Pathophysiology of Congenital Heart Disease in the Adult

Part I: Shunt Lesions

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C ongenital heart disease is common, occurring in \approx 8 of 1000 live births. With the successes in cardiothoracic surgery over the past 3 decades and the ongoing improvements in the diagnostic, interventional, and critical care skills of pediatric cardiologists, \approx 90% of children born with heart defects now survive to adulthood. In addition, using improved noninvasive techniques, adult cardiologists are increasingly identifying adults with septal defects that were undiagnosed in childhood. The adult congenital heart disease patients carry a spectrum of disease, from small septal defects and minor valvar obstructions to complex single-ventricle lesions that have been palliated with staged surgical repairs. It is estimated that \approx 1 million adults in the United States now have congenital heart disease, outnumbering their pediatric counterparts for the first time.

While the adult cardiology community struggles with a population that once was the exclusive domain of pediatricians, governmental agencies, national physician associations, and cardiology advisory boards are trying to define the scope of this national healthcare issue and to figure out how to train current and future generations of doctors. This specialized cardiac care will require the diagnosis of adult congenital heart disease in patients presenting de novo with new or chronic symptoms, the long-term maintenance of those previously diagnosed, and the ability to recognize when primary or additional interventions are required. As these patients increasingly present to cardiologists’ offices for care, healthcare professionals will need to develop a better level of comfort with adult congenital heart disease.

This 3-part series focuses on the pathophysiology of congenital heart lesions, which are seen commonly in adult patients. In this first portion, simple shunt lesions are reviewed. For each, the natural history and common clinical presentations resulting from the shunt are discussed. A discussion of therapeutic options and the literature supporting these options is beyond the scope of this series. Patient management is limited to a discussion of which patient requires intervention. The second article in the series examines the pathophysiology of simple congenital obstructive lesions; the third looks at the fascinating physiologies of some of the more complex congenital heart malformations.

Shunting Lesions

Perhaps no aspect of cardiology is as uniquely identified with congenital heart disease as intracardiac shunting lesions. Most adult congenital heart disease patients who require therapy present with a shunt.

With normal cardiac anatomy, there is complete septation of oxygenated and deoxygenated blood. The 2 circulations run in parallel, each feeding the other, and maintain a 1-to-1 volume relationship on the systemic and pulmonary sides of the circulation. The deoxygenated, systemic venous return to the right atrium (RA) is pumped to the lungs as the pulmonary blood flow (abbreviated Qp). Once oxygenated, the blood returns via the pulmonary veins to the left atrium (LA) and is pumped to the aorta as the systemic blood flow or cardiac output (Qs). The term “shunt” refers to an abnormal connection allowing blood to flow directly from one side of the cardiac circulation to the other. A left-to-right shunt allows the oxygenated, pulmonary venous blood to return directly to the lungs rather than being pumped to the body. A right-to-left shunt allows the deoxygenated, systemic venous return to bypass the lungs and return to the body without becoming oxygenated. In each case, the circulation is less efficient and creates increased demand on the ventricles. In most patients, the volume of shunted blood determines the severity of symptoms.

Left-to-Right Shunting

The metabolic needs of the body’s tissues are highly variable, depending on the patient’s level of activity. To maintain normal aerobic respiration at the cellular level, oxygen must be delivered in quantities sufficient to meet those needs. One measure of how well the cellular needs are being supplied is tissue oxygen delivery, the mathematical product of systemic arterial oxygen content and cardiac output. By definition, a left-to-right shunt allows a portion of the pulmonary venous return to escape back to the lungs, thereby reducing the cardiac output by the amount of the shunted volume. Tissue

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oxygen delivery is thereby reduced. The pathophysiology associated with each congenital shunt is reviewed in more detail below.

**Right-to-Left Shunting**

With normal cardiac anatomy, lung function, and hemoglobin levels, arterial blood oxygen contents vary only to the extent that pulmonary alveolar oxygenation changes. Under most physiological conditions, the blood oxygen content changes little and is more than adequate to supply the needs of the tissues. With a right-to-left shunt, however, deoxygenated systemic venous blood returns directly to the systemic arterial circulation. The oxygen content of the systemic arterial blood falls in proportion to the volume of systemic venous blood mixing with the normal pulmonary venous return. With reduced oxygen content, even with normal cardiac output, tissue oxygen delivery falls and the work capacity of the muscles is limited.⁶

**Quantifying Shunt Volumes**

The ratio of total pulmonary blood flow to total systemic blood flow, the Qp/Qs ratio, is a useful tool for quantifying the net shunt. A Qp/Qs ratio of 1:1 is normal and usually indicates that there is no shunting. A Qp/Qs ratio of >1:1 indicates that pulmonary flow exceeds systemic flow and defines a net left-to-right shunt. Similarly, a Qp/Qs ratio of <1:1 indicates a net right-to-left shunt. Both left-to-right and right-to-left (bidirectional) shunting may be present in the same patient. If the left-to-right shunt equals the right-to-left shunt in magnitude, it is possible to have a Qp/Qs of exactly 1:1.

**Atrial Septal Defect**

The formation of the atrial septum is a complex process, consisting of the growth and partial reabsorption of 2 tissue membranes, septum primum and septum secundum; the fusion of these membranes to the forming endocardial cushions; and the reabsorption of the fetal sinus venosus into the structure that will ultimately become the RA. In ≈4 of 100 000 newborns,⁷ an error in this developmental process will result in a defect in the wall separating the 2 atria, an atrial septal defect (ASD). There are a number of types of ASD (Figure 1), including the ostium primum defect (a result of the deficiency of endocardial cushion tissue), the ostium secundum defect (a result of excessive reabsorption of septum primum), and the sinus venosus defect (resulting from an error in the incorporation of the sinus venosus chamber into the RA).⁸ Although the following discussion of ASD pathophysiology is true for all types of ASD, the sinus venosus ASD also may be associated with anomalous pulmonary venous return and the ostium primum ASD with significant atioventricular (AV) valve abnormalities. These additional features may complicate the physiology further and are beyond the scope of this review.

**Pathophysiology**

The pathophysiology of an ASD is complex and multifactorial.⁹ Flow across the defect occurs in both systole and diastole. In most patients, flow is predominantly left to right, but transient right-to-left shunts are common, particularly with isometric strain. The bulk of the shunt flow occurs during diastole. In this phase, blood in each atrium has 2 alternative pathways: following the normal route through the AV valve to the ventricle on that side or passing through the ASD to fill the opposite ventricle. The direction of flow across the ASD during diastole is determined by the instantaneous differences in the compliance and the capacity of the 2 ventricles.

Ventricular chamber compliance is determined to a large extent by afterload. (Other factors such as intravascular volume status, myocardial muscle mass, chamber geometry, coronary perfusion, and pericardial and intrathoracic pressures also contribute to the intrinsic distensibility of the chamber.) In an otherwise normal patient, the left ventricle (LV), pumping to the systemic circulation, faces a substantially larger workload than the right ventricle (RV), pumping to the lungs. The LV becomes physiologically hypertrophied, reflecting its level of work, whereas the RV myocardium remains thin. The thick-walled LV will stretch/distend to accept additional volume less readily than the thinner RV. As a result, in the usual ASD patient, the difference in chamber compliance favors a left-to-right shunt because the blood in the LA finds it easier to fill the more compliant RV. In patients with increased RV afterload resulting from congenital obstructions in the pulmonary arteries or veins or with high pulmonary vascular resistance resulting from pulmonary parenchymal disease or primary pulmonary hypertension, the RV will be hypertrophied and less compliant. Left-to-right shunting at the ASD may be minimal, reflecting little overall difference between the 2 ventricles. With more severe RV noncompliance or distensibility, flow across the ASD may be predominantly from right to left. In some patients with reduced RV compliance, the RV may be able to handle a
normal cardiac output at rest but will not readily accept additional flow (when cardiac output increases), and a right-to-left shunt may occur only with exertion. Other factors such as a prior RV myocardial infarction, extrinsic compression of the RV, or any associated congenital abnormality that results in RV or tricuspid valve hypoplasia may reduce the effective RV capacity and impede its filling.

When the AV valves are closed, ventricular compliance no longer affects blood flow across the defect at the atrial level. Several factors determine flow volume and direction in systole. As in diastole, the size of the defect is a critical determinant in the volume but not the direction of flow. The atria may have differential capacities or compliances themselves, which may affect flow direction during systole. In patients with a large left-to-right shunt in diastole, pulmonary venous return will exceed systemic venous return (because Qp>Qs). Volumes in the 2 atria tend to equilibrate during systole, resulting in a left-to-right flow during that phase of the cardiac cycle. AV valve regurgitation also may affect the direction of ASD flow during systole. Significant mitral or tricuspid regurgitation may impede flow across an ASD, increasing or decreasing shunting during systole.

Finally, the size of the ASD itself helps to determine the volume of shunting. If the ASD is large, the defect creates little or no resistance to flow. Blood flow across the defect in diastole is determined entirely by the relative properties of the ventricles as above. With a smaller, restrictive defect, blood flow is limited by the resistance of the ASD itself, no matter how large the difference in ventricular compliance.

### Natural History

In a patient with an ASD, shunt direction and magnitude are variable and age dependent. In fetal life, RV noncompliance, a result of high pulmonary vascular resistance, allows nearly unidirectional right-to-left flow at the atrial level. Immediately after birth, with RV compliance comparable to that of the LV, there may be little net shunting through an ASD. Over several months, with the physiological fall in pulmonary vascular resistance, the RV thins, compliance falls, and the typical left-to-right shunt develops in children and young adults.

As a result of normal physiological changes associated with aging, the LV myocardium tends to become more hypertrophied and less compliant. With similarly sized ASDs, therefore, adults tend to have larger shunts as they age. It is part of the reason why children are rarely symptomatic but patients in their fourth or fifth decade may begin to develop the symptoms frequently associated with ASD. There are 4 common clinical presentations of ASD in the adult population.

Most frequently, adult patients complain of progressive shortness of breath with exertion. Studies have shown a reduction in maximum oxygen consumption in the unrepaired ASD population because of the inherent inefficiency of a continuously preload-reduced LV in combination with a volume overload in the pulmonary circulation. After repair of the ASD, exercise capacity improves within days to weeks.

Atrial arrhythmia, resulting from stretching of the conduction system, may be the first presenting sign of an ASD. An adult who presents with atrial arrhythmia at a young age should be evaluated for dilatation of the right-side cardiac chambers and evidence of an atrial level shunt. Prevention of long-term atrial fibrillation is one of the reasons for repairing ASD in young asymptomatic patients, although the subsequent development of atrial fibrillation may depend more on the patient’s age at intervention and may occur despite surgery in patients >25 years of age. Although both RA and RV volumes are reduced acutely with ASD repair and both chambers return to normal dimensions in children, there appears to be persistent RA enlargement when the ASD is closed in adult patients. This may explain an ongoing, increased risk of atrial fibrillation after adult ASD repairs compared with patients who underwent closure at a younger age.

Rarely, a patient with ASD will present with stroke or other systemic ischemic event caused by paradoxical embolization of thrombus through the defect similar to the patent foramen ovale (PFO; see below). Although most patients have a significant net left-to-right shunt through the defect, virtually all have transient flow reversal with the Valsalva maneuver or other isometric strain.

A small number of adult patients also may be identified echocardiographically when a heart murmur or unrelated cardiac symptoms in the absence of exercise, rhythm, or embolic symptoms bring them to a physician’s attention.

Pulmonary hypertension is uncommon with ASD, even in patients with large defects, in part because of the large capacitance of the pulmonary bed. Natural history studies dating to the presurgical and pre-echocardiography eras suggested an incidence of 15% in the ASD population. The observations that pulmonary vascular disease may develop in patients with a tiny ASD and that it is absent in the vast majority of patients with large ASDs suggest that the ASD may be an associated marker of pulmonary hypertension but not necessarily causative. More recent reviews suggest a rate of 6% to 9%. Once a patient has reached adulthood with normal PA pressures, the natural history is established: They no longer develop significant pulmonary hypertension related to the shunt, but they may have pressure elevation, like any other patient, as a result of the development of pulmonary parenchymal disease, left-sided heart dysfunction, or obstructive sleep apnea. It would be fair to say that the overall risk of and specific risk factors for developing pulmonary vascular disease with an ASD remain unknown.

When severe pulmonary hypertension from any cause results in RV systolic failure, high RV end-systolic volumes impede filling from the RA. With an intact atrial septum, there is systemic venous stasis and symptoms of “classic” right-heart congestive failure (anasarca and low cardiac output) because the LV can pump out only what it receives back from the lungs. In a patient with pulmonary hypertension and an ASD, however, the defect allows decompression of the right heart via a right-to-left shunt. The systemic venous blood does not need to traverse the lungs to reach the LV. It may cross through the ASD, mixing with the pulmo-
nary venous return in the LA, to augment LV preload. These patients are cyanosed from the right-to-left shunt and show minimal response to supplemental oxygen. However, tissue oxygen delivery is often better than in the patient without an ASD because the detrimental reduction in blood oxygen content is far outweighed by the maintenance of a normal or nearly normal cardiac output. For this reason, it is likely that repair of adult patients with ASD and moderate or severe pulmonary hypertension may not improve survival. Similarly, in patients with end-stage primary pulmonary hypertension, the creation of an ASD has been demonstrated to be of benefit in prolonging life and as a bridge to lung transplantation.

### Indications for Intervention

Significant questions remain about which ASDs should be closed because the natural history of the disease remains elusive. Generally accepted indications for closure of ASD include patients with ASD and echocardiographic evidence of right-sided cardiac volume loading, patients with ASD who are asymptomatic (principally exercise related), patients with ASD with exercise-related cyanosis (without pulmonary hypertension), patients with ASD who have suffered an episode of paradoxical thromboembolization, and potentially as prophylaxis in patients who require a noncardiac procedure with high risk of paradoxical embolization (ie, joint replacement therapy). A traditional open heart approach, dating back to 1954, and newer minimally invasive and robotic techniques are all available for surgical repair of the defects. The success and safety of transcatheter techniques have significantly increased the number of percutaneous closure procedures.

As above, pulmonary hypertension, with right-to-left shunting at rest (or a pulmonary vascular resistance of >14 Woods units), is the principal contraindication to ASD closure. However, patients may present with intermediate degrees of pulmonary hypertension with bidirectional or predominantly left-to-right shunts. It may be difficult with the limited data available in the literature to decide which of these patients should be offered closure. We have used temporary balloon occlusion of the ASD in the catheterization laboratory as our primary determinant. With occlusion of the defect and elimination of the right-to-left shunt, one can directly assess the acute impact on RA and pulmonary artery pressures and on cardiac output.

Similarly, patients may present with signs of left-sided congestive heart failure with a left-to-right shunt at the atrial level. Typically occurring in the elderly, this is related to changes in LV compliance (ie, status after myocardial infarction). In this scenario, the stiffer the LV chamber becomes, the larger the left-to-right shunt is. The shunt acts as a “popoff” for the LA, allowing the patient to maintain manageable pulmonary venous pressures, but also reduces LV preload and cardiac output. With closure of such a defect, the full impact of the LV diastolic dysfunction is felt (because all pulmonary venous return is forced into the LV), resulting in an acute rise in LA pressure and the potential development of pulmonary edema. Temporary balloon occlusion in the catheterization laboratory, with simultaneous LA pressure measurement, can be used to decide which patient will tolerate ASD closure.

### Patent Foramen Ovale

PFO, another communication in the atrial septum, is a remnant of the normal fetal circulation. Anatomically, the foramen ovale comprises overlapping portions of septum primum and septum secundum, acting as a 1-way flap valve allowing continuous right-to-left flow during fetal life. Because all venous blood (both deoxygenated systemic and the high-oxygen umbilical venous return) drains to the RA throughout fetal life, right-to-left flow is critical for perfusion and growth of the left heart. Postnatally, septum primum fuses to septum secundum, completing septation of the atria. However, in 20% to 25%, incomplete fusion leads to the persistence of the flap valve, leaving a PFO. Because it is present in all newborns, a PFO technically is not a “congenital” defect. But as the most common “hole in the heart” and currently the most common catheter intervention for structural heart defects, the PFO is deserving of mention in this discussion.

### Pathophysiology

Immediately after birth, with the acute increase in pulmonary blood flow, LA pressure rises to exceed RA pressure, pushing septum primum rightward, against septum secundum, shutting the flap of the PFO. When RA pressure rises intermittently with Valsalva or other isometric strain, the leaflets of the PFO may separate, with leftward excursion of septum primum, allowing flow from RA to LA, as was the norm throughout fetal life.

The degree to which the leaflets separate, the frequency with which the flap valve opens, and the amount of blood that crosses from right to left depend on a number of variables, including RV compliance, the difference in RA and LA pressure, distortion of the anatomy (ie, dilated aortic root, elevation of right hemidiaphragm), and most important, the tissue characteristics of septum primum. With a relatively rigid septum primum, right-to-left flow may occur only with strain. At the other extreme, the septum primum may be extremely thin and mobile, the so-called atrial septal aneurysm, and may open spontaneously with the changing phases of the cardiac or respiratory cycle. If septum secundum is less sturdy or in the case of LA hypertension, septum secundum may be pushed rightward and left-to-right shunting can be seen, the functional equivalent of a prolapsing or regurgitant valve. It is common for such a PFO to be labeled an ASD, although with clear overlap of septum primum and septum secundum, it is preferentially called a PFO.

### Natural History

In general, patients with PFO are never identified because they have no symptoms. Paradoxical embolization of thrombotic material is the most frequent clinical presentation. Although thromboembolic events to noncritical systemic structures may go unnoticed, cerebral embolization may produce stroke or transient ischemic attack, and coronary embolization may result in myocardial infarction in the absence of atherosclerotic disease.
and retinal infarcts have all been seen in our practice in patients with no risk factors other than PFO. Therefore, when no other source of thromboembolism can be detected, a PFO may be suspected.31

A number of other clinical syndromes are being studied for their apparent relationship to PFO, including migraine headache,32,33 hypoxemia,34 and decompression illness in divers and in people who work at altitude,35 as well as high-altitude pulmonary edema.36 The mechanism of the migraine relationship to PFO remains entirely unknown. Hypoxemia may occur in a patient with PFO, like in ASD, when RV compliance or capacitance is diminished and hemodynamics favor a right-to-left flow across the PFO. This physiology has been described for patients with obstructive sleep apnea,37 after pulmonary embolic events,38 and with RV infarction.39

In addition, significant hypoxemia can occur in the presence of normal right-heart pressures when anatomic distortion of the atrial septum accentuates right-to-left shunt at the atrial level, the platypnea orthodeoxia syndrome.40 These patients experience an acute fall in arterial oxygen saturation on changing from a supine to an upright position. Decompression illness is presumed secondary to right-to-left air embolization through the PFO in divers or people who work at altitude.35

Indication for Intervention

Despite the rapid growth, relative ease, safety, and efficacy of transcatheter devices,41–44 particularly compared with surgical closure, there are currently no approved indications for transcatheter PFO closure in the United States. Each patient with PFO should be considered individually. Treatment depends on the presenting symptom. Because the vast majority of patients with isolated PFO never have symptoms, there is no rationale for prophylactic closure in asymptomatic patients at this time.

For patients who have had paradoxical embolization, treatment options include antithrombotic agents, entrance in a randomized trial comparing blood thinners and closure, “off-label” transcatheter closure with a non-PFO device, or surgical repair. Because prospective, randomized, controlled trials are not yet completed, there is no definitive answer as to which therapy provides the best long-term prophylaxis from recurrent stroke. Similarly, there are few prospective data to date to support the closure of PFO in migraine sufferers. Multiple studies addressing this question are underway in the United States and Europe.

In contrast, patients with the platypnea orthodeoxia syndrome should have their PFO closed in all cases. Closure results in immediate elimination of right-to-left shunting and normalization of oxygen saturation. Recurrent decompression illness in divers may be preventable with PFO closure, although few data exist at this point.

Ventricular Septal Defect

Ventricular septal defect (VSD) is the most common form of congenital heart defect in children, accounting for ≈20% of human cardiac malformations. This is undoubtedly based on the complexity of the embryological development of the ventricular septum, which involves the fusion of multiple distinct septal components.45 The membranous septum, the site at which all of these components fuse, sits behind the septal leaflet of the tricuspid valve and immediately below the aortic valve in the LV outflow tract. The perimembranous type of VSD, which accounts for ≈80% of all VSDs, occurs in this location. Defects of the muscular septum are the next most frequent, are the result of excessive fetal muscular resorption, can be single or multiple, and can be located anywhere in the muscular septum. Endocardial-cushion–type VSDs (associated frequently with primum ASD as part of a complete AV canal defect), malalignment defects, and other defects of the outlet septum are less common (Figure 2). Endocardial-cushion VSDs often are associated with AV valve insufficiency, and outflow defects often are associated with aortic insufficiency, which further complicate the physiological consequences of the lesion.

Pathophysiology

The hemodynamic effects of a VSD are very different than those of an ASD. With a VSD, blood in each ventricle has 2 possible systolic pathways: through the usual outflow tract of that ventricle or through the VSD to the outflow tract of the other ventricle. It is the comparative resistance of each pathway that determines both the direction and volume of systolic flow across the VSD according to Ohm’s law.46 For example, with normal pulmonary vascular resistance and a large, nonrestrictive VSD, the sum of resistors from the LV to the pulmonary artery is very low compared with the resistance of flow to the systemic circulation, resulting in a large left-to-right systolic flow across the defect. If the VSD is very small, there is high resistance at the defect itself, limiting the left-to-right shunt, even with low pulmonary resistance. With elevation of pulmonary vascular resistance and a large defect, the sum of the resistors may approximate the aortic resis-
rance, and net shunting will be minimal. With pulmonary resistance higher than systemic resistance, the shunt will be right to left, no matter what size the defect is.

A left-to-right shunt at the ventricular level reduces LV output by the amount of the shunt. However, the body’s compensatory mechanisms will increase intravascular volume in response to a lower cardiac output until LV end-diastolic volume is sufficient to pump both a normal cardiac output and the proportionate left-to-right shunt. This results in significant LV volume overload. If, for example, 50% of the blood is shunted across the VSD to the lungs, the LV volume at end diastole must be 200% of normal to maintain a normal cardiac output. High LV volumes elevate LA filling pressures and may cause pulmonary venous congestion at rest or during periods of exertion.

A secondary effect of the large VSD is the transmission of LV pressure to the pulmonary vascular bed. With a large enough defect, the LV and RV become a functionally common chamber. With no RV outflow obstruction, the pressure in the pulmonary artery in systole equals the pressure in the aorta in systole. This pulmonary artery pressure elevation distinguishes a shunt at the ventricular level from a shunt at the atrial level. Although the volumes may be the same, the ASD does not generate the same pressure head/shear forces in the pulmonary bed. The combination of the volume and pressure contributes to the development of pulmonary vascular disease or Eisenmenger’s syndrome.46 Compared with the volume that crosses a VSD in systole, there is little flow in diastole. Diastolic flow across the VSD is much like that across the ASD in systole. Relative chamber volumes and compliance, as well as differences in ventricular contractile and relaxation properties,47,48 determine instantaneous flow direction. Flow outside of systole does not contribute significantly to the net shunt volume.

Natural History: Small VSDs

Patients with VSD present initially in infancy. With a small VSD and normally falling pulmonary vascular resistance, the patient develops a heart murmur in the first week as left-to-right flow develops. But because the shunt is small, these babies remain asymptomatic, and they grow and develop normally. With time, the septal leaflet of the tricuspid valve may become adherent to the ventricular septal surface, spontaneously closing the perimembranous VSD. Similarly, a muscular VSD may close spontaneously with progressive compression of the defect by the growing myocardial tissue. Once closed, these defects usually present no further medical issue for the patient. Endocardial-cushion defects and outlet defects do not close without intervention.

For adults with small persistent VSDs that have not closed who have nondilated LV and normal pulmonary artery pressure, there are only 2 ongoing risks. Infective endocarditis (any type of VSD) may be prevented with antibiotic prophylaxis for dental procedures.49 Progressive aortic insufficiency also may develop with either perimembranous or subpulmonary VSD as a result of aortic cusp prolapse into the VSD.50 Lifelong follow-up with echocardiographic evaluation is recommended.

Natural History: Large VSDs

In patients with moderate to large defects, symptoms of congestive heart failure become evident in the first few weeks of life. Untreated, these infants with high pulmonary blood flow and high pulmonary artery pressures will present with congestive heart failure: poor growth, rapid/labored breathing, tachycardia, and diaphoresis. They will be at risk for recurrent pulmonary infection. If they survive without therapy, they will develop pulmonary vascular disease in the first few years of life and progress to Eisenmenger’s physiology. In this process, the medial layer of the pulmonary arterioles becomes hypertrophied in response to the volume and the pressure transmitted from the LV.46 As pulmonary arteriolar vessel lumens shrink, pulmonary vascular resistance begins to rise. The pathway from the LV through the VSD to the lungs is no longer a low-resistance alternative, and the left-to-right flow diminishes. By history, children who have been in severe heart failure for the first few years of life “get better” as Qp/Qs returns to 1:1. The medial muscle layer of the pulmonary arterioles continues to hypertrophy, however, until small vessels are obliterated. Pulmonary resistance will eventually rise to exceed systemic resistance. At this point, patients will shunt from the RV through the VSD to the aorta, and the patient will become cyanotic. Intervention to close the defect at this time would lead to acute RV failure, venous stasis, low cardiac output, and a shorter life expectancy than if the defect were left open.51

Rarely, adults may present with new symptoms of exercise intolerance as a result of a moderate VSD associated with a left-to-right shunt sufficient to cause LV dilatation. These patients have had no symptoms through childhood but may become ill as the LV becomes less compliant with normal aging. In contrast to the ASD in which the volume is shunted to the right heart in response to LV chamber noncompliance, the LV must receive the shunted blood back from the lungs. When diastolic filling properties begin to change, the LV can no longer accommodate the additional volume at diastolic pressures as low as it had in childhood. LA pressures rise, and pulmonary venous congestion leads to symptoms of dyspnea on exertion.

In ≈0.2% of patients after myocardial infarction, rupture of the ventricular septum can produce a significant left-to-right shunt, with physiological consequences identical to those of the congenital VSD.52 Unfortunately for these patients, the acute reduction in LV stroke volume (reduced by the amount of the shunt) and the resulting volume load imposed on the LV compound the global or segmental myocardial dysfunction from the ischemic insult. Over the first 10 to 14 days after the infarct, shunting across the septal defect may increase, potentially dramatically, as surrounding tissue continues to necrose, enlarging the diameter of the defect.53 Supportive care alone results in ≈90% mortality.54,55 Iatrogenic VSDs also may occur after aortic valve replacement, septal ablations, and the Konno procedure to enlarge the LV outflow tract.

Indication for Intervention

Because the natural history of the congenital VSD is well established by the time patients reach adulthood, intervention
Pathophysiology

As in the patient with VSD, shunt direction and volume depend on the relative resistances to flow in each pathway. In most patients, systemic resistance is significantly higher than pulmonary resistance, resulting in left-to-right flow (aorta to main pulmonary artery). As in VSD physiology, the size of the PDA is the critical resistor in the circuit and is the principal determinant of the volume of flow. As with a VSD, in a patient with a large PDA, the LV end-diastolic volumes (preload) must increase to allow the stroke volume to supply both the normal cardiac output and the left-to-right shunt at the PDA. LA filling pressures rise, and pulmonary venous congestion may limit exertion. In contrast to the VSD patient, aortic blood has a route to the pulmonary circuit in both systole and diastole, so flow occurs throughout the cardiac cycle. In large enough defects, this diastolic “runoff” (similar to a patient with aortic valve regurgitation) may result in impaired coronary and splanchnic perfusion.

Natural History

The clinical course of PDA is similar to that of patients with VSD. If the PDA is large, the patient presents with symptoms of congestive heart failure in infancy and usually goes on to develop Eisenmenger’s physiology if the defect is not repaired. As pulmonary vascular resistance rises, a right-to-left shunt develops at the PDA. This creates a unique clinical picture. The aorta proximal to the PDA receives fully saturated flow from the LV, and the postductal aorta receives a mixture of LV and desaturated RV blood. “Differential cyanosis” is the result, with normal or nearly normal oxygen saturation in the arms and head and hypoxemia/desaturation in the lower body. Patients may be identified by this differential coloration and by selective clubbing in the feet. These PDAs cannot be closed for the same physiological reasons that the Eisenmenger patients do not tolerate VSD closure.

If the PDA is small in the child or young adult, there are no clinical symptoms because of the relatively small volume of left-to-right flow. The risk of endarteritis remains, and prophylaxis is required for dental work.

More frequently than in the VSD population, we have seen small to moderate PDAs present with new symptoms in adulthood. The development of systemic hypertension, with its rise in systemic resistance, increases shunting at the PDA. This, combined with diminishing LV compliance (as the ventricle hypertrophies), may substantially increase LV filling pressures and lead to pulmonary venous congestion. In patients with moderate shunts but normal PA pressure, chronic LA volume loading and dilatation may lead to the development of atrial arrhythmia.

Finally, the diastolic runoff from the aorta may lead to a coronary “steal” phenomenon as the ductus competes for aortic diastolic flow. Patients may present with exertional angina in the absence of obstructive coronary artery disease.

Indications for Intervention

There are several clinical indications for intervention in adult patients with PDA, including a significant left-to-right shunt with LV and LA volume overload (without pulmonary hypertension), clinical symptoms as above, or a history of endarteritis at the PDA or adjacent structures. There are no data to suggest that closure of a small, non–volume-loading PDA in an asymptomatic adult is superior to dental prophylaxis alone. Surgical closure of PDA, first performed in 1938, has been replaced over the last decade by transcatheter closure devices in both children and adults.

Pulmonary Arteriovenous Malformations

Pulmonary arteriovenous malformations (AVMs) are abnormal connections between branches of the pulmonary arterial and pulmonary venous systems that bypass the small arterioles and the air-containing spaces of the lung. They occur...
most frequently as part of the hereditary hemorrhagic telangiectasia syndrome, an autosomal-dominant disorder, and may occur as isolated or multiple defects that develop later in life. Isolated pulmonary AVM also may be congenital in nature or secondary to trauma or infection. Small pulmonary AVMs distributed diffusely throughout the lung fields may be a product of pulmonary parenchymal disease or the result of end-stage liver disease. In complex congenital heart disease patients, diffuse small pulmonary AVMs also may occur with a long-standing Glenn shunt (superior vena cava to pulmonary artery).

**Pathophysiology**

In the presence of a pulmonary AVM, flow through the pulmonary artery has 2 potential pathways: the high-resistance blood vessels of the pulmonary arteriolar and capillary bed and the low-resistance, fistulous pathway back to the pulmonary vein and LA. This creates an intrapulmonary right-to-left shunt because the desaturated blood bypasses the filtering and oxygenation mechanisms at the alveolar level.

The magnitude of the shunt depends on the resistance of the fistulous pathway and on the number of fistulas present. With smaller shunts, patients are usually asymptomatic. In such a patient, the first clinical presentation of the pulmonary AVM may be occlusive stroke or another thromboembolic event secondary to paradoxical embolization. With much larger single lesions or more numerous pulmonary AVMs, patients may be hypoxemic because of the flow of desaturated blood to the LA. Rarely, postural changes may redistribute pulmonary flow to the lung segment(s) that contain the pulmonary AVM, increasing shunting and creating postural desaturation (orthodeoxia). Recent studies also have linked migraine headache with aura to right-to-left shunting in the hereditary hemorrhagic telangiectasia syndrome population.

**Indications for Intervention**

In the presence of clinical cyanosis, transcatheter embolization is the treatment of choice for individual pulmonary AVMs. Surgical lung resections are rarely required. The choice of transcatheter closure device depends entirely on the size and location of the fistula to be closed. With multiple pulmonary AVMs, some or all of the defects may be closed, provided that pulmonary blood flow and pulmonary artery pressures are not adversely affected. Diffuse, microscopic pulmonary AVMs such as those seen in end-stage liver disease cannot be treated with embolic therapy. Closure of pulmonary AVMs to prevent recurrent paradoxical embolization and migraine headache remains unproven, similar to PFO closure.

**Coronary Fistulas**

Communications between the coronary arteries and the cardiac chambers (coronary-cameral fistulas) or low-pressure veins (coronary arteriovenous malformations) are most often congenital in nature. They also may be acquired secondary to trauma or from invasive cardiac procedures such as pacemaker implantation, endomyocardial biopsy, coronary artery bypass grafting, or coronary angiography. Fistulas may arise from any branch of the coronary artery system. In congenital fistulas, drainage is most often to the RV, RA, or the pulmonary arteries and less frequently to the superior vena cava, coronary sinus, pulmonary veins, or LA.

**Pathophysiology**

The physiological derangement depends principally on the resistance of the fistulous connection and on the site of fistula termination. The resistance is determined by the size, tortuosity, and length of the pathway. As in a PDA, flow from the coronary artery to a venous structure, or right-sided cardiac chamber, occurs throughout the cardiac cycle. Blood follows the lower-resistance pathway through the fistula rather than traversing the smaller arterioles and capillaries of the myocardium. With larger fistulas, a “diastolic runoff” may occur, drawing blood away from the normal coronary pathway with a widened pulse pressure and a coronary “steal.” There is a left-to-right shunt if the fistula drains to the systemic venous side of the circulation. Unlike the left-to-right shunt of either ASD (RV volume load) or VSD/PDA (LV volume load), such a shunt volume loads both ventricles. When the drainage site is the LA or pulmonary vein, there is an effective “left-to-left” shunt, volume overloading the left heart only.

**Natural History**

Most coronary artery fistulas are small, and patients are asymptomatic because myocardial blood flow is not compromised. A continuous murmur may be audible at the left lower sternal border. With increased flow, the coronary artery branches proximal to the shunt site become significantly enlarged. Small coronary fistulas in children tend to grow with age. If untreated, fistulas cause clinical symptoms in 19% of patients <20 years of age and in 63% of older patients. Symptoms and sequelae include chronic myocardial ischemia and angina, congestive heart failure, cardiomyopathy, myocardial infarction, pulmonary hypertension, endocarditis, and rarely fistula rupture.

**Indications for Intervention**

Small fistulas in asymptomatic patients should be followed up clinically for signs of growth and increasing flow. Large, hemodynamically significant fistulas should be closed electively at the time of diagnosis. Surgical closure usually is performed on a beating heart from the epicardial surface, is associated with low mortality and morbidity, and has excellent immediate and long-term outcomes. Various transcatheter occlusion techniques have been used with excellent outcomes for fistulas with shorter, less tortuous courses.

**Conclusions**

Intracardiac and intravascular shunting is a common clinical condition for patients with adult congenital heart disease. These patients can present de novo with a previously undetected lesion when shunt-related symptoms first occur in adulthood. They may suffer from paradoxical embolization, endocarditis, or valve deterioration indirectly related to the defect, which draws attention to the defect for the first time.
Familiarity with the pathophysiology of each lesion will help the cardiologist care for these unusual patients.

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Disclosures

None.

References


