complications [14].

NPWT may be used for both acute and chronic wounds such as pressure injuries, surgical wounds, and deep sternal wounds. To determine whether NPWT is the treatment of choice for any wound bed, assessment of the patient and wound and wound preparation is necessary. Assessment of the patient and wound along with the bedside nurse or advanced practice nurse's expertise and judgment should determine if NPWT is appropriate treatment strategy for wound healing [14]. Preparation of the wound bed includes mechanical debridement of the deep sternal wound by the surgeon, advanced practice nurse or trained bedside nurse in order to promote accurate wound assessment and healing, and decrease the possibility of infection.

Comprehensive orders written by the prescriptive advanced practice nurse or surgeon for NPWT should include specifications of the wound in relation to size and location; intermittent or continuous pressure setting; interval of the dressing change; materials for dressing change; cleansing instructions for the wound including exact solution to use for irrigations; any pain or sedatives need for dressing changes; and clinical signs and symptoms to notify physician and/or skin care team/wound specialists [14]. Bedside nurses should perform ongoing assessments to ensure little to no complications occur during the NPWT.

Strategies for bedside nurses to use to promote patient safety while patient is using NPWT include adhering to manufacturer's usage guidelines; preparing wound bed appropriately, especially removing any infected or necrotic tissue; complete medication reconciliation before initiation of NPWT giving careful attention to the use of anticoagulants; if patient is using anticoagulants, monitor therapeutic dosage parameters and laboratory tests; place dressing material loosely into the wound to prevent in growth of tissue or bleeding; and identify and inform physicians for signs and symptoms of infection [14].

61.7 Special Populations at Risk: Delayed Sternal Closure

There are limited number of publications which address the use of open sternotomy and delayed sternal closure (DSC) to facilitate postoperative recovery in the pediatric cardiovascular ICU following surgery and preventive skin care regimens for the infant or child with DSC. Closing the median sternotomy is the last surgical step following palliative or reparative cardiac surgery. However, infants and children may experience hemodynamic instability once the open sternotomy is closed. Heart surgery may lead to pericardial and pericardiomediastinal edema [19]. Decreased cardiac output and elevated pulmonary venous pressure related to decrease in ventricular filling and compliance may occur when the heart is compressed by sternal closure. Continual cardiac compression may cause a progressively low cardiac output which leads to hemodynamic compromise and instability. The cardiothoracic surgeon may elect to leave the sternum open and use DSC after complex congenital heart disease repairs, intracardiac placement of cannulas for extracorporeal membrane oxygenation (ECMO) or ventricular assist devices (VAD), and emergently reopening the chest in the pediatric cardiovascular ICU.

Once the decision is made to leave the sternotomy opened, the choice of sterile dressing used is based on the surgeon's preference. Diligent nursing care of infants and children postcardiovascular surgery is essential to reduce morbidity and improve patient outcomes. Pediatric critical care nurses caring for an infant or child with DSC should constantly assess hemodynamic parameters, markers of cardiac output, and patient's response to inotropic infusions [19]. Preventive pressure-related injury interventions include ongoing shift assessments with a validated skin risk assessment tool, use of pressure-relieving dressings or devices, repositioning the infant or child every 2 h, and notifying medical team of changes in the skin (temperature, color, texture) associated with pressure-related injury development. Bedside clinicians should perform eye care by seeking an order for a preventive lubricant to prevent corneal abrasions. The nurse may need to tape the eyelid in a closed position or cover the eye with a gauze pad especially if the postoperative infant or child is receiving paralytic medications.

61.8 Special Populations at Risk: Extracorporeal Membrane Oxygenation (ECMO)

No research exists to specifically support the effectiveness of reducing hospital-acquired pressure injuries (HAPIs) by using bundle methodology in infants and children receiving extracorporeal membrane oxygenation (ECMO) [20]. Infants and children on ECMO often are not repositioned every 2 h for various reasons which creates challenges in preventing the development of pressure injuries [21]. Trepidation of healthcare providers to reposition ECMO patients has been documented in the literature. Reasons cited for critical care nurses' hesitancy and/or fear to reposition ECMO patients are potential for decannulation, hemodynamic instability, lack of staff available to assist with repositioning, the infant or child's size in comparison to the ECMO cannulas and

medical equipment, and the child's pain level [20]. Pressure injuries may also develop due to the secured position of the ECMO cannulas directly to the skin. Three foci in two research studies came to the forefront which supports the proven strategies within HAPU prevention bundles. The foci for an increased risk of developing pressure injuries in critically ill infants and children include prevention of HAPIs, association with medical devices, and ECMO therapy [20]. Strategies associated with significant reductions in the development of HAPIs are head-of-bed elevation (<30°); maximizing nutritional support; the use of specialty beds or mattresses, dry-weave diapers, disposable pads, blanket rolls, draw sheets, and pillows; and repositioning the patient at least every 2 h. "The HAPI prevention bundle includes these five elements: (1) ensuring patients were on the correct support surface to decrease tissue interface pressure; (2) frequent patient turning; (3) providing appropriate nutritional management; (4) incontinence management; and (5) education of the nursing staff" ([20], sic 3).

61.9 Special Populations at Risk: Ventricular Assist Devices (VAD)

Ventricular assist devices (VADs) are used in patients with severe end-stage heart failure as a bridge to transplant or recovery. The incidence of infection has been shown to be around 35% in the pediatric population. The incidence of infection across pediatric and adult population of those requiring VADs has been shown to be anywhere from 19% to 60%. Infection decreases the overall chance for patient survival. If a patient has an overt clinical infection, transplant is not possible until the infection is clear. These infections include but are not limited to blood, urine, and VAD driveline infections. In order to decrease VAD infections close attention to infection control and meticulous surgical site care are imperative [22].

Initially, VAD driveline site dressings are changed every 24 h. Once the drainage decreases from the sites, then the dressing change frequency is decreased. The goal is to change the dressing once a week. The dressing is also changed when its integrity is compromised. This is indicated if more than a quarter size of drainage is noted on the dressing. Also, if the patient develops fever, the dressing must be changed to assess the site. If purulent drainage is noted, then a surface culture of the drainage is sent.

A nonadherent type occlusive dressing is applied using sterile technique. The person performing the procedure must wear a sterile gown, gloves as well as mask, and a surgical cap. Any person present in the room during a dressing change should wear a surgical cap and mask. The old dressing is removed using sterile gloves and a new pair of gloves should be worn to finish the dressing (see Fig. 61.1 for exposed driveline sites for cleaning). The driveline sites are cleansed with a 1/2 saline and 1% chlorhexidine solution (see Fig. 61.2 for cleansing of drivelines). They are rinsed with saline solution and thoroughly dried with sterile gauze prior to applying the dressing ensuring that all residue is removed (see Fig. 61.3 for drying drivelines). If purulent drainage is present, a calcium/sodium alginate dressing is wrapped around the driveline site prior to applying the above-noted dressing (see Figs. 61.4 and 61.5 for applying a sterile Telfa island dressing under and on top of the driveline to create an occlusive dressing). An immobilization binder should be applied over the dressing. This should be worn at all times to help ensure maturation of the exit sites.

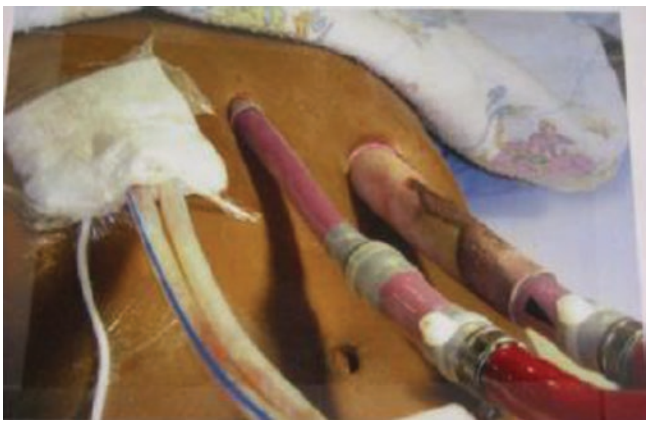

Fig. 61.1 Exposed drivelines for cleaning

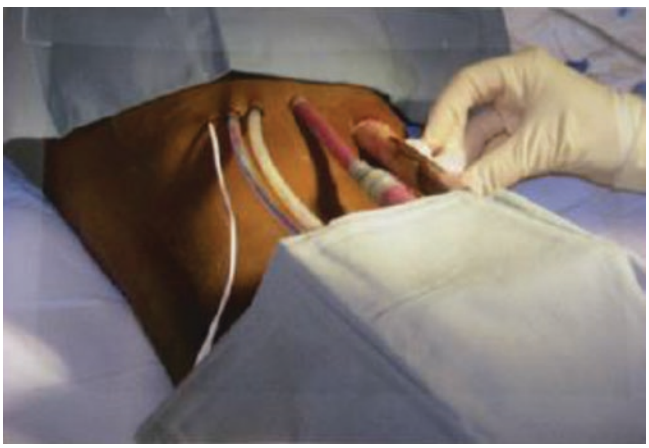

Fig. 61.2 Cleansing of drivelines

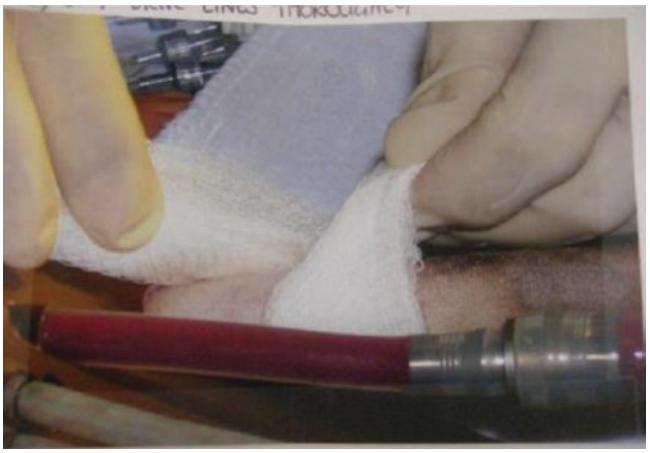

Fig. 61.3 Drying the drivelines

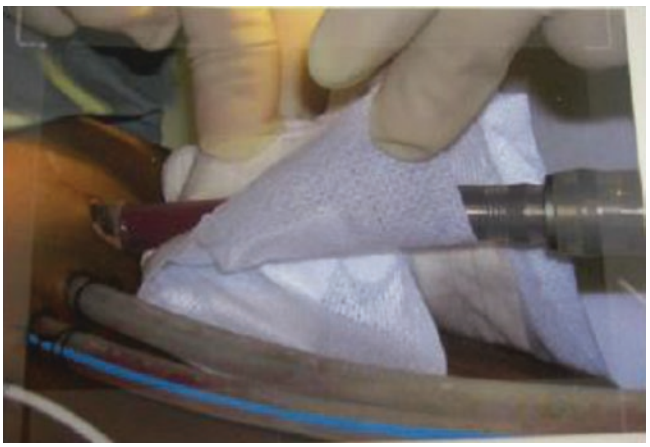

Fig. 61.4 Applying a sterile Telfa Island Dressing under the driveline

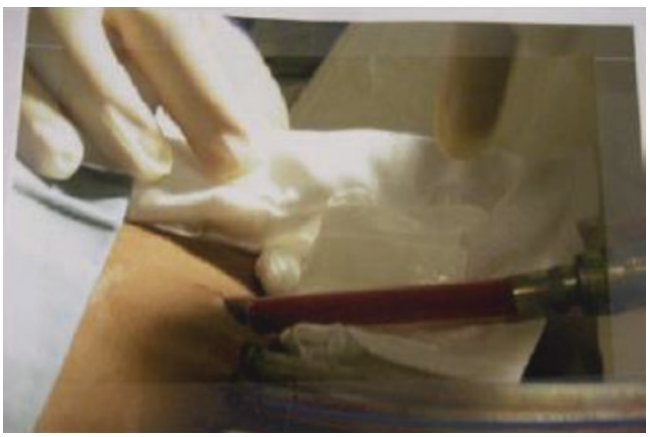

Fig. 61.5 Applying a sterile Telfa Island Dressing on top of the driveline

Strict adherence to sterile technique and monitoring for infectious complications will decrease the mortality and morbidity of children and adults with VADs [23].

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Chapter 62
Cardiac Intensive Care Medication Guide

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Abstract This chapter provides a guide to commonly prescribed medications in a pediatric cardiac intensive care unit. The list is not intended to be all-inclusive, and one should use clinical judgment and consult additional references for validation and additional information.

Abbreviations

CI	Continuous infusion
conc.	Concentration
E	Evaluate for dosing adjustment in renal impairment
F	Consult additional references for complete dosing guidelines
LD	Loading dose
MD	Maintenance dose
PE	Phenytoin equivalent

62.1 Analgesics/Sedatives [1–4]

Acetaminophen 10–15 mg/kg/dose PO/PR q 4–6 h PRN (max 4 g/day)

Chloral hydrate 8–25 mg/kg/dose PO q 4–6 h PRN (max 1 g/dose) – procedural (60 min prior): 25–75 mg/kg/dose; may repeat 30 min after initial dose (total max dose: 120 mg/kg or 1 g infant, 2 g total for child/adult)

Dexmedetomidine CI 0.2–1 mcg/kg/h

Diphenhydramine 1 mg/kg/dose IV q 6 h PRN (max 50 mg/dose)

Etomidate 0.2–0.6 mg/kg/dose IV over 1 min (0.3 mg/kg/dose)

Fentanyl 1–2 mcg/kg/dose IV q 1–2 h PRN; *CI*: initial dose 1 mcg/kg/h (*E*)

Haloperidol 0.02–0.04 mg/kg/day IV ÷ 2–4 doses (max 0.15 mg/kg/day or 2 mg/dose)

Hydromorphone 0.015 mg/kg/dose IV q 4–6 h PRN (max 0.2–0.6 mg/dose); *CI:* initial dose 0.003–0.005 mg/kg/h

Ibuprofen 5–10 mg/kg/dose PO q 6–8 h PRN (max 3.2 g/day) (*E*)

Ketamine IV 0.5–1 mg/kg/dose; 3–7 mg/kg *IM* ×1; *CI*: 5–20 mcg/kg/min

Ketorolac (Toradol) 0.5 mg/kg/dose (max 30 mg) IV q 6 h × 2–5 days

Lorazepam 0.02–0.1 mg/kg/dose IV/PO q 4–6 h PRN (max 2 mg/dose)

Methadone 0.05–0.1 mg/kg/dose IV/PO q 6 h (*F*) (*E*)

Midazolam 0.025–0.2 mg/kg/dose IV q 1–2 h PRN; *CI*: 0.05–0.1 mg/kg/h (neonates: 0.01–0.06 mg/kg/h)

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Morphine 0.02–0.1 mg/kg/dose (max 5 mg/dose) IV q 1–2 h PRN; *CI*: initial dose 0.02–0.04 mg/kg/h (neonates 0.01 mg/kg/h) (*E*)

Propofol 1 mg/kg/bolus; titrate 25–100 mcg/kg/min (*F*)

62.2 Anticonvulsants [1–4]

Diazepam >1 month/children 0.05–0.3 mg/kg/dose IV over 3–5 min, q 15–30 min (max total dose: <5 years 5 mg, ≥5 years 10 mg)

Fosphenytoin Children (all ages) and adults *LD*: 15–20 mg *PE*/kg/dose IV/IM; *MD:* 4–6 mg *PE*/kg/day IV/IM ÷ q 8–12 h

Lorazepam 0.05–0.1 mg/kg/dose IV over 2–5 min; may repeat 0.05 mg/kg ×1 in 10–15 min (max 2 mg/dose)

Phenobarbital (PO/IV) *LD*: 15–20 mg/kg/dose; *MD*: neonates 3–5 mg/kg/day ÷ q 12–24 h; infant 5–6 mg/kg/day ÷ q 12–24 h; child 1–5 years 6–8 mg/kg/day ÷ q 12–24 h; child 5–12 years 4–6 mg/kg/day ÷ q 12–24 h; >12 years/adults 1–3 mg/kg/day ÷ q 12–24 h

62.3 Antibiotics [1–4]

Acyclovir 15–60 mg/kg/day IV ÷ q 8 h (*F*) (*E*)

Amoxicillin (Asplenia) 20 mg/kg/day ÷ q 12 h (max 250 mg/dose)

Amphotericin B (test dose) 0.1 mg/kg/dose (max 1 mg) followed by *MD*: 0.5–1 mg/kg/day IV once daily (max 1.5 mg/kg/day)

Amphotericin B liposomal (AmBisome) 3 mg/kg/day IV once daily

Ampicillin *Postnatal age ≤7 days* 75 mg/kg/dose IV q 8 h; *postnatal age >7 days* 75 mg/kg/dose IV q 6 h; (*F*) (*E*)*;* infant/child 100–200 mg/kg/day IV ÷ q 6 h (max 12 g/day); meningitis 200–400 mg/kg/day IV ÷ q 6 h (*E*)

Ampicillin/sulbactam 100–200 mg/kg/day as ampicillin IV ÷ q 6 h (max 8 g/day)

Cefazolin *Postmenstrual age 37–44 weeks*, *≤7 days* 25 mg/kg/dose IV q 12 h; *>7 days* 25 mg/kg/dose IV q 8 h (*F*)*; infant/child*: 50–100 mg/kg/day IV ÷ q 8 h (max 6 g/day) (*E*)

Cefepime <1 month 30 mg/kg/dose IV q 12 h; ≥1 month 50 mg/kg/dose IV q 8–12 h (max 4 g/day) (*E*)

Cefotaxime <7 days 100–150 mg/kg/day IV ÷ q 8–12 h; infant: 150 mg/kg/day IV ÷ q 6–8 h (max 12 g/day); meningitis 300 mg/kg/day (*F*) (*E*)

Ceftazidime *Neonate >2 kg ≤7 days* 50 mg/kg/dose IV q 12 h; *>7 days* 50 mg/kg/dose IV q 8 h (*F*)*; infant/child:* 150 mg/kg/day IV ÷ q 8 h (max 6 g/day) (*E*)

Ceftriaxone ≥44 weeks postmenstrual age (non-CNS infection) 50 mg/kg/day IV once daily (max 2 g/day); (CNS infection) 100 mg/kg/day IV ÷ q 12–24 h (max 2 grams/dose, 4 g/day)

Ciprofloxacin *Neonates:* 10 mg/kg/dose IV q 12 h; *children:* 15 mg/kg/dose (max 400 mg) IV q 12 h (*E*)

Clindamycin *Postmenstrual age 37–44 weeks, <7 days* 5–7.5 mg/kg/dose IV q 12 h; *>7 days* 5–7.5 mg/kg/dose IV q 8 h (*F*); *infant/child*: 25–40 mg/kg/day IV ÷ q 6–8 h (max 4.8 g/day)

Erythromycin 15–20 mg/kg/day IV ÷ q 6 h (max 4 g/day)

Fluconazole PO/IV ≤7 days 12 mg/kg/dose q 48 h; >7 days 12 mg/kg/dose q 24 h; infants and children 3–12 mg/kg/day q 24 h (max 800 mg/day) (*E*) (*F*)

Gentamicin *Neonate*: *postmenstrual age ≥35 weeks:* 4 mg/kg/dose IV q 24 h; >1 month to <18 years: 2.5 mg/kg/dose IV q 8 h; *adult:* 3–6 mg/kg/day IV ÷ q 8 h (*E*)

IVIG Kawasaki: 2 g/kg IV over 12 h; Myocarditis: 2 g/kg IV over 24 h; *Immunodeficiency*: 400 mg/kg/dose q 4 weeks)

CMV-IVIG 150 mg/kg IV

Meropenem 20 mg/kg/dose IV q 8 h; meningitis: 40 mg/kg/dose IV q 8 h (max 2 g IV q 8 h) (*E*)

Metronidazole 30 mg/kg/day IV/PO ÷ q 6 h (max child 2 g/day, adult 4 g/day)

Oxacillin 150–200 mg/kg/day IV ÷ q 4–6 h (max 12 g/day)

Penicillin VK (Asplenia) <5 years 125 mg PO q 12 h; >5 years 250 mg PO q 12 h

Piperacillin/tazobactam (Zosyn) *Neonate*: *postmenstrual age 37–44 weeks; ≤7 days* 50–100 mg/kg/dose IV q 12 h; *>7 days* 50–100 mg/kg/dose IV q 8 h (*F*); infants, children, and adolescents 300 mg/kg/day ÷ q 6–8 h (max 12 g/day) (*E*)

Tobramycin *Neonate*: *postmenstrual age ≥35 weeks* 4 mg/kg/dose IV q 24 h; (*F*); *>1 month* to *<18 years*: 2.5 mg/kg/dose IV q 8 h; *adult* 3–6 mg/kg/day IV ÷ q 8 h (*E*)

Vancomycin *Postmenstrual age 37–44 weeks ≤7 days* 10 mg/kg IV q 12 h; meningitis: 15 mg/kg IV q 12 h; *>7 days* 10 mg/kg IV q 8 h; meningitis 15 mg/kg IV q 8 h; *>1 month* to *12 years* 15 mg/kg/dose (max 1500 mg) IV q 6 h; *>12 years* 15 mg/kg/dose (max 1500 mg) IV q 8 h (*F*)(*E*)

62.4 Antiarrhythmic Agents [1–4]

Adenosine 0.1 mg/kg RAPID IV (max first dose 6 mg); *if* not effective, repeat with 0.2 mg/kg IV (max second dose 12 mg)

Amiodarone *IV LD:* 5 mg/kg/dose over 20–60 min; *MD* as *CI:* 5–15 mcg/kg/min; *PO LD*: 10–20 mg/kg/day ÷ 2 doses × 4–14 days (*F*); *PO MD:* 2.5–5 mg/kg/day once daily; adult *IV LD:* 150 mg over 10 min, 360 mg over 6 h, 540 mg over 18 h, then *MD as CI:* 0.5 mg/min

Atenolol Children 1–2 mg/kg/dose PO daily; adult 50–100 mg/dose PO once daily (*E*)

Diltiazem *LD*: 0.25 mg/kg IV over 2 min; *MD as CI*: 0.05–0.15 mg/kg/h; adult *MD as CI*: 5–15 mg/h

Esmolol *LD*: 100–500 mcg/kg over 1 min, then *CI:* 200–500 mcg/kg/min (max 1000 mcg/kg/min)

Lidocaine *LD*: 1 mg/kg IV ×1; *CI:* 20–50 mcg/kg/min; adult *CI:* 1–4 mg/min

Mexiletine 1.4–5 mg/kg/dose (adult 200–300 mg) PO q 8 h (max 1.2 g/day) (*E*)

Procainamide *IV:* Children: *LD:* 15 mg/kg/dose over 30 min, not to exceed 500 mg/30 min; *MD* as *CI*: 20–80 mcg/kg/min (max 2 g/day); adults: *LD*: 15 mg/kg/dose over 30 min (max dose 1–1.5 g); *MD as CI*: 1–6 mg/min (*E*)

Propranolol (*IV differs PO*) *neonate*: 0.25 mg/kg/dose *PO* q 6–8 h (max 5 mg/kg/day); 0.01 mg/kg slow *IV* (max 0.15 mg/kg/dose q 6–8 h); *child*: 0.5–4 mg/kg/day *PO* ÷ q 6–8 h (max 16 mg/kg/day *or* 240 mg/day); 0.01–0.1 mg/kg slow *IV* over 10 min (max 1 mg/infant; 3 mg/child); *adult*: 10–20 mg/dose *PO* q 6–8 h*;* 1 mg/dose slow *IV*, repeat every 5 min up to a total of 5 mg

Sotalol 30–50 mg/m^2/dose PO TID (max 240 mg/m^2/day) (*E*) (*F*)

62.5 Antihypertensive Agents [1–4]

Amlodipine Infants and children <50 kg: 0.05–0.1 mg/kg/dose PO once or twice daily (max 20 mg/day); adults: 2.5–10 mg/day PO (max 10 mg/day)

Captopril Neonate: 0.05–0.1 mg/kg/dose PO q 8–24 h; infant/child: 0.1–0.5 mg/kg/dose PO q 8 h (max 6 mg/kg/day or 150 mg/day); older child/adult: 6.25–25 mg/dose PO BID/TID (*F*) (*E*)

Enalapril Infant/child 0.1 mg/kg/*day PO* ÷ q 12–24 h; adult 2.5–5 mg/*day PO* ÷ q 12–24 h; as *enalaprilat* infant/child 5–10 mcg/kg/*dose IV* q 8–24 h; adult: 0.625–1.25 mg/*dose IV* q 6 h

Esmolol 500 mcg/kg IV ×1 over 1 min, then 50–250 mcg/kg/min IV as a *CI*

Hydralazine 0.1–0.2 mg/kg/dose IV q 4–6 h (max 20 mg/dose)

Labetalol 0.25–1 mg/kg/dose IV q 4–6 h (max 20 mg/dose); *CI:* 0.25–1.5 mg/kg/h; adult dose: 20 mg IV initially, then 40–80 mg IV every 10 min up to 300 mg total dose

Nicardipine *CI*: 0.5–5 mcg/kg/min; adults 5–15 mg/h

Sildenafil Initial 0.25–0.5 mg/kg/dose PO q 6–8 h; may increase up to 1 mg/kg/dose PO q 6 h; usual max dose 20 mg PO q 8 h

62.6 Anti-inflammatory Agents [1–4]

Dexamethasone (Airway edema/extubation) 0.5–2 mg/kg/day PO/IV ÷ q 6 h ∗begin 24 h prior to extubation, continue 4–6 doses after (*F*)

Hydrocortisone (*stress dose*) *LD:* 50 mg/m^2 IV ×1; *MD:* 50 mg/m^2/day as a *CI* or IV ÷ q 3–6 h

Methylprednisolone *LD:* 2 mg/kg/dose IV; *MD*: 0.5–1 mg/kg/dose IV q 6 h

62.7 Cardiac Transplant Medications [1–4]

Cotrimoxazole (*PCP prophylaxis*) 5 mg/kg/dose (based on TMP) PO Q MWF (max 160 mg TMP per dose) (*E*)

Epoetin Alfa 50–150 units/kg/dose IV/SC 3 times/week

Ganciclovir Initial 10 mg/kg/day IV ÷ q 12 h x 14 days; *MD*: 5 mg/kg/day IV once daily (*E*)

Methylprednisolone IV: (induction) 15 mg/kg ×1 in OR, then 2 mg/kg on day 1 (up to 60 mg), 1.5 mg/kg on day 2, 1 mg/kg on day 3 (up to 30 mg), 0.5 mg/kg on day 4, and 0.25 mg/kg on day 5, given 1 h prior to thymoglobulin dose on each day. (acute rejection) 10–15 mg/kg/day IV once daily × 3–5 days (max 1 g/day)

Mycophenolate Mofetil 30–40 mg/kg/day PO ÷ q 12 h (max 2 g/day)

Tacrolimus Initial dose 0.2 mg/kg/day PO ÷ BID (max 4 mg PO BID)

Thymoglobulin (induction) 1.5 mg/kg/dose IV over 6–12 h every 24 h X 5 days; pretreat with acetaminophen 10 mg/kg PO; methylprednisolone IV (see above); diphenhydramine 1 mg/kg IV about 30–60 min prior to thymoglobulin (acute rejection) 1.5 mg/kg/dose IV over 6–12 h

62.8 Diuretics [1–4]

Acetazolamide 5 mg/kg/dose (max 250 mg/dose) IV q 6–12 h

Aminophylline Neonate to 1-year-old 1.5 mg/kg IV q 6 h; 1 year to 16 years 2.5 mg/kg IV q 6 h

Bumetanide 0.015–0.1 mg/kg/dose IV q 6–24 h (max 10 mg/day); *CI* 0.005–0.02 mg/kg/h (max 1 mg/h)

Chlorothiazide 20–40 mg/kg/day PO ÷ q 12 h; 5–20 mg/kg/day IV ÷ q 12 h; adults IV 250–1000 mg/dose 1–2 times daily (max 2 g/day)

Ethacrynic acid 0.5–1 mg/kg/dose IV q 8–12 h (max 50 mg/dose); 1 mg/kg/dose PO every 24–48 h (max 50 mg dose initially)

Fenoldopam *CI*: 0.2–0.8 mcg/kg/min

Furosemide 1–2 mg/kg/dose IV/PO q 6–12 h (max PO 6 mg/kg/day); adults 20–80 mg/dose IV/PO q 6–12 h; *CI*: initial 0.05 mg/kg/h (max 0.4 mg/kg/h)

Metolazone 0.2–0.4 mg/kg/day PO ÷ q 12–24 h; adults 2.5–5 mg/day PO once daily (max 20 mg/day)

Mannitol Initial 0.5–1 g/kg/dose IV; maintenance 0.25–0.5 g/kg IV q 4–6 h

Spironolactone 1.5–3.5 mg/kg/day (max 200 mg) PO ÷ q 12–24 h (*E*)

Torsemide 0.25–1 mg/kg/dose IV/PO once daily (extrapolated from adult dosing) adult: 5–20 mg IV/PO once daily initially up to 200 mg max

62.9 Electrolyte Replacement [1–4]

Acetate (sodium or potassium) *initial:* add 1 mEq/kg to daily TPN

Calcium chloride 10–20 mg/kg/dose IV, repeat q 4–6 h PRN (max 1 g/dose)

Calcium gluconate 50–100 mg/kg/dose IV ×1 (max 2 g/dose)

Magnesium sulfate 0.2–0.4 mEq/kg/dose IV (max 16 mEq/dose)

Potassium chloride 0.2–0.5 mEq/kg/dose at 1 mEq/kg/h IV (max 40 mEq/h); adults 10–20 mEq/h IV, not to exceed 40 mEq/h and 150 mEq/day

Phosphate (sodium or potassium) 0.15–0.5 mMol/kg/dose IV over 4–6 h; adults 0.15–0.3 mMol/kg/dose IV over 12 h

Sodium bicarbonate 1 mEq/kg/dose IV (use 0.5 mEq/ml conc. if <1-year-old)

62.10 Emergency Medications [1–4]

Adenosine 0.1 mg/kg RAPID IV/IO (max first dose 6 mg); if no effects, repeat with 0.2 mg/kg IV (max second dose 12 mg)

Amiodarone Infants and children: 5 mg/kg/dose IV/IO rapid IV bolus; adults: 300 mg IV rapid IV push, 150 mg IV for subsequent doses

Atropine 0.02 mg/kg/dose IV (may repeat once in 3–5 min) (max single dose 0.5 mg) (total dose 1 mg; adults 3 mg)

Calcium chloride 10–20 mg/kg slow IV push (max 1 g/dose)

Calcium gluconate 50–100 mg/kg slow IV push (max 2 g/dose)

Dantrolene Initial: 2.5 mg/kg IV, may repeat up to four times; then 1 mg/kg IV q 6 h

Dextrose Neonate 0.1–0.2 g/kg/dose; >1 month to <6 month; 0.25–0.5 g/kg/dose; >6 month 0.5–1 g/kg/dose (max 25 g/dose); adults 10–25 g

Epinephrine 0.01 mg/kg IV (max 1 mg/dose) q 3–5 min; endotracheal 0.1 mg/kg

Lidocaine 0.5–1 mg/kg IV ×1; CI: 20–50 mcg/kg/min (adult 1–4 mg/min)

Sodium bicarbonate 1 mEq/kg/dose IV (use 0.5 mEq/ml conc. if <1-year-old)

Vasopressin *Adult*: *for asystole or pulseless VT/VF*: 40 units IV/IO X 1 dose only

For SVT/VT with pulse 0.5 Joules/kg synchronized ×1, then
1 Joule/kg synchronized ×1

V-fib/pulseless V-tach 2 Joules/kg ×1, 4 Joules/kg ×2; adults: 200 J, 300 J, 360 J

62.11 Neuromuscular Blocking Agents [1–4]

Cisatracurium 0.1 mg/kg IV ×1, then *CI*: 0.1–0.3 mg/kg/h

Rocuronium 0.6–1.2 mg/kg/dose IV ×1; *CI:* 10–12 mcg/kg/min; may be given IM: infants 1 mg/kg; children 1.8 mg/kg

Vecuronium 0.1 mg/kg/dose IV; CI*:* 0.1 mg/kg/h

Sugammadex (Routine reversal rocuronium-induced moderate blockade) 2 mg/kg single dose

62.12 Reversal Agents [1–4]

Flumazenil (Reverse benzodiazepines) 0.01 mg/kg/dose IV (max 0.2 mg/dose)

Naloxone (Reverse post-op narcotics) 0.01 mg/kg/dose, repeat q 2–3 min PRN (opiate intoxication) 0.1 mg/kg/dose repeat q 2–3 min PRN (max 2 mg/dose)

Neostigmine (Reverse nondepolarizing neuromuscular blocking agents) infant, 0.025–0.1 mg/kg/dose; children, 0.025–0.08 mg/kg/dose (max 2 mg/dose); adult, 0.5–2.5 mg (total dose 5 mg)∗∗Premedicate with atropine 0.02 mg/kg/dose or give glycopyrrolate 0.2 mg for each 1 mg neostigmine given.

62.13 Gastrointestinal Agents [1–4]

Famotidine IV: <12 months: 0.5 mg/kg/dose q 24 h; ≥12 months: 0.5 mg/kg/dose IV q 12 h; adult 20 mg/dose IV q 12 h (*E*)

Lansoprazole <15 years 0.5–1.6 mg/kg PO once daily; adults 30 mg PO once daily

Metoclopramide 0.1–0.2 mg/kg/dose q 6–8 h IV/PO (max 40 mg/day) (E)

Octreotide Chylothorax initial: 1 mcg/kg IV, then CI: 1–4 mcg/kg/h (titrate); can also give SQ 10–40 mcg/kg/day divided q 8 h

Ondansetron >2 years, <40 kg: 0.1 mg/kg/dose IV; >40 kg 4 mg/dose IV

Pantoprazole 0.5–1 mg/kg/dose IV daily; adults 40 mg IV once daily

Sodium polystyrene sulfonate 1 g/kg/dose PO/PR q 6 h; adults 15 g PO q 6 h; 30 g PR q 6 h

Sucralfate 40–80 mg/kg/day PO ÷ q 6 h; adults 1 g PO q 6 h

Ursodiol 10–30 mg/kg/day PO divided in two to three doses; adults 13–15 mg/kg/day PO divided in four doses (*F*)

62.14 Hematologic Agents [1–4]

Alteplase (t-PA) Venous thrombosis: initial: 0.03 mg/kg/h (0.06 mg/kg/h in neonates) (*F*)

Aminocaproic acid *LD:* 100 mg/kg (max 5000 mg); *MD*: 100 mg/kg/dose PO/IV q 6 h or *CI* 25–30 mg/kg/h (up to 1000 mg/h) (*E*)

Argatroban *CI:* 2–10 mcg/kg/min; use initial dose of 0.5 mcg/kg/min in hepatic impairment or reduced cardiac output

Aspirin Antiplatelet: 1–5 mg/kg/day PO (max 10 mg/kg/day and 325 mg/dose); Kawasaki: 100 mg/kg/day PO ÷ q 6 h for 2 weeks, then 10 mg/kg/day PO daily

Desmopressin (DDAVP) 0.3 mcg/kg IV (dose for bleeding)

Enoxaparin Age: <2 months: treatment dose: 1.5 mg/kg/dose SubQ q 12 h; prophylaxis dose: 0.75 mg/kg/dose SubQ q 12 h; ≥2 months: treatment dose: 1 mg/kg/dose SubQ q 12 h; prophylaxis dose: 0.5 mg/kg/dose SubQ q 12 h

Heparin Bolus 75 units/kg over 10 min; then *MD* as *CI*: <1 year 28 units/kg/h and >1 year 20 units/kg/h; *adults:* 80 units/kg over 10 min, then 18 units/kg/h; adult prophylaxis dose: 5000 units SubQ every 8–12 h

Protamine (Reverse heparin) given IV: 0.25–1 mg neutralizes 100 units of heparin depending on time of last heparin dose (*F*)

Warfarin Initial dose: *infants and children:* 0.2 mg/kg/day (max 5 mg) PO follow INRs; adult: 2–10 mg/day PO and follow INRs

62.15 Inotropes/Vasoactive Agents [1–4]

Alprostadil (prostaglandin E1) *CI*: 0.01–0.4 mcg/kg/min

Digoxin See Table 62.2.

Dobutamine *CI*: 1–20 mcg/kg/min IV (max 40 mcg/kg/min)

Dopamine *CI*: 1–20 mcg/kg/min IV (max 50 mcg/kg/min)

Epinephrine *CI*: 0.05–1 mcg/kg/min IV

Isoproterenol *CI*: 0.05–2 mcg/kg/min IV

Liothyronine (T3) 0.3 mcg/kg IV over 15 min; *CI*: 0.03–0.06 mcg/kg/h

Milrinone 50 mcg/kg IV ×1 over 15 min; *CI*: 0.25–1 mcg/kg/min

Nitroglycerin Initial *CI*: 0.25 mcg/kg/min IV (max 5 mcg/kg/min)

Nitroprusside Initial *CI*: 0.5 mcg/kg/min IV (max 10 mcg/kg/min)

Norepinephrine *CI*: 0.05–2 mcg/kg/min

Phenylephrine Bolus 5–20 mcg/kg/dose; *CI*: 0.1–0.5 mcg/kg/min

Vasopressin (shock) *CI*: 0.0005 0.002 units/kg/min IV

62.16 Bronchodilators [1–4]

Albuterol 1.25–5 mg neb q 1 h (continuous neb) or PRN

62.17 Mucolytics [1–4]

Acetylcysteine 20% Infants, 1–2 ml; children, 3–5 ml neb q 6–8 h

Dornase Alfa 2.5 mg neb once daily or BID (Tables 62.1 and 62.2)

Table 62.1 Standard concentrations for peripheral and central line admixtures

Drug		Drip conc.	Dose	Line
Alprostadil		30 mcg/ml	0.1 mcg/kg/min	P/C
Alteplase (t-PA)		1 mg/ml	0.1 mg/kg/h	P/C
Aminocaproic acid		20 mg/ml	30 mg/kg/h	P/C
Amiodarone		1 mg/ml	10 mcg/kg/min	P/C
		6 mg/ml	10 mcg/kg/min	C
Calcium chloride		100 mg/ml	10 mg/kg/h	C
Cisatracurium		1 mg/ml	0.1 mg/kg/h	P/C
		2 mg/ml	0.1 mg/kg/h	P/C
Dexmedetomidine		4 mcg/ml	0.2 mcg/kg/h	P/C
Diltiazem		1 mg/ml	0.1 mg/kg/h	C
Dobutamine	<5 kg:	1500 mcg/ml	5 mcg/kg/min	P/C
	>5 kg:	3000 mcg/ml	5 mcg/kg/min	C
		6000 mcg/ml	5 mcg/kg/min	C
Dopamine	<5 kg:	1500 mcg/ml	5 mcg/kg/min	P/C
	>5 kg:	3000 mcg/ml	5 mcg/kg/min	C
		6000 mcg/ml	5 mcg/kg/min	C
Epinephrine		50 mcg/ml	0.1 mcg/kg/min	C
Esmolol		20,000 mcg/ml	50 mcg/kg/min	C
Fentanyl		20 mcg/ml	2 mcg/kg/h	P/C
		50 mcg/ml	2 mcg/kg/h	P/C
Furosemide		2 mg/ml	0.1 mg/kg/h	P/C
Heparin		100 units/ml	20 units/kg/h	P/C
Insulin (reg human)		1 unit/ml	0.1 units/kg/h	P/C
Isoproterenol		30 mcg/ml	0.1 mcg/kg/min	P/C
Ketamine		1 mg/ml	5 mcg/kg/min	P/C
Labetalol		1 mg/ml	0.4 mg/kg/h	P/C
Lidocaine		8000 mcg/ml	20 mcg/kg/min	P/C
Liothyronine (T3)		0.1 mcg/ml	0.04 mcg/kg/h	P/C
Midazolam		2 mg/ml	0.1 mg/kg/h	P/C
Milrinone		200 mcg/ml	0.5 mcg/kg/min	P/C
		600 mcg/ml	0.5 mcg/kg/min	C
Nicardipine		100 mcg/ml	0.5 mcg/kg/min	P/C
		1000 mcg/ml	0.5 mcg/kg/min	C
Nitroglycerin		600 mcg/ml	1 mcg/kg/min	P/C
Nitroprusside		300 mcg/ml	1 mcg/kg/min	P/C
		600 mcg/ml	1 mcg/kg/min	C
Norepinephrine		15 mcg/ml	0.1 mcg/kg/min	C
Phenylephrine		60 mcg/ml	0.1 mcg/kg/min	C
Procainamide		4000 mcg/ml	20 mcg/kg/min	P/C
Vasopressin		1 unit/ml	0.0005 units/kg/min-0.002 units/kg/min	C
(shock)				C
		0.5 units/ml	0.0005 units/kg/min-0.002 units/kg/min	C
				C
Vecuronium		2 mg/ml	0.1 mg/kg/h	P/C

Note. Diluent: all drips may be diluted with D5W or NS (exceptions: amiodarone and nitroprusside should be diluted with D5W; norepinephrine should be diluted with D5W or D5/NS, not NS alone).
P Peripheral line, *C* Central line

Table 62.2 Digoxin dosing recommendations[a]

Age	Total digitalizing dose (mcg/kg)		Daily maintenance dose (mcg/kg)	
	PO	IV or IM	PO	IV or IM
Preterm infant	20–30	15–25	5–7.5	4–6
Full-term infant	25–35	20–30	6–10	5–8
1 month to 2 years	35–60	30–50	10–15	7.5–12
2–5 years	30–40	25–35	7.5–10	6–9
5–10 years	20–35	15–30	5–10	4–8
>10 years	10–15	8–12	2.5–5	2–3
Adults	0.75–1.5 mg	0.5–1 mg	0.125–0.5 mg	0.1–0.4 mg

Give one-half of the total digitalizing dose (TDD) in the initial dose, and then give one-quarter of the TDD in each of two subsequent doses at 6–12-h intervals

Divide maintenance dose every 12 h in infants and children ≤10 years of age. Given once daily to children >10 years of age and adults

[a]Based on lean body weight and normal renal function for age. Decrease dose in patients with decreased renal function (E)

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Chapter 63
Standard Drug Concentrations in the Cardiac Intensive Care Unit

Kelli L. Crowley

Abstract In 2003, the Joint Commission on Accreditation of Healthcare Organizations (currently known as The Joint Commission [TJC]), introduced the concept of standardization and limitation of the quantity of drug concentrations available within an organization on a national level through National Patient Safety Goal 3b: "Improve the safety of using high-alert medications." Organizations were directed to transition over to standardized concentrations for all pediatric and neonatal patients. TJC later incorporated drug concentrations in the elements of performance to meet compliance with Medication Management Standard. The Institute for Safe Medication Practices (ISMP) also endorses standardized medication concentrations as integral to the utilization of smart pump technologies. Individual pediatric institutions have developed home-based standard drug concentrations and incorporated them into their usual medication processes. The most common approaches have been to target the most frequently ordered infusion drugs or a particular subset of the pediatric population. The ultimate achievement of the development of one set of concentrations that would be used nationally or even globally has proven more challenging. A large barrier to utilization of standard concentrations in the pediatric population is concern for fluid overload particularly in lower weight infants.

63.1 Background

In 2003, the Joint Commission on Accreditation of Healthcare Organizations (currently known as The Joint Commission [TJC]), introduced the concept of standardization and limitation of the quantity of drug concentrations available within an organization on a national level through National Patient Safety Goal 3b: "Improve the safety of using high-alert medications" [1]. Organizations had until December 2008 to completely transition over to standardized concentrations for all pediatric and neonatal patients [2]. This idea was further focused upon during a multi-stakeholder safety summit in Maryland in 2008 whose members were tasked with examining patient harm and death resulting from intravenous medications and prevention stratagem. This panel named a lack of standardization for intravenous medications as a main barrier [3]. TJC took notice of this recommendation and incorporated drug concentrations in the elements of performance to meet compliance with Medication Management Standard MM.02.01.01: "The hospital selects and procures medications" during accreditation survey in 2009. That same year, The Institute for Safe Medication Practices (ISMP) also endorsed standardized medication concentrations as integral to the utilization of smart pump technologies [4].

Limiting available drug concentrations within organizations has proven more difficult. Despite heightened awareness by TJC as well as government safety agencies, many hospitals and healthcare systems have not restricted the number of standard infusion concentrations having upwards of four concentrations of commonly used high-risk medications as self-reported in a 2008 survey [5]. The current recommendations are to have one concentration designated per drug ideally but it is acknowledged that an additional, or in some specific cases two additional, concentrations may be necessary.

Similarly, there has been international interest in the concept of standardized concentrations with the United Kingdom (UK) taking a comparable approach as the US. Multiple publications in the mid-2000's calling for standardization [6–8] led to establishment of a 16-drug list of common intensive care medications promoted by the Intensive Care Society. The guideline was comprised of a table containing recommended concentrations as well as infusion composition [9].

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Over the 7 years since inception, the list, now titled "Medication Concentrations in Adult Critical Care Areas," has grown to 18 medications, and central versus peripheral access guidance has been added [10].

The American Society of Health-System Pharmacists (ASHP) received a contract in September of 2015 to develop and implement national standardized concentrations for intravenous (IV) medications through the Food and Drug Administration's Safe Use Initiative program. (A second arm of this task deals with oral liquid standardization.) The first phase of this undertaking known as Standardize 4 Safety, completed in October of 2016, was to establish concentrations and dosing units for IV continuous infusion medications for adult patients. Phase II of the project, creating continuous infusion concentrations for the pediatric population defined as patients weighing less than 50 kg was predicted to be made available in 2017 [11]. ASHP has connected with the Pediatric Pharmacy Association, ISMP, The Association for the Advancement of Medical Instrumentation, and regional and local healthcare organizations to collaborate in this endeavor [12].

This has proven to be a difficult undertaking with so many competing variables in play. Individual pediatric institutions have developed home-based standard drug concentrations and incorporated them into usual medication processes. The most common approaches have been to target the most frequently ordered infusion drugs or a particular subset of the pediatric population. In preparation for an anticipated purchase of smart syringe pumps, Primary Children's Medical Center (Salt Lake City, UT) identified a list of 32 drugs that made up ~95% of the medications in infused continuously via syringe pumps at their facility [13]. Conversely, a multidisciplinary team out of Boston focused on neonatal patients selecting nine medications that would be high risk for this population. Concentrations were determined based upon reasonable infusion rates, predictable fluid intake restrictions, and effects on glucose infusion rate [14]. Four years later, the Vermont Oxford Network which is a collaborative of health care professionals from approximately 1000 neonatal intensive care units internationally, teamed up with ISMP to publish "Standard Concentrations of Neonatal Drug Infusions." This list has eleven recommendations for continuous infusion concentrations with some overlap of medications with the Boston list but with different concentrations endorsed [15].

63.2 Safety

The ultimate achievement for proponents of standardizing medication infusions would be the development of one set of concentrations that would be used nationally or even globally. There are multiple reasons why the concept of universal standardization adds to the culture of safety. During transition of care between locations, whether within a single facility or external transfers, staff would only have to be familiar with one set of dilutions. It makes even more sense when taking into consideration that healthcare providers are often expected to transition between settings and nursing may be supplied by per diem personnel [16]. This also hold true when staff are inexperienced or urgent situations occur [17].

The San Diego Patient Safety Consortium, in one of the first efforts of its kind, developed a "getting started kit" detailing a how-to guide for intra- and inter-hospital standardization with a focus on treatment of adult patients. A finalized list of medications was published in 2006 which regional facilities were urged to adopt [18]. In 2009, the Indianapolis Coalition for Patient Safety followed in their footsteps, promoting a similar type of list to be implemented locally in six major health systems located within the city. In 2013, representatives from regional coalitions across Indiana formed a statewide group encompassing 81 hospitals within 9 health systems. A final list of 28 concentrations of 26 medications was identified and published as "the Indiana List" by that interdisciplinary work group [19]. Again, this list was generated with the adult patient in mind. These efforts demonstrate that it is possible to implement standardized strategies over large geographic areas successfully. It should be noted, however, that there are differences between the San Diego and Indiana lists in composition and recommended concentrations also inconsistent with the national recommendations put forth by the Standardize 4 Safety initiative.

There has likewise been success with standardizing infusion concentrations for pediatric intensive care unit patients with publications originating from Canada and Ireland. Following the development and implementation of a pediatric drug library of infusion concentrations in the pediatric intensive care unit (PICU), operating rooms, and cardiac ward of a large tertiary Dublin children's hospital, a project was commenced to further distribute it for use across multiple sites including the pediatric acute transport services. Howlett et al. remarked that cross-site collaboration is achievable and speculated that it has the potential to reduce medications errors as healthcare providers and patients transfer among practice sites [20]. In a similar scenario, practices developed at Children's Hospital of Eastern Ontario were adopted by the Clinical Pathway-Based Pediatric Emergency Outreach Program, with aims to "to deliver standardized, evidence-based pediatric emergency care" throughout the emergency departments of 14 community hospitals within a specified geographical area. This was introduced through the implementation of clinical pathways that include infusion concentration standardization [21].

Point-of-care pump technology goes hand-in-hand with standardized medication concentrations. Smart pumps have decision-support software that works in conjunction with a

drug library that is downloaded by purchasing institution or organization. Drug libraries contain a list of medication names, the standardized concentrations that will be available and an appropriate dosing range for that drug. When used in conjunction with smart pump technology, Larsen et al. showed that standardization of medication infusion concentrations led to a 73% reduction in the number of reported errors which was an absolute risk reduction of 2.3 errors per 1000 doses and an 80% decrease in the number of tenfold dosage errors at their tertiary pediatric hospital [13].

63.3 Cardiac Intensive Care Unit Population Concerns

A large barrier to utilization of standard concentrations in the pediatric population is concern for fluid overload particularly in lower weight infants. Fuhrman et al. quantified the medication-related fluid intake of mechanically ventilated, intensive care unit patients, and examined associated fluid overload. It was found that a substantial portion of the cohort received total daily fluid quantities that exceed their polyuria threshold and almost 40% of patients demonstrated a 10% or greater overload that was not thought to be the result of reduced renal function [22]. Fluid overload is associated with impaired oxygenation in critically ill children [23] as well as increased morbidities such as pulmonary edema and cardiac failure [24]. Administration of diuretics may be sufficient, but restrictive fluid management strategies and continuous renal replacement must be considered when overload is excessive enough to surpass the kidneys' abilities [24].

This can be compounded in the pediatric cardiac intensive care unit patient where fluid balance management is very rigorous. In the immediate post-operative period, initial 72 hours, fluid overload is a frequent occurrence. The dangers of fluid overload were found to be an increase in-hospital mortality, low cardiac output syndrome, and prolonged mechanical ventilation with one of the primary risk factors being an underlying renal dysfunction [25]. Hazle et al. examined fluid overload in infants following congenital heart surgery. An association between early postoperative fluid overload and suboptimal outcomes in infants following cardiac surgery was found. A preponderance of the patients developed kidney injury without needing renal replacement therapy; however, fluid overload appears to be an important risk factor for adverse outcomes with any intensity of kidney injury [26].

Care must be taken to ensure that standardized concentrations may be used across populations. When Children's Hospital of Eastern Ontario in Ottawa was in the planning stages prior to conversion to standard concentrations, consultant stakeholders raised concerns regarding possible fluid overload in lower weight patients. In order to examine the effects on fluid load of standard concentration infusions, Irwin et al. evaluated the volumes administered using traditional practices versus volumes that would be administered using the new system in 48 PICU patients weighing less than 20 kg, one third of whom were less than 5 kg. They found that there was no statistically significant difference in the total daily volumes infused and the anticipated volumes with standard concentrations when compared. Actual daily volumes administered were often within 10% of the anticipated amounts with standard concentrations. It was discovered that adjustments to morphine standard concentrations were needed as those selected were generating larger volumes than desirable. The simulation allowed a problem to be detected and resolved prior to program implementation [27].

Standardization of medication concentrations is a phenomenal patient safety improvement concept. Being spotlighted by safety and accreditation organizations has increased awareness among healthcare providers, and a variety of efforts have been implemented within institutions, healthcare systems, and even geographical areas. National consensus on standards and full implementation of them may be a bit more challenging especially as varying lists are being developed independently by numerous workgroups and organizations. Prudent selection of concentrations in the design phase, though, is essential to accommodate the fluid needs of patients in the cardiac intensive care unit.

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Chapter 64
Monitoring Outcomes in Nursing: Quality Improvement

Ashlee Shields, Ashley Cole, Marcie Tharp, and Jean Connor

Abstract This chapter explores quality assessment and its importance in the Cardiac Intensive Care Unit (CICU). Patient outcomes are dependent upon the care provided and experience of healthcare providers. There are hospital wide and population specific care standards to monitor and improve outcomes. Healthcare providers need to collaborate both within and outside of their organization to aide in identifying problems and improving processes.

64.1 Introduction

The delivery of nursing care is an important part of a patient's hospital stay, but monitoring outcomes is essential. To monitor patient outcomes, various quality indicators are measured to reduce length of stay and prevent hospital-acquired infections and adverse events. A collaborative approach to quality improvement is beneficial to have a greater impact on patient outcomes.

It is important to know the weight of individual quality measures, recognizing the significance in selecting and ranking indicators. Accrediting agencies may drive hospital or system wide quality indicators. Facilities may also implement quality-monitoring measures that are thought to be important or identified through process improvement within an organization. Health care providers who work in congenital heart disease populations should seek involvement in organizations who develop care measures that are specific to this specialized and vulnerable population.

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64.2 Quality Improvement

64.2.1 Multidisciplinary Team Approach

One approach to improving outcomes is collaborating in a multi-disciplinary environment. Bringing staff together from different specialties provides the necessary support through knowledge sharing to accomplish set goals. Literature also suggests a potential benefit to improving both patient and employee satisfaction [1]. The purpose of these groups is to identify and review hospital events and to participate in patient care rounds.

The CICU Infection Prevention team consists of physicians from all service lines within the heart and vascular institute and infectious disease, nurse specialists and administration, research coordinators, and quality improvement specialists. In the beginning, this team focused on preventing central line bloodstream infections. Overtime, the team assessed all nosocomial events and continued evaluation to improve efforts and reduce future events. Additionally, attention is directed to discovering strategies to decrease future incidences, and preventing nosocomial infections.

64.2.2 Hospital/System Level

System or hospital level quality measures can vary between organizations and accrediting agencies. Measures monitored hospital wide are most likely related to patient outcomes, but could also be based on health care provider performance and reimbursement (Table 64.1). Typically, outcomes are expressed numerically and based on patient days (central line days, foley days, etc.). It is imperative to evaluate data, implement best practices, and reevaluate outcomes after making changes to practice or products used in care.

Patient outcomes are an important piece of a nurse's job, but are also the responsibility of other health care providers

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and should be visible for all to see and understand. This can be accomplished by displaying chosen quality outcomes via a dashboard (Fig. 64.1) housed in a venue for all health care providers to view.

64.2.3 Program-Based Measures

Program-based measures have a greater impact on the patient population being cared for, and these measures are directed by the area, CICU, caring for the patient. Population-based efforts may have a more tailored approach to managing the patient and/or care and could be center-specific. Reducing hospital acquired infections and improving patient outcomes are important, but several factors play a role in a successful quality improvement project. Consideration should be taken to identify key staff members to understand problems and implement change. Examples of program-based quality improvement projects include but are not limited to Methicillin-Resistant Staphylococcus Aureus (MRSA) surveillance screening, early mobility, nutrition protocols, and nosocomial infection reduction.

Table 64.1 Hospital-based nursing quality metrics

Quality Indicators
Central line-associated bloodstream infections
Catheter-associated urinary tract infections
Pressure injuries
Ventilator-associated pneumonia
Adverse drug events
Pain assessment
Handwashing

64.3 Mediastinitis Prevention

Surgical site infection (SSI) is a complication that increases length of stay with an associated increase in mortality and morbidity [1]. Guidelines to prevent SSI in pediatric cardiac surgery do not exist [2]. Protocol development to prevent SSI has been developed [2], but further research is needed to find

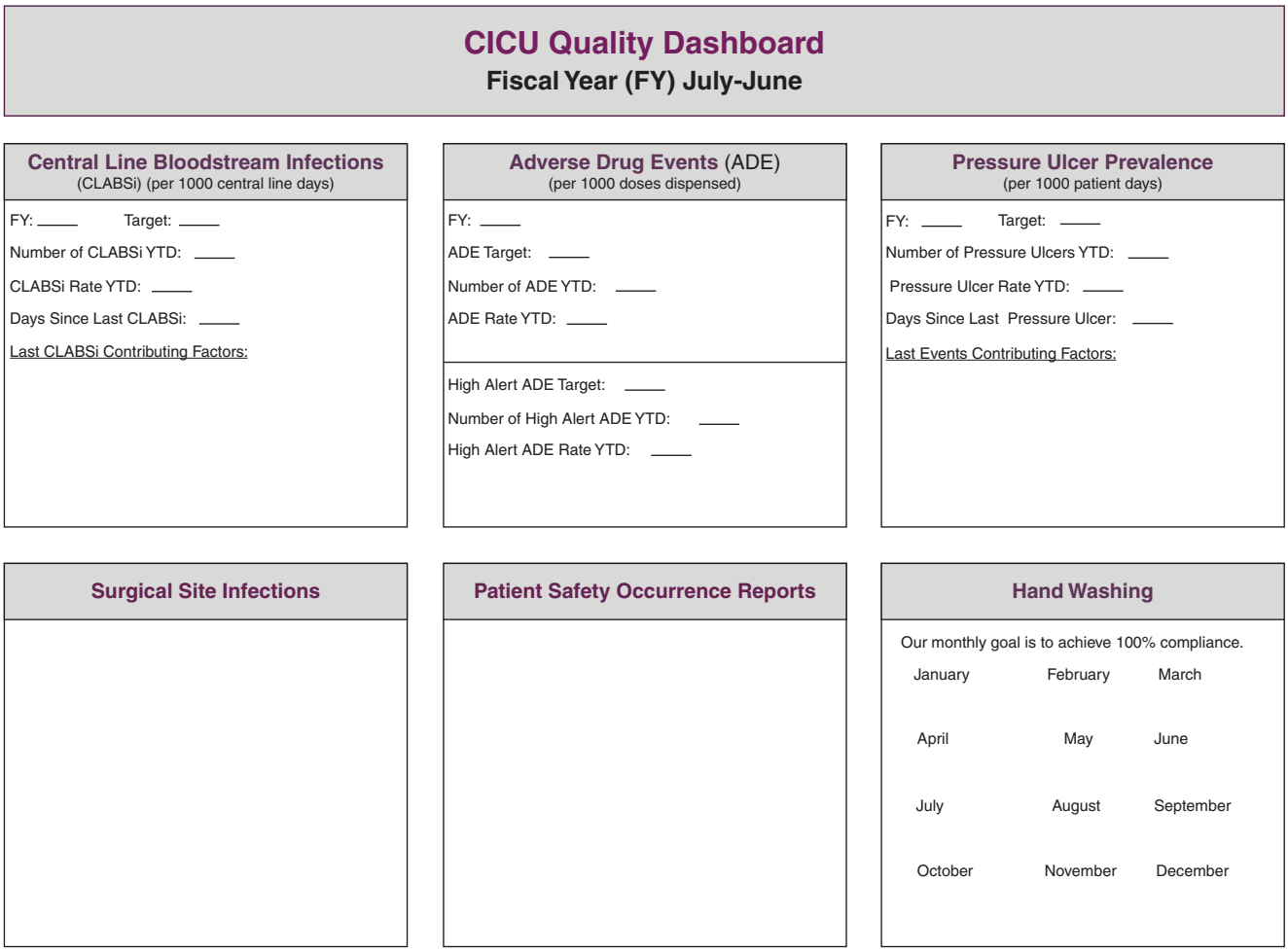

Fig. 64.1 Poster of unit dashboard

evidence to reduce SSI. Implementation of a mediastinitis prevention bundle may aid in reducing the incidence of surgical site infections. The bundle includes items related to pre- and postoperative bathing, antibiotic use (timing, delayed sternal closure), routine nursing care, and decolonization needed for MRSA.

64.4 MRSA Surveillance Screening for Pediatric Cardiac Patients

Guidelines for MRSA screening in the adult cardio-thoracic population, along with subsequent decolonization and antibiotic prophylaxis are well established [3]. The overall prevalence of MRSA colonization rates on admission are 1.5–5.9% for Pediatric Intensive Care Unit (PICU) and Neonatal Intensive Care Unit (NICU) patients [4, 5]. Hospital acquisition rates for NICU patients are 4.1% and 6.1% for PICU patients [5]. There is a relative paucity of literature related to MRSA colonization in pediatric cardiac surgery patients and very little is known about hospital MRSA acquisition rates in pediatric CICU patients. It is crucial for healthcare providers to perform MRSA surveillance screening to indicate those colonized with MRSA and treat appropriately if having a surgical procedure or invasive monitoring. The MRSA screening process was broken into phases: screening, preoperative decolonization, and intraoperative and postoperative antibiotic use. Surgical patients are screened in their outpatient visit prior to surgery. Patients admitted to the CICU, medical or surgical, are cultured within the first 24 hours of admission. The decolonization regimen was dependent on the location of the positive cultures. A guideline was also developed for intraoperative antibiotics.

64.5 Clinical Effectiveness Guidelines

Clinical effectiveness guidelines (CEGs) standardize care and identify variances [6] from the expected care, while decreasing length of stay, number of laboratory tests, use of blood products, and decrease in hospital costs [7–9]. In addition to clinical aspects of managing care, patient and family-centered care are integrated into guidelines while serving as a tool to provide education earlier during hospitalization. Information within these guidelines provides an understanding of the diagnosis, procedure, and recovery phase through discharge [10]. CEGs provide consistency in care, optimize outcomes, and increase patient safety [11]. Through the reduction of variations in care, patient safety is increased by reducing unnecessary medication use, laboratory work, and blood product administration [10].

64.6 Collaboration with Outside Organizations

64.6.1 Consortium of Cardiac Care Measurement of Nursing Practice

The Consortium of Cardiac Care Measurement of Nursing Practice (C4-MNP) is a nurse-led collaborative committed to developing and evaluating pediatric cardiovascular nurse-sensitive quality indicators to improve and standardize nursing practices [12, 13]. The consortium was established in 2011 to identify nursing care actions for measurement in the pediatric cardiovascular environment and to test standardized measures representative of pediatric nursing care of the cardiovascular patient for benchmarking [12–14]. Boston Children's Hospital serves as the lead site and is responsible for the coordination of consortium activities and data management. With representation from 32 cardiovascular programs within freestanding children's hospitals across the United States, the consortium is a national community of bedside clinicians, advanced practice nurses, clinical nurse specialists, researchers, and nursing administrators.

C4-MNP utilized a collaborative, consensus-based method that incorporated the National Quality Forum criteria and an external review period to develop and evaluate ten standardized quality measures eligible for testing across freestanding children's hospitals. The measures were implemented in 9 of 32 collaborating centers over the course of a six-month pilot testing phase that began in January 2016. Pilot data revealed variation in nursing workforce characteristics across pilot sites including percent of nursing staff with 0–2 years of experience, Bachelor of Science in Nursing (BSN) preparation, and Critical Care Registered Nurse (CCRN) or Certified Pediatric Nurse (CPN) certification, and percent of nurse turnover. Pilot data also revealed opportunities to improve pediatric cardiovascular care processes, including weight gain prior to discharge for cardiac surgery infants, utilization of early warning scores to prevent unplanned transfers to a higher level of care, and timely and effective management of pain scores ≥4. Pilot sites consistently performed well on the device-related pressure ulcer and adverse feeding measures. Results from pilot testing will support development of benchmarks for C4-MNP member sites to compare performance and sharing of best practices to improve the quality of pediatric cardiovascular nursing care.

The field of pediatric nursing is in need of measures that accurately capture the unique care provided to patients and families, and that demonstrate the impact of this care on outcomes. The work of C4-MNP provides a model by which such measures can be designed, implemented, and tested, using a collaborative approach that builds upon the knowledge and expertise of nurses from across the country and a variety of practice settings.

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