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

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Education Gap

An understanding of the pathophysiology, diagnosis, and appropriate initial management of acyanotic congenital heart disease is needed to appropriately care for infants in the NICU.

Abstract

Acyanotic congenital heart diseases or left-to-right shunting lesions are the most common form of congenital heart disease. Although most resolve spontaneously, many will remain hemodynamically significant, particularly in the premature infant. Understanding the difference in pathophysiology, diagnosis, and management between the term and preterm infant is imperative to minimize the risk of secondary organ dysfunction and ensure proper growth and development.

Objectives  After completing this article, readers should be able to:

1. Explain the pathophysiology, initial presentation, and management of left-to-right pre-tricuspid shunt lesions.
2. Explain the pathophysiology, initial presentation, and management of left-to-right post-tricuspid shunt lesions.
3. List the genetic mutations associated with the different left-to-right shunt lesions.
4. Differentiate the effects of these lesions on term and preterm infants.

INTRODUCTION

Congenital heart disease (CHD) is the most common genetic abnormality, with an incidence that increases from approximately 8 per 1,000 term births to 12.5 per 1,000 premature births. (1)(2) More important, however, are the significantly increased hemodynamic consequences of CHD in preterm infants compared with their term peers. This review will focus on acyanotic CHD defined as an anatomic connection between the pulmonary and systemic circulations in which oxygenated
systemic blood flow on the left side of the heart shunts to the partially deoxygenated pulmonary blood flow on the right side of the heart. The vast array of acyanotic heart lesions will be grouped into 2 physiologic subtypes of pre-tricuspid valve and post-tricuspid valve shunting. Further consideration will be given to gestational age when appropriate.

**PRE-TRICUSPID VALVE SHUNTS**

The physiologic distinction of pre-tricuspid valve shunts describes shunting across an atrial septal defect (ASD) during ventricular diastole and atrial systole. The direction of flow across an atrial communication is dictated by differences in ventricular compliance. Ventricular compliance can change when chronic atrial contraction occurs into a ventricle that has become stiff and noncompliant either from myopathic changes (ie, hypertrophic cardiomyopathy) or from chronically elevated afterload (ie, pulmonary/aortic valve stenosis or elevated pulmonary or systemic vascular resistance).

Shortly after birth, ASD shunt magnitude is low because neonatal right ventricular stiffness and compliance are very similar to those in the left ventricle. With physiologic declines in pulmonary vascular resistance, compensatory in utero right ventricular hypertrophy regresses, resulting in a more compliant right ventricle and atrium. This allows a progressive left-to-right increase in ASD shunt volume that is further pronounced with larger defect size. (3) ASDs are considered volume-loading defects to the right heart (as opposed to pressure-loading defects; see Post-Tricuspid Valve Shunts section), with larger defects producing right atrial and ventricular dilation.

**Incidence**

Excluding patent foramen ovale, which persists in up to 35% of adults, ASDs exist in approximately 1 in 1,500 children, comprise 6% to 10% of all cardiac anomalies, (4) and are the most commonly recognized mutation in nonsyndromic CHD. (5) Although ASDs frequently occur with other congenital heart lesions, isolated ASDs have been associated with NKX2.5, GATA4, GATA6, and TBX20 mutations. Mutations in the TXB5 gene are associated with Holt-Oram syndrome.

Several anatomic classifications of atrial defects can occur in utero when the septum primum and septum secundum do not appropriately fuse with each other, the endocardial cushions, and posterior aspect of the atria. Ostium secundum type defects compose 75% of all ASDs and are essentially identical to a patent foramen ovale with the major distinction being size. (4) The foramen ovale is a critical connection maintained throughout fetal life, directing oxygenated ductus venous blood across its opening to the left atrium, left ventricle, preductal aortic vessels, and the developing brain. Primum ASDs exist in the setting of atrioventricular septal defects (AVSDs) but their physiologic presentation is typically determined more by the associated lesions. Sinus venosus type ASDs comprise 4% to 11% of all ASD types and are commonly associated with anomalous return of at least 1 pulmonary vein, resulting in a significantly larger left-to-right shunt. (6) Coronary sinus ASDs not only produce ASD physiologic but are commonly associated with systemic desaturation as they functionally “unroof” the coronary sinus, adding markedly desaturated blood into the left atrium.

**Diagnosis**

ASDs are rarely associated with clinical findings in the term neonate. At 2 to 3 years of age, classic findings include a widely split S2 and a systolic ejection murmur along the left sternal border because of increased flow across the pulmonary valve. Echocardiography is the diagnostic tool of choice (Fig 1). Chest radiography may show an enlarged cardiac silhouette and increased pulmonary vascular markings, but this can be difficult to appreciate in an infant with lung disease. Electrocardiography (ECG) will show right ventricular hypertrophy and right axis deviation, but this is true in all newborns and is usually not helpful.

**Management**

Term neonates with isolated ASDs are typically asymptomatic and rarely require intervention. Should the patient develop significant signs of congestion with increased work of breathing, tachypnea, hepatomegaly, and poor growth, diuretics are the first-line treatment. As such, ASD closure is not common until at least 2 years of age, with both device closure in the catheterization laboratory and surgical closure having excellent results. (7)(8)

**Premature Infants**

The premature infant with chronic lung disease represents a unique challenge. When subjected to chronic hyperoxia and positive pressure ventilation, the immature lung parenchyma exhibits alveolar simplification. (9) The subsequent reduced number of alveoli renders these infants particularly sensitive to any increase in pulmonary blood flow, particularly when coupled with aspiration, inflammation, or acquired pulmonary vein stenosis, all of which result in congestion from increased intra-alveolar fluid. Therefore, premature infants not following the expected perinatal course (ie, respiratory distress out of proportion to their lung disease) who have an ASD deemed amenable to device closure in the cardiac catheterization laboratory should be considered for this therapy to improve outcomes. (10)(11)
POST-TRICUSPID VALVE SHUNTS

Left-to-right shunting lesions distal to the tricuspid valve include various ventricular septal defects (VSDs; eg, perimembranous VSD and atrioventricular canal defects) and systemic to pulmonary shunts (eg, patent ductus arteriosus [PDA] and aortopulmonary window). The hemodynamic significance of a shunt depends on the size and resistance within the defect, and the relationship between pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR). In utero and immediately after birth, the PVR and SVR are approximately equal, producing a PVR/SVR ratio of 1:1. After a healthy newborn takes the first breath, the pulmonary vascular bed is exposed to oxygen, promoting pulmonary arteriolar relaxation and a progressive decrease in the PVR/SVR ratio. PVR reaches its nadir between 8 weeks and 6 months of age, resulting in a PVR/SVR ratio of 0.2:1 or less. Regardless of the size and resistance within a post-tricuspid valve communication, net shunting of blood will not occur until the PVR/SVR ratio has deviated significantly from 1:1 (ie, an increase in pulmonary blood flow relative to systemic blood flow cannot occur until PVR is less than SVR).

The PVR/SVR ratio effectively acts as the second in a series of 2 resistors, with the first being the communication itself. The Hagen-Poiseuille equation states that resistance to flow across a vessel is directly related to its length and inversely related to its radius to the fourth power ($R = L/ r^4$). VSDs have no length and act as a static resistor in the neonate, therefore, the resistance to flow across the VSD is entirely determined by the radius or size of the defect. By comparison, a PDA has significant length and its radius is affected by both contraction of oxygen-sensitive ductal tissue and angulations within a tortuous ductus. However, the relative resistance that exists within the pulmonary and systemic vascular beds is markedly greater than that found within the defects themselves, and is subsequently the largest determinant of shunting volume and direction. These complex interactions ultimately determine whether a post-tricuspid valve shunting lesion produces a pressure and/or volume burden on the heart and lungs.

VSD shunting occurs exclusively during systole. Large nonrestrictive VSDs are associated with pulmonary arterial pressures identical to systemic arterial pressures, regardless of the PVR/SVR ratio. This is because pressure generation within a vascular bed is the product of its vascular resistance (PVR and SVR) and pulmonary (Qp) and systemic (Qs) blood flow ejected into that bed. For example, if the ratio of resistance is 1:1, there is no net shunting ($Qp:Qs = 1:1$), but if the PVR/SVR ratio is 0.5:1 and the $Qp:Qs$ is 2:1, the pulmonary circulation is exposed to twice as much blood flow as is the systemic circulation.

VSDs in the setting of a low PVR/SVR ratio (ie, <0.5:1) produce a volume burden on both the lungs and left ventricle. Excess pulmonary blood flow shunted from the left ventricle combines with the right ventricular output and produces hydrostatic pressures that overwhelm oncotic forces, resulting in intra-alveolar water or pulmonary edema. This total blood volume must then return to the left atrium and ventricle, progressively dilating both chambers. Newborns with such ventricular level shunting become increasingly tachypneic, intolerant of oral feedings, and fail to thrive, producing the classic presentation of congestive heart failure. This rate of decline is reduced with smaller defects and if the PVR/SVR is closer to 1:1. Large,
long-standing, unrepaired VSDs cause progressive pulmonary arteriolar vasoconstriction and PVR elevation that eventually becomes irreversible, resulting in Eisenmenger syndrome; this is exceedingly rare in the first few years of age. Although the length of a PDA directly increases resistance, compared with a large VSD, PDAs typically produce a larger volume burden on the pulmonary vascular bed for 2 reasons. First, a newborn’s ductus arteriosus is large, with a cross-sectional area equal to the descending aorta, largely counteracting the resistance effect of its length. Second, shunting occurs throughout both systole and diastole.

VENTRICULAR SEPTAL DEFECT

Incidence
VSDs are the most common form of CHD, representing 20% to 30% of isolated lesions and occurring in 1.3 to 3.9 of 1,000 live births. (12)(13) VSDs are classified as 4 types, with perimembranous VSDs being the most common. (14) Isolated VSDs are the most common CHD seen in patients with trisomy 21, 18, and 13, but only 5% to 8% of patients with an isolated VSD will have a chromosomal disorder. (13) TBX5, GATA4, and NKX2 mutations have been associated with isolated VSDs. (13)

Diagnosis
Small, restrictive VSDs are often found incidentally with a holosystolic murmur at the left sternal border, but only after PVR has begun to fall. Because of the lack of flow acceleration and associated murmur, large defects may not become clinically evident until an infant becomes symptomatic, as described earlier. Chest radiography may show signs of pulmonary congestion and an enlarged cardiac silhouette. An ECG may show signs of left and right ventricle hypertrophy with disease progression, but are typically not diagnostic. Echocardiography is the diagnostic tool of choice (Fig 2) and additional testing is not usually indicated.

Management
Up to 45% of VSDs spontaneously close during the first year of age. (12) For those that become hemodynamically significant, surgical closure is the primary option, depending on the location of the defect and size of the child, with low morbidity and mortality rates and excellent outcomes. (12) Premature infants with VSDs are particularly challenging because their incomplete pulmonary arteriolar development produces an extremely compliant pulmonary vascular bed, resulting in an earlier onset of pulmonary overcirculation and congestive heart failure. This is further complicated in patients with chronic lung disease. Pulmonary artery banding may be considered if there are multiple defects within the ventricular septum or if the infant’s size or gestational age precludes cardiopulmonary bypass. (12)

ATRIOVENTRICULAR SEPTAL DEFECT

Incidence
AVSDs comprise a wide variety of congenital heart lesions involving endocardial cushion formation. The spectrum ranges from partial defects with a primum ASD and mitral valve cleft (most common type) to a complete defect with an ASD, VSD, and single atrioventricular valve to an unbalanced AVSD with heterotaxy syndrome and single ventricle physiology. (15)(16) The incidence of AVSDs ranges from 0.24 to 0.31 per 1,000 live births or 4% to 5% of congenital heart defects and 40% of cases will be associated with trisomy 21. (16)(17) AVSD is associated with tetralogy of Fallot in 5% of cases. (16)

Diagnosis
A complete AVSD is commonly diagnosed prenatally. (16)(17) Defects with large ventricular components will present earlier in life when PVR falls, as discussed earlier. Diagnosis is made with echocardiography (Fig 3), but ECG can be a helpful screening test because it commonly shows the unique finding of a superior QRS axis between –90 and –120 degrees (Fig 4).

Management
Definitive management is surgical, with current mortality rates less than 3% when performed between 3 and 6 months of age, which increases in younger, smaller infants. (18) The concurrent diagnosis of trisomy 21 syndrome does not significantly alter morbidity or mortality rates unless surgical intervention is made significantly later than 6 months of age, because of an inherently earlier development of irreversible pulmonary vascular disease. (16)

PATENT DUCTUS ARTERIOSUS

Incidence
The PDA is a vital structure in utero, redirecting blood from the right ventricle to the lower body. After a term gestation, the PDA will usually close within 72 hours of age, but frequently this does not occur until much later in preterm infants, making it the most common lesion of prematurity. (19)(20)

Diagnosis
Patients may demonstrate a widened pulse pressure with bounding distal pulses; auscultation of the left upper sternal border will demonstrate either a continuous murmur.
produced by shunting throughout the cardiac cycle or an isolated systolic murmur either when the PVR remains high or as the ductus begins to close and diastolic flow ceases. As with other left-to-right shunts, echocardiography is the diagnostic tool of choice. Some investigators have demonstrated serum brain natriuretic peptide to be another indicator of PDAs in premature infants. (19)(21)

Management
Spontaneous PDA closure is more likely to occur in infants without respiratory distress syndrome, those born after 28 weeks’ gestation (~73%), and those born with birthweights greater than 1,000 g (~ 94%). (19)(22) When closure does not occur, it is reasonable to consider intervening in the setting of chronic renal insufficiency, feeding intolerance, hemodynamic instability, or inability to separate from supplemental respiratory support. Nonsteroidal anti-inflammatory agents such as indomethacin and ibuprofen are commonly considered first-line therapy. However, their mechanism of action (cyclooxygenase inhibition with downstream inhibition of prostaglandin formation) (23)(24) also carries a significant risk of acute renal injury, intracranial hemorrhage, and spontaneous intestinal perforation. This challenge has prompted investigation into alternative medical interventions such as intravenous acetaminophen. (24)

Surgical ligation is another option, but is associated with risks of vocal cord or diaphragm paresis, scoliosis, or accidental ligation of the pulmonary artery or aorta. (25) Percutaneous device occlusion is yet another option, but higher rates of arterial injury and device embolization are reported in infants who weigh less than 4 kg. (23) Considering the complicated risk-benefit profile associated with these options, the decision...
to intervene in an infant with a PDA should not follow a protocol, but instead be individualized for each patient.

Premature Infants
Some data suggest that the premature ductus arteriosus is less sensitive to the vasoconstrictive properties of oxygen and more sensitive to the vasodilatory effects of endogenous prostaglandin E2, resulting in the higher prevalence of ductal patency in this population. As with VSDs in the premature infant, PDAs can be especially challenging because they contribute to heart failure, bronchopulmonary dysplasia, necrotizing enterocolitis, renal insufficiency, cerebral palsy, and prolonged need for ventilator support.

AORTOPULMONARY WINDOW
Aortopulmonary windows are a rare (0.2%–0.6% of CHD) systemic to pulmonary communication associated with severe pulmonary overcirculation, heart failure, and respiratory failure. This defect occurs during embryonic septation of the truncus arteriosus in which the 2 vessels have a region devoid of intervening tissue. Without any interposing resistor such as a semilunar valve or length of ductus arteriosus, there is no functional separation between the systemic and pulmonary vascular beds and patients become symptomatic at very young ages. Physical examination findings are typically indistinguishable from those of a large PDA. Echocardiographic diagnosis can be challenging but should be suspected in patients with a clinical picture of heart failure without a PDA or VSD. Surgical patch septation is the definitive intervention.

CONCLUSION
Left-to-right shunting lesions should be physiologically and anatomically subcategorized into pre- and post-tricuspid valve. Pre-tricuspid valve lesions include ASDs in which shunting is determined by defect size and differences in ventricular compliance. These lesions produce right heart enlargement and are usually asymptomatic throughout infancy. Post-tricuspid valve lesions include VSDs, AVSDs, PDAs, and aortopulmonary windows, in which shunting is determined largely by the relationship between the systemic and pulmonary vascular resistances but also by the resistance inherent in the interposing defect. Initially, these lesions produce a volume burden on the lungs and left ventricle, and can lead to progressive respiratory failure, heart failure, and failure to thrive. Untreated, any of these lesions can progressively result in Eisenmenger syndrome, which is associated with a significantly worse prognosis. Premature infants and those with chronic lung disease are particularly sensitive to left-to-right shunting lesions and should be considered for early medical or surgical intervention.

American Board of Pediatrics Neonatal-Perinatal Content Specifications
- Know the anatomy and pathophysiology (including genetics) of a neonate with a left-to-right shunt lesion.
- Recognize the clinical features of a neonate with a left-to-right shunt lesion.
- Recognize the laboratory, imaging, and other diagnostic features of a neonate with a left-to-right shunt lesion.
- Formulate a differential diagnosis for a neonate with a left-to-right shunt lesion.
- Know the evaluation and medical and/or surgical management and associated potential complications or adverse effects of such management for a neonate with a left-to-right shunt lesion.

References
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This journal-based CME activity is available through Dec. 31, 2020, however, credit will be recorded in the year in which the learner completes the quiz.

1. A newborn with a murmur undergoes echocardiography and is noted to have an atrial septal defect (ASD). It is reported that ASDs occur in approximately 1 in 1,500 children and account for 6% to 10% of all cardiac anomalies. Which of the following subtypes constitutes the most common type of ASD?
   A. Ostium primum ASD.
   B. Sinus venosus type ASD.
   C. Ostium secundum ASD.
   D. Coronary sinus ASD.
   E. Mixed ASD.

2. In utero and immediately after birth, the ratio of pulmonary vascular resistance (PVR) to systemic vascular resistance (SVR) is approximately 1:1. With exposure of the pulmonary vascular bed to oxygen, the PVR/SVR ratio progressively decreases. When does the PVR nadir occur in a healthy neonate?
   A. At 1 week of age.
   B. Between 2 and 4 weeks of age.
   C. Between 4 and 8 weeks of age.
   D. Between 8 weeks and 6 months of age.
   E. Between 6 months and 12 months of age.

3. A male term newborn is noted at 1 day of age to have a holosystolic murmur. Echocardiography reveals a ventricular septal defect (VSD). VSDs are the most common form of congenital heart disease, representing 20% to 30% of isolated lesions and occurring in 1.3 to 3.9 of 1,000 live births. Which of the following statements is FALSE regarding the physiology of VSDs?
   A. VSDs in the setting of a low PVR/SVR ratio (ie, <0.5:1) produce a pressure burden on both the lungs and left ventricle.
   B. Pulmonary edema is the result of excess pulmonary blood flow with resultant increased hydrostatic pressures.
   C. The classic presentation of a large hemodynamically significant VSD includes tachypnea, intolerance of oral feeds, and failure to thrive.
   D. If untreated, excess pulmonary blood flow can lead to progressive pulmonary arteriolar vasoconstriction and irreversible PVR elevation (Eisenmenger syndrome).
   E. Due to the lack of flow acceleration and associated murmur, large defects may not become clinically evident until an infant becomes symptomatic.

4. A female term newborn has features of trisomy 21 and part of the evaluation includes echocardiography, which reveals an atrioventricular septal defect (AVSD). AVSDs account for 4% to 5% of congenital heart defects and 40% of cases are associated with trisomy 21. Which of the following electrocardiographic (ECG) findings is unique to AVSDs?
   A. Presence of right ventricular hypertrophy and right axis deviation.
   B. Presence of a superior QRS axis between ~90 and ~120 degrees.
   C. Presence of peaked, large amplitude p waves in lead II.
   D. Presence of left ventricular hypertrophy with left axis deviation.
   E. Presence of prolonged PR interval.

5. An infant born at 34 weeks’ gestational age has respiratory distress and is placed on continuous positive airway pressure. Chest radiography shows a large cardiac shadow and cardiac murmur. The patient continues to have respiratory distress and oxygen requirement at 2 days of age and echocardiography is performed. Patent ductus arteriosus (PDA) is present, but otherwise the cardiac anatomy is normal. In full-term infants, the PDA usually closes within 72 hours of age. Which of the following statements is also correct regarding PDAs?
A. As with ventricular septal defects, shunting occurs exclusively in systole.
B. The premature ductus arteriosus is less sensitive to the vasodilatory effects of endogenous prostaglandin $E_2$.
C. The PDA is more likely to spontaneously close in infants without respiratory distress syndrome.
D. The PDA spontaneously closes in approximately 75% of preterm infants with a birthweight above 1,000 g.
E. The rate of complications associated with percutaneous device occlusion of the PDA is similar in older children and neonates weighing more than 2,500 g.
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