LEFT-TO-RIGHT CARDIAC SHUNT: PERIOPERATIVE ANESTHETIC CONSIDERATIONS

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Abstract

Congenital heart disease (CHD) affects roughly 8/1000 live births. Improvements in medical and surgical management in recent decades have resulted in significantly more children with left-to-right cardiac shunts surviving into adulthood. Surgical care of these patients for their original cardiac defect(s) or other non-cardiac medical conditions requires thorough understanding of cardiopulmonary changes and mastery of treatment options. Commonly encountered CHD with left-to-right shunt include atrial septal defect (ASD), ventricular septal defect (VSD), endocardial cushion defect (ECD) and patent ductus arteriosus (PDA). The key pathological change is increased pulmonary vascular resistance (PVR) and pressure secondary to increased blood flow from the left-to-right shunt. Increasing PVR and pulmonary arterial hypertension (PAH) will lead to reversed direction of blood flow through the cardiac defect (Eisenmenger Syndrome) and heart failure. Cardiac defects with left-to-right shunt generally require surgical or trans-catheter repair at an early age. We review the current concepts and general principles of perioperative anesthetic management of CHD, including neuraxial anesthesia. Current techniques and unique pharmacodynamic and pharmacokinetic effects of some commonly used anesthetic agents in patients with left-to-right shunt are also reviewed.

Introduction

Congenital heart disease (CHD) affects about 8/1000 live birth[1,2]. Both genetic and environmental factors play important roles in the pathogenesis of CHD. However, those identifiable environmental risk factors can only be identified in 10% of clinical patients[2]. The number of infants born with CHD has increased significantly over the past fifty years, largely due to advancement in medical imaging technology which allows for the detection of a greater number of cardiac abnormalities[2,3]. With the advancement in medical and surgical management of those patients

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with CHD, many of them now survive into adulthood. Currently, it is estimated that there are nearly one-million adult CHD patients in the USA alone, which outnumbers children with CHD[4]. These patients will need surgical interventions in their adult life either for their original cardiac abnormalities or other non-cardiac co-existing medical conditions. A thorough understanding of the anatomy, pathophysiology, clinical presentation, preoperative evaluation, and management of those patients with left-to-right (systemic to pulmonary) cardiac shunt is essential for the optimal anesthetic management for cardiac and non-cardiac surgical procedures.

CHD can be cyanotic and noncyanotic. CHD can be atrial, ventricular, septal, or vascular if categorized according to the site of the abnormality. CHD has been divided into 5 major categories according to the pathophysiology of the congenital cardiac lesions[5] (Table 1).

Table 1

Pathophysiological classification of CHD[5]

| CHD w CHD with increased pulmonary blood flow (septal defects without pulmonary obstruction and left-to-right shunt) |
| --- |
| CHD w CHD with decreased pulmonary flow (septal defects with pulmonary obstruction and right-to-left shunt) |
| CHD C CHD with obstruction to blood progression and no septal defects (no shunt) |
| CHD S CHD so severe as to be incompatible with postnatal blood circulation |
| CHD si CHD silent until adult age |

This review will focus on left-to-right cardiac shunts and the anesthetic considerations for patients with these malformations undergoing cardiac or noncardiac surgical procedures. The commonly-encountered congenital cardiac defects with left-to-right shunt include ventricular septal defect (VSD), atrial septal defect (ASD), endocardial cushion defect (ECD), and patent ductus arteriosus (PDA). Though these cardiac defects are not always isolated entities, often times they are associated with other congenital abnormalities. For the convenience of discussion, single lesions rather than various syndromes with multiple defects will be discussed.

Pathophysiological changes induced by left-to-right cardiac shunt

In the presence of a cardiac septal defect, blood flows through the defect secondary to a pressure gradient existing at the different sides, usually from the left side (higher pressure) to the right side of the heart. The direction and the quantity of the blood flow through the defect are dependent upon the pressure gradient. A Left-to-right shunt sends some oxygenated blood back through the pulmonary circulation instead of entering the systemic circulation. Therefore, the patient does not develop cyanosis, at least at earlier stages, which may potentially delay the patient from seeking medical intervention and establishing the correct diagnosis. Some patients will develop cyanosis later in life due to reversed direction of the blood flow through the cardiac defect secondary to pulmonary hypertension. The persistently increased pulmonary blood flow due to left-to-right shunt may result in the following pathophysiological changes:

1. **Increase in pulmonary vascular resistance (PVR) and development of pulmonary arterial hypertension (PAH)**: The increased blood flow and potentially higher pressure due to the left-to-right shunt leads to damage of small pulmonary arteries and arterioles with intimal and medial smooth muscle cell proliferations, arteriolitis and necrosis of the arterial wall, aneurysmal dilatation, and glomoid-like plexiform lesions[5]. These changes consequently result in obstructive vascular lesions (or pulmonary vascular disease) due to the arterial wall thickening and lumen narrowing, as shown in Figure-1, which increase vascular resistance[5]. When PVR increases to a certain extent, the quantity of shunted blood will decrease due to lowered pressure gradient across the cardiac defect. With increase of PVR, the shunting volume of blood will decrease and the ratio of pulmonary circulation/systemic circulation (Qp/Qs) will decrease. With increases in pulmonary blood pressure, the direction of blood flow through the defect may be reversed from "left-to-right" to "right-to-left" if right-sided pressure surpasses that of the left side. This converts the noncyanotic congenital cardiac defect into a cyanotic disease (as Eisenmenger Syndrome). To prevent the pathogenesis of the permanent/irreversible pulmonary vascular changes and eventual pulmonary hypertension
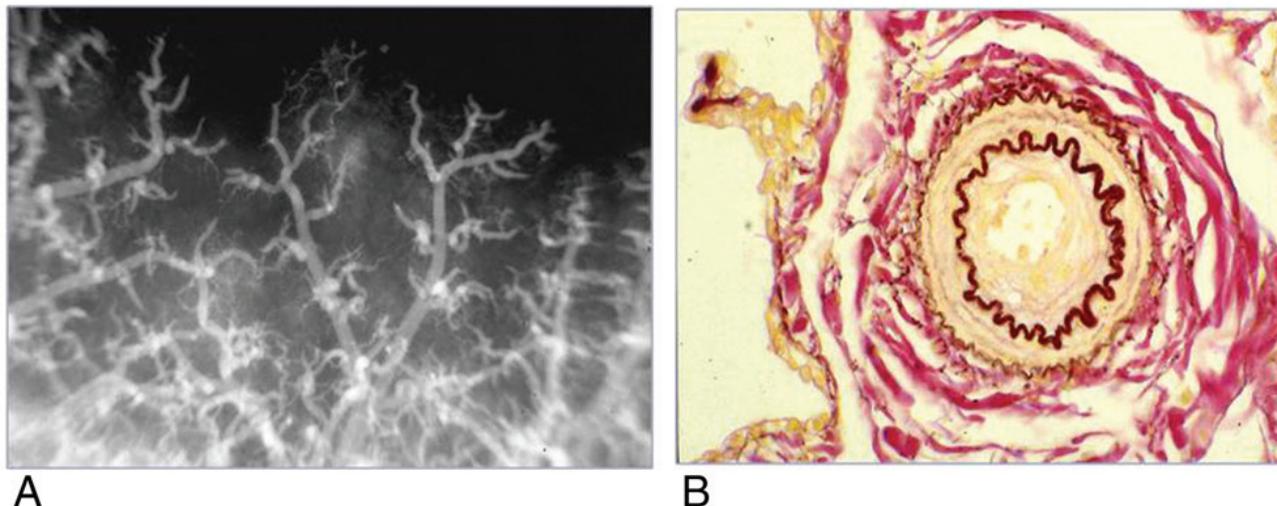
(A) Pulmonary vascular disease in a patient with complete AV septal defect. Postmortem injection of contrast material in the pulmonary arteries showing the typical "winter tree" appearance of the distal arterial circulation.
(B) Histology of the lung of the same patient showing subocclusion of the lumen of a small artery due to concentric intimal fibrosis[5].
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and Eisenmenger Syndrome, it is highly recommended that these cardiac defects be repaired within 1-2 years of life either surgically or non-surgically[5].

With an ever-increasing PVR, PAH will ensue. PAH is a serious complication of CHD which will ultimately lead to heart failure. Without early surgical intervention, about one-third of pediatric CHD patients will develop significant PAH. Data from the Netherlands indicates that more than 4% of adult CHD patients have PAH[5]. The incidence is higher in those with septal defects and left-to-right shunt. Pulmonary hypertension seems to occur more likely in patients with VSD. Eisenmenger's syndrome, characterized by reversed pulmonary-to-systemic (right-to-left) shunt, represents the most advanced form of PAH in patients with CHD and affects as many as 50% of those with PAH and left-to-right shunts. It is associated with the poorest outcome among CHD patients with PAH[5]. Morbidity increases as older patients are at increased risk of arrhythmia, heart failure, valve regurgitation and PAH. Data demonstrates that the probability of PAH increases with age in patients with cardiac defects[6]. The increase in pulmonary pressure is due to increased volume load to the right heart and physical narrowing of pulmonary vascular lumen. It can also be caused by the increased pulmonary vascular tonicity and impaired

relaxation induced by the left-to-right shunt-associated endothelial dysfunction and its associated biochemical changes. The support for this theory is the study of MacLean with experimental pulmonary hypertension associated with left-to-right shunt. This study revealed that intracellular cAMP was reduced due to increased degradation of cAMP by phosphodiesterase[7]. In humans with pulmonary vascular disease associated with left-to-right shunt, PGI_2-synthase has been shown to be reduced, which may lead to decreased synthesis of PGI_2, an arachidonic acid metabolite, which relaxes arterial vessels[8]. However, Loukanov *et al* reported plasma cAMP levels in patients with left-to-right shunt do not correlate with hemodynamic findings. This observation should be taken into account when assessing potential changes in plasma cAMP in patients treated with vasoactive substances known to interfere with the synthesis of cAMP[9].

Genetic factors appear to predispose certain patient to develop pulmonary hypertension. A recent study correlated the Glu298Asp polymorphism of the endothelial nitric oxide synthase gene and pulmonary hypertension in children with congenital cardiac diseases[10]. They looked at a total of 80 children with congenital cardiac diseases at a median age of 3.8 years, ranging 0.136.2- years. The Glu298Asp

polymorphism was identified using PCR and restriction fragment length polymorphism. The study found that although gene frequency for Glu298Glu, Glu298Asp, and Asp298Asp was not different in the control group compared to these patients, the endothelial nitric oxide synthase polymorphism was related to acute post-operative elevation of pulmonary artery pressure (genotypic frequency 53.3% versus 25%; Armitage trend test: p50.038). In addition, the allelic frequency of the Glu298Asp was related to post-operative pulmonary hypertension (Fischer's exact test: p50.048). The authors believe that patients with left-to-right shunt are more likely to develop acute elevation of pulmonary artery pressure after cardiopulmonary bypass when presenting with the Glu298Asp polymorphism of the gene endothelial nitric oxide synthase[10]. This could be used as a genetic marker for the predisposition for the development of pulmonary hypertension after intra-cardiac repair[10]. Yap *et al* found that PAH is a high risk predictor of postoperative complications for patient with CHD and PAH to have cardiac and non-cardiac surgical procedures[11].

2. **Cardiomegaly and cardiac remodeling:** Persistent left-to-right shunting of blood can lead to the enlargement of the right atrium and/or right ventricle depending upon the location of the CHD and the severity of the volume and/or pressure overload. Dilated cardiomegaly has been reported in patients with ASD[12]. Chronic blood overload in the cardiac chambers potentially initiate a cardiac remodeling process. Sugimoto *et al* studied serum level of procollagen type III N-terminal amino peptide (PIIIP) and the severity of CHD. The increased serum PIIIP levels in proportion to the severity of ventricular load or cyanosis suggest enhanced myocardial synthesis of collagen type III in patients with CHD. Suppression of the PIIIP level by an angiotensin converting enzyme (ACE) inhibitor suggests the involvement of the renin-angiotensin-aldosterone system in myocardial fibrosis. This remodeling mechanism seems to be similar to other pathological condition-related cardiac hypertrophy and remodeling, in which the renin-angiotensin-aldosterone system (RAA) is contributing. There is plenty of evidence that ACE inhibitors and direct RAA inhibitors are effective in affecting cardiac remodeling process[13,14]. Additional future understanding of the cellular mechanism of this remodeling process will likely provide the basis for the development of newer diagnostic and therapeutic strategies in patients with CHD.

3. **Dysrhythmias:** Atrial, ventricular and other types of dysrhythmias can occur in patients with left-to-right cardiac shunt. These rhythm disturbances likely are due either to the intrinsic nature of the anomaly or to morphological changes secondary to blood overloading the right-side of the heart, or surgical palliation. Tachyarrhythmias, either supraventricular or ventricular, and bradyarrhythmias, either sinus node dysfunction or atrioventricular block, may occur frequently. Technological advances in intervention and surgical approaches have led to prophylactic and therapeutic reduction in arrhythmias[15]. Nagao *et al.* studied the relationship of duration of ASD and the occurrence of atrial fibrillation, and found that the incidence of atrial fibrillation in patients with CHD is highly related to the aging/duration of ASD[16].

4. **Myocardial ischemia**: Left-to-right shunt related hemodynamic overload in patients with CHD may induce myocardial ischemia. Sugimoto *et al.* studied the changes of troponin I and Brain Natriuretic Peptide (BAP) and its N-terminal prohormone fragment (NT-proBNP) in 412 children with CHD (30 ASD, 32 VSD) and 350 normal children (control group) over a five year period. Troponin I is currently believed to be the most sensitive marker of myocardial injury. The study found that serum troponin I levels in healthy children with CHD are increased[17] and troponin I levels in pediatric patients with ASD and VSD are significantly higher than in those of healthy children. More interestingly, patients with VSD and significantly elevated levels of troponin I were associated with pulmonary hypertension[17].

Anatomical changes of left-to-right cardiac shunt

ASD: Based on the portion of the atrial septum that has failed to develop normally, ASDs are anatomically classified into four types: ostium secundum (85%), ostium primium (10%), sinus venosus (5%), and coronary sinus defects (rare)[18]. Spontaneous closure occurs by 18 months in almost all patients born with ASDs <3 mm diameter and in 80% of those with

defects 3-8mm[19,20]. Defects with diameters >8 mm rarely close spontaneously and may require surgery later in life[20].

VSD: Ventricular septum is composed of a smaller membranous part and a larger muscular portion. The membranous part of the septum is separated into the pars atrioventricularis and the pars interventricularis by the tricuspid valve. True membranous VSD lesion is completely bordered by fibrous tissue. If the lesion penetrates into any portion of the muscular septum, the defect is named a perimembranous, paramembranous, or infracristal defect[21]. The muscular portion is composed of three sections: inlet, trabecular, and infundibular. Inlet VSDs are located in the inlet portion of the muscular septum which is inferioposterior in relation to the membranous section of the septum. There are no muscular fibers that separate this type of defect from the atrioventricular valve. The muscular portion that makes up the majority of the septum is termed the trabecular subunit. Lesions within this section that are encompassed by muscular tissue are termed muscular lesions. Finally, the infundibular subunit is the portion of the septum that divides the outflow tracts of both ventricles[21]. Depending on the size of the lesion, small VSDs are usually clinically insignificant, whereas the larger ones usually cause more hemodynamic instability and can lead to other pathologies, such as CHF and PAH[22]. Generally, only a portion of the patients with VSD become clinically symptomatic. Moderate to large defects become hemodynamically significant left-to-right shunts in the first 2-6 weeks of life[23]. The size and morphology of a VSD are important determinants of spontaneous closure and to the need for surgical intervention. Early age at presentation, in contrast, is not predictive of the need for surgical intervention. In early childhood, there appears to be very little risk of endocarditis or aortic valvular prolapse.

ECD: Endocardial cushion defects (also referred to as atrioventricular canal defects) are the result of irregular development of the fetal heart. The endocardial cushions are the portions of the fetal heart that form the adult atrioventricular valves. They also develop into the contiguous portions of the atrial and ventricular septums[24]. When the endocardial cushions fail to fuse and develop properly, the result can be either a single defect in the atrial septum known as an atrial primum defect or a defect that involves any of the structures that the endocardial cushions develop into. When all of the structures that the endocardial cushions develop into are abnormal, it is known as a complete atrioventricular canal defect[25]. ECDs are not among the most common forms of congenital heart defects in the general population. On the contrary, those with Down's syndrome have a much higher chance of being affected. This is particularly true for the complete form of endocardial cushion defect-those with abnormal atrioventricular valves and septums[25]. It is thought that approximately 33 % of patients with the complete form also suffer from Down syndrome[21]. Although a single defect in the atrial septum may not pose a huge problem for a patient, a complete atrioventricular canal defect can cause major dilemmas. The issues arise from left-to-right shunts that form at the points of both the atrial and ventricular septal defects[25]. As mentioned earlier, this allows blood to flow from the systemic circulation into the pulmonary circulation. Because of the significance of the shunt, early onset CHF is common. Surgical repair is generally recommended when CHF is present. Surgery is usually suggested prior to one year of age[26].

PDA: Patent ductus arteriosis is not an intracardiac left-to-right shunt; but, it causes similar pathophysiological alterations as other left-to-right cardiac abnormalities. PDA is not considered an abnormality until it persists beyond 2 to 3 days post-natal[27]. With some functional similarities, PDA is like a mild form of ASD. PDA usually does not have a detrimental effect on the developing child. However, it is generally recommended that these be surgically corrected at an early age to prevent future complications, such as pulmonary hypertension and CHF[2]. Interestingly, there are some associated congenital heart abnormalities that require a patent PDA in order for survival. In such cases as tricuspid or aortic atresia, it may be necessary to give PGE_1 in order to maintain the patency of the ductus[2].

Clinical Presentation

The clinical manifestations of left-to-right cardiac shunt depends on the age of the child, site and

size of the anomaly. Failure to thrive is a very common presentation in children with CHD and influences the metabolic response to injury and outcome after corrective cardiac surgery. Energy imbalance is a major contributing factor. The age and time of corrective surgery affects the potential for nutritional recovery. Although the immediate postoperative period is characterized by a hypermetabolic state, low total and resting energy expenditure are reported within 24 hours of surgery. After 5 days, resting energy expenditure returns to preoperative levels. Significant improvements in weight and growth occur within months after corrective surgery. However, limited postoperative recovery in nutritional status and growth occurs in infants with a low birth weight, intellectual deficit, or residual malformation. Further studies are needed to elucidate the timing of corrective cardiac surgery to maximize nutritional outcomes and to identify those infants who may benefit from aggressive preoperative nutrition support[28]. Avitzur et al. studied the Resting Energy Expenditure (REE) in 29 children younger than 3 years of age with CHD (14 cyanotic and 15 noncyanotic CHD) before and after open heart surgery. The study found that REE was similar in the cyanotic and the noncyanotic children before and after surgery. These parameters, REE, VCO2, and VO2, were similar in children with cyanotic versus noncyanotic CHD, similar before and after surgery. The Schofield equation is more accurate than the WHO equation in predicting energy needs of children with CHD, but measurement of REE is preferred over calculation of REE[29].

ASD: Small ASDs are usually asymptomatic in early life and the defects may close spontaneously[19]. Larger defects will cause symptoms such as shortness of breath, fatigue, and lethargy. Later in life, some patients may present with atrial dysrhythmias and even Eisenmenger's syndrome. Severe defect may present with symptoms of CHF as early as the first year of life.

VSD: Moderate to large VSDs can cause delayed growth and development, decreased exercise tolerance, pulmonary infections, and congestive heart failure during infancy. On physical examination, a systolic thrill at the left lower sternal border, increased P_2 intensity, regurgitant holosystolic or early systolic murmur, or an apical diastolic rumble may be heard.

ECD: ECD usually presents in the immediate neonatal period with cyanosis due to large intracardiac communications and relatively high pulmonary vascular resistance. Undernourishment with failure to thrive, repeated respiratory infections, tachycardia, tachypnea, and CHF present early in infancy. Physical examination usually reveals a systolic thrill, holosystolic regurgitant murmur, and a mid-diastolic rumble at the left sternal border.

PDA: Large PDAs may cause atelectasis, lower respiratory tract infections, CHF, tachycardia, exertional dyspnea, tachypnea, and poor weight gain. When pulmonary vascular obstructive disease ensues (Eisenmenger's syndrome), cyanosis in the lower half of the body and left arm develops. On physical examination, a continuous "machinery" murmur, a systolic thrill at the left upper sternal border and bounding peripheral pulses with wide pulse pressure can be appreciated.

Diagnosis

With current medical technologies, it is generally not too difficult to make a diagnosis for most CHDs. Physical examination, auscultation with stethoscope, EKG, chest radiograph (CXR), and echocardiography offer reasonably accurate diagnosis. There are occasions in which other strategies are needed for the establishment of diagnosis or assessment of cardiac functions or hemodynamic status. Additionally, transesophageal echocardiography may be required in older children and adults when transthoracic 2-D echocardiography cannot adequately visualize all cardiac structures. Cardiac catheterization can be a useful technique not only in establishing the correct diagnosis, but also in assessing cardiac functions. It can be especially important for preoperative evaluation for certain surgical procedures. Angiographic CT imaging has been used in the cardiac catheterization laboratory for the diagnosis of congenital heart disease.

Clinically, a patient with a small PDA defect is usually asymptomatic. If the PDA shunt is large, an apical diastolic rumble may be heard. A PDA patient usually has left ventricular hypertrophy, left atrial hypertrophy, right ventricular hypertrophy, and cardiomegaly on x-ray. 2-D echocardiography is

diagnostic and dimensions of the left atrium and left ventricle provide important assessment of the size of the left-to-right shunt across the PDA[30].

An ECD patient has an accentuated S_1, a narrowly split S_2, and an accentuated P_2 present. ECD patients usually have superior axis deviation of the QRS complex, which lies between 0 and-150 degrees. The symptoms of patients with VSD are dependent upon the size of the shunt; Cardiomegaly involving the left atrium, left ventricle, and right ventricle may be seen on chest X-ray with increased pulmonary vascular markings. 2-D echocardiography with Doppler can identify the size and exact location of the defect[31].

Predictors of clinical outcome

1. Pulmonary hypertension and Eisenmenger Syndrome: Without early surgical repair, about one third of patients with CHD will develop PAH[6]. Eisenmenger's syndrome, characterized by reversed pulmonary-to-systemic (right-to-left) shunt, represents the most advanced form of PAH-CHD and affects as many as 50% of those with PAH and left-to-right shunts. It is associated with the poorest outcome among patients with PAH-CHD[6]. In patients with suspected pulmonary vascular disease anticipating a two-ventricle repair, although preoperative testing via cardiac catheterization with vasodilators is reasonable, the preoperative parameters and the precise values of these parameters that best correlate with early and late outcome remain unclear[32].

2. Vasodilator responders have a better outcome: Krasuski *et al* studied 215 patients with PAH. The vasoreactivity of patients was assessed during inhalation of 40 parts per million nitric oxide (iNO) and vasodilator responders were defined as those participants who achieved a mean pulmonary artery pressure (PAP) of ≤ 40 mm Hg and a drop in mean PAP $\geq$ the median for the cohort (13%). There were 51 deaths (25.9%) over a mean follow-up period of 2.3 years. It was found that vasodilator responders had significantly improved survival regardless of whether or not they had idiopathic or nonidiopathic PAH or whether or not they had Dana Point class 1 or non-Dana Point class 1 PAH. In multivariate modeling, advanced age, elevated right atrial pressure,

elevated serum creatinine, and worsened functional class significantly predicted shorter survival, whereas vasodilator response predicted improved survival. It was concluded that vasodilator responsiveness to iNO is an important method of risk stratifying PAH patients, with results that apply regardless of clinical etiology[33].

3. Older age: As discussed previously, older patients with CHD have higher morbidity and mortality rate if they undergo a surgical procedure. They are at increased risk of arrhythmia, valve regurgitation, PAH and heart failure. Data showed that probability of PAH increases with age in patients with cardiac defects[6].

4. Gender: Shapiro *et al.* investigated the gender differences in patients with CHD and pulmonary hypertension. 2318 female and 651 male patients were studied and a greater number of females had PAH associated with connective tissue disease (P <0.001). Further, more males had portopulmonary hypertension (P <0.001); more females had congenital heart disease-associated PAH (P = 0.017), thyroid disease (P <0.001), and depression reported (P $\leq$0.001). At diagnosis, males had higher mean pulmonary arterial pressure (53 $\pm$ 14 vs. 51 $\pm$ 14.3 mm Hg; P = 0.013) and mean right atrial pressure (10 $\pm$ 6 vs 9 $\pm$ 6 mm Hg; P = 0.031). Females had better survival estimates for 2 years from enrollment and for 5 years from diagnosis[34]. However, Klitzer *et al.* showed the opposite results in mortality with the female gender associated with an 18% higher in-hospital and 30-day post-discharge mortality as compared with male gender. There was no difference in length of hospital stay between males and females[35]. Therefore, the precise effect of gender on the short-term and long-term survival of patients with CHD will require additional investigation.

Treatment

ASD: Management of an ASD is by either surgical or trans-catheter correction of the defect. Usually, small ASDs require no treatment, whereas larger ones are corrected surgically at an early age. And correction of an ASD should not occur prior to 2 years of age owing to the chance of natural closure of the defect[19], Defects that close on their own are generally located within the ostium secundum portion of the atrial septum[26]. The degree of shunt should

be determined prior to correcting an ASD. This can be determined by cardiac catheterization or pulsed Doppler echocardiography which will both show the pulmonary-to-systemic blood flow ratio (Qp/Qs)[36]. A ratio greater that 2:1 is indicative of a significant left-to-right shunt[37]. Surgical correction of ASDs has been demonstrated to be slightly more effective than trans-catheter methods; however, the latter are less invasive and therefore have shorter hospital stays and fewer complications[38]. Defects that require surgical repair are usually located within the ostium primum or sinus venosus portion of the atrial septum[26]. Following successful repair, children usually have no significant future problems. There are no special considerations for these patients if they were to undergo future non-cardiac surgery[26].

VSD: Medical management is the first choice for infants with a moderate to large VSD who develop CHF and growth failure. If improvement is not noted, a trans-catheter or surgical closure should be performed before 6 months of age[39,40]. Surgical mortality is 2%-5% after the age of 6 months and is higher for those <2 months old, infants with associated defects, or those with multiple VSDs. The surgical approach is preferably through the right atrium as opposed to a ventriculotomy because of an increased risk of right bundle branch block with the ventriculotomy approach[39].

ECD: One distinguishing feature is the superior axis deviation of the QRS complex that generally lies between 0 and-150 degrees. Most patients with ECD are refractory to medical treatment and need surgical repair. Mortality rate is 5%. Mitral valve replacement may be necessary, which increases the risk of complete heart block after surgery[41,42]. Repair is usually performed around 3-8 months old. Early repair is extremely important in Down's syndrome infants with complete ECD due to the increased risk of developing early pulmonary vascular obstructive disease, PAH and even Eisenmenger Syndrome.

PDA: PDA is usually ligated not long after birth and these patients generally do not develop significant complications. However, there are some adult patients with PDA. All PDAs identifiable by physical examination should be closed[41,42]. In premature infants, this can usually be done with indomethacin.

The dosage of indomethacin is generally 0.2mg/kg given intravenously in 2 doses that are separated by approximately 12 hours[43]. In term infants and children, closure must be through a catheter or through surgery. Catheter closure has varying degrees of success with hemolysis, residual leaks, left pulmonary artery stenosis, peripheral coil embolization, and femoral vessel occlusion presenting as potential complications. Surgical closure is performed between 6 months to 2 years old or with first diagnosis in an older patient. Infants with CHF, pulmonary hypertension, or recurrent pneumonia usually require emergent surgery. The procedure is classically performed through a left posterolateral thoracotomy without cardiopulmonary bypass. Newer techniques include video-assisted thoracoscopy. The mortality of surgery is usually less than 1%[41,44].

Considerations in anesthetic management

Pre-operative anesthetic evaluation

1. Assessment of hemodynamic status: In addition to basic preoperative tests including ECG, chest x-ray, hemoglobin and hematocrit, and type and cross-match of blood, hemodynamic assessment is an important component of preoperative evaluation. There are other critical clinical, radiological, and echocardiographic correlates of changes in the pulmonary vasculature that assist the clinician in decision-making regarding operability. Early in the course of the disease (left-to-right shunt), when the shunt is operable, there is often clear evidence of increased pulmonary blood flow. With the increase in PVR to generate right atrial pressure higher than left atrial pressure, patients develop clinical cyanosis from shunt reversal (Eisenmenger syndrome). Notwithstanding the uncertainties surrounding the predictive value of preoperative hemodynamics on postoperative outcomes, accurate hemodynamic assessment is of particular importance in determining the operability, at intermediate levels of elevation in PVR where clinical signs can be subtle. Decision-making regarding operability can be critical in some patients as closure of the defect can potentially cause

progression of pulmonary hypertension and adversely affect the natural history of a disease that would otherwise allow survival into the third or fourth decade of life[44]. Hemodynamic assessment is especially pivotal for those less invasive repair strategies such as trans-catheter closure. Hemodynamic assessment assists in appropriate device selection in trans-catheter closure. The fenestrated ASD device, which has been used in patients with pulmonary hypertension and in the closure of ASDs in the elderly with decreased left ventricular compliance, can be considered in selected patients with elevated PVR. In similar fashion, the ASD or VSD device has been used in patients with PDA patients with pulmonary hypertension. However, using an Amplatzer PDA plug possesses the risk of embolization to the aorta because of absence of a retention disc on the pulmonary arterial end[45].

2. Cardiac function: Cardiac functional status not only determines the operability of patients with CHD, but also helps intraoperative anesthetic management. CHF does not necessarily preclude surgical repair of patients with CHD. Some of these patients with CHF may need surgery to improve the symptoms, as in the case of patients with ECD who present with CHF[26]. Some patients with significantly decompensated cardiac dysfunction may not be ideal candidates for surgical intervention, as in the case of moderate to large VSD patients who develop CHF and growth failure, requiring medical treatment for optimization before surgery[39,40].

3. Existence of complications: Preoperative existence and severity of pulmonary complications are a key element of a preoperative workup. Pneumonia secondary to pulmonary congestion due to cardiac dysfunction may require optimization before elective surgical repair.

4. Co-existing medical issues: other co-existing medical illnesses either related to CHD or not, may determine the candidacy of a patient for surgery.

Intraoperative management

1. General Considerations:

Throughout the perioperative period, the goals of anesthetic management for left-to-right shunts are to decrease the shunt flow and maintain cardiovascular and respiratory stability to provide adequate tissue perfusion and oxygenation. The strategies potentially affecting the shunt flow are discussed below:

(1). Effects of Ketamine versus propofol in children with cardiac shunting: the principal hemodynamic effect of propofol is a decrease in systemic vascular resistance (SVR). Thus, in patients with intracardiac shunting, this decrease in SVR results in an increase in right-to-left shunting and a decrease in the ratio of pulmonary to systemic blood flow, which may lead to arterial desaturation[46]. This effect is especially detrimental in patients with congenital right-to-left shunt, where a patient may develop a reversed direction of shunting (Eisenmenger Syndrome) from left-to-right shunt[46]. Williams *et al.* studied the hemodynamic effects of propofol in children with CHD and found that after intravenous administration of propofol, systemic MAP and SVR decreased significantly and systemic blood flow increased significantly in all patient groups. However, heart rate, pulmonary MAP, and PVR were unchanged. The Qp/Qs ratio increased. In patients with cardiac shunt, propofol resulted in decreased left-to-right flow and increased right-to-left flow; the pulmonary to systemic flow ratio significantly decreased[47]. Ketamine did not produce the changes induced by propofol. The authors suggested that during pediatric cardiac catheterization, both anesthesiologists and cardiologists need to know that anesthetic agents can significantly alter the hemodynamic status in children with complex congenital heart defects and affect the results of hemodynamic calculations that are important for decision-making and treatment of these patients[46]. In this regard, loss of an airway for a patient with CHD can cause quicker decompensation due to limited reserve and potential morbidity and mortality. Securing intravenous access is prudent, whenever possible, prior to anesthetic induction as CHD patients have, in general, limited and reduced cardiopulmonary physiology.

(2). Inhaled iloprost (prostaglandin): Zhang *et al.* looked into the effects of inhaled iloprost on mean PAP and PVR in 50 adult patients with CHD and significantly PAH. This study found that PAP decreased in 39 out of 50 patients and PVR reduced

in 43 out of 50 patients. Intravenous adenosine also decreased PAP but not PVR[48], indicating that inhaled iloprost can have selective pulmonary vasodepressor effects and potentially be beneficial for patients with PAH[48]. Other prostaglandin analogs have also been found to be beneficial to patients with PAH[49]. Recently, Ruan *et al.* converted gene-transfected cells into a stable cell line and planted them into mice, in which the cells constantly expressed the hybrid enzyme and were capable of producing large-amounts of PGI_2. The PGI_2-producing cell line not only exhibited an approximate 50-fold increase in PGI_2 biosynthesis, but demonstrated superior anti-platelet aggregation in vitro and increased reperfusion in a mouse ischemic hindlimb model in vivo. They concluded that gene-transfected cells provide an experimental intervention for PGI_2-diminished heart diseases, such as PAH[50].

(3). ACE inhibitors: The renin-angiotensin II-aldosterone axis is a critical regulator of blood pressure and fluid homeostasis. Local renin-angiotensin II systems have been discovered and novel actions of angiotensin peptides have emerged: AngII can act as an immunomodulator and profibrotic molecule. The enzyme responsible for its synthesis, Angiotensin-converting-enzyme (ACE), is present in high concentrations in lung tissue. A literature review revealed AngII and functional polymorphisms of the ACE gene increase ACE activity with increased susceptibility for asthma, chronic obstructive pulmonary disease (COPD), and for PAH. Drugs that inhibit the synthesis of AngII (ACE inhibitors) or that antagonize its actions on its receptors (AT1 receptor antagonists) have been shown to provide beneficial effects[51]. enalaprilat and captopril were also found to benefit patients with VSD and heart failure in children. All patients showed clinical improvement in weight gain, respiration and echocardiographic findings[52].

(4). Avoiding airway obstruction, hypoventilation, and hypoxemia: These pathological states are known factors which result in increased pulmonary arterial pressure[45]. For those patients with Eisenmenger Syndrome, further increase in pulmonary blood pressure will worsen symptoms. However, in patients with PAH and existing left-to-right shunting, further increases in pulmonary pressure will potentially decrease left-to-right shunting volume through the defect, theoretically benefiting the patient but may lead to right heart failure[45].

2. Special considerations:

(1). Neuraxial anesthesia decreases SVR, which may decrease left-to-right shunt. However, if a parturient is hypovolemic, decreased CVP due to epidural or spinal administration may increase left-to-right shunt. Other changes may offset this potential benefit. The net result of shunting volume through the cardiac defect is difficult to generalize during epidural or spinal administration in obstetric patients, and is dependent upon volume status and the severity of pulmonary hypertension. Niijima *et al.* reported that intraoperatively, neuraxial anesthesia decreased the ratio of Qp/Qs[53].

(2). Parturient with CHD: Parturient with unrepaired left-to-right shunt pose challenges for surgical and anesthesia teams. As more women with CHD survive into reproductive age and become pregnant, Anesthesia providers need to mitigate the negative impact of the escalated hemodynamic demands of labor and delivery. Continuous epidural analgesia attenuates increased sympathetic activation associated with labor and delivery. Avoidance of hypoxemia in patients with PAH and appropriate fluid management can be pivotal in the management of these patients. Appropriate blood volume assists in providing adequate intravascular volume and to minimize the vasodilation with drop in blood pressure or cardiac failure from overload. This may be a daunting task because of increased hemodynamic demand due to labor and delivery. CVP may be needed to help manage the parturient with uncorrected left-to-right shunt, especially in those with cardiac failure[54]. Parturient mortality is ~0.1-1% in low risk patients, 1-5% in patients with moderate risk, and mortality increases to 5-30% with high risk heart disease. Even in the first 20 weeks of gestation, the parturient may experience significant cardiac problems due to increased cardiac output (CO) (40% above normal levels by 20 weeks) and blood volume by 50%[55]. These changes place great strain on an already overworked heart. Specifically, decrease in SVR may facilitate right-to-left shunt. Maternal and fetal oxygen requirements increase dramatically in a parturient while functional respiratory capacity reduces in pregnancy, causing

potential maternal and fetal hypoxemia[55]. Parturient with unrepaired left-to-right shunt may theoretically have decreased left-to-right shunting volume related to reduction in SVR, however, this theoretical benefit may be offset by other maternal changes during pregnancy such as increased CO and blood volume, decreased FRC, and increased metabolism. Under-resuscitation of intravascular volume will be hazardous because it may increase left-to-right shunt. Left-to-right shunt volume may increase with lowered CVP from vena cava compression induced reduction in venous return.

Effects of oxytocin on hemodynamic parameters during the peripartal period in patients with CHD and left-to-right shunt: The cardiovascular side effects of standard doses of oxytocin are well-described with decreased MAP by 30% and SVR by 50%; decreasing shunting flow in left-to-right shunt. However, oxytocin also increases cardiac output by 50% and heart rate and stroke volume by 20-30%, which may be problematic for the parturient. This creates a dilemma in terms of withholding oxytocin after delivery[55].

(3). Patients with PDA are more vulnerable to coronary ischemia due to ongoing pulmonary runoff during the diastolic phase of the cardiac cycle and potential for low diastolic blood pressure. Fluri *et al.* reported a case of fatal myocardial ischemia in a patient with PDA[56]. Therefore, patients with PDA should be monitored closely for hemodynamic changes and for EKG changes indicating myocardial ischemia.

(4). Trans-Catheter repair of cardiac defects: Significant hemodynamic instability exists during trans-catheter cardiac defect repair. The anesthetic records and catheterization data of 70 consecutive trans-catheter VSD closures between February 1989 and September 1992 were reviewed by Laussen *et al.*, and risk factors associated with hemodynamic instability evaluated. In 28 of 70 procedures (40%), hypotension (>20% decrease in systolic blood pressure from baseline) occurred; 12 patients responded to intravascular fluid administration alone, while 16 patients required additional acute resuscitation. Significant dysrhythmias occurred during 20 (28.5%) anesthetics associated with hypotension and requiring treatment or catheter withdrawal. American Society of Anesthesia (ASA) physical status, precatheterization indication for device placement, and patient size

were not predictive of hemodynamic instability during the procedure[57]. Blood transfusions were necessary in 38 (54.4%) cases and were size-related, with patients weighing less than 10 kg requiring a significantly larger transfusion volume (25.1 +/- 12.4 mL/kg). After 35 procedures (50%) patients were admitted directly to Intensive Care Unit due to hemodynamic instability or procedure duration; 24 (68%) required mechanical ventilation. No deaths occurred; there was no late morbidity due to catheterization-related events. Intravenous sedation was used for the initial catheterizations, maintained with a combination of midazolam, ketamine, and morphine. Subsequently, general intravenous or inhaled anesthesia was predominantly used during transesophageal echocardiography and internal jugular vein cannulation. Hemodynamic instability, therefore, is common during device closure of VSDs, and is likely to be an inescapable feature of these procedures in many patients because of the technique necessary for device placement[57]. The utilization of transesophageal echocardiography (TEE) is a routine tool for guidance of trans-catheter closure of secundum-type ASD and has demonstrated excellent results[57].

(5). Intracardiac echocardiography (ICE) has currently been studied to determine its efficacy compared to other monitoring modalities such as TEE for guiding trans-catheter device closure of ASD, patent foramen ovale (PFO), and VSD. Rigatelli *et al.* studied 258 patients over a period of 5 years to look into the efficacy of ICE as a guiding tool for transcatheter repair of cardiac defects. ICE helped decision-making in cancelling 18 patients for transcatheter closure due to unsuitable rims, atrial myxoma not diagnosed by preoperative transesophageal echocardiography or inaccurate transesophageal echocardiography measurement of defects more than 40 mm. The remaining 240 patients underwent transcatheter closure: transesophageal echocardiography-planned device type and size were modified in 108 patients (45%). Rates of procedural success, predischarge occlusion and complication were 100%, 94.2% and 5%, respectively. On mean follow-up of 65±15.3 months, the follow-up occlusion rate was 96.5%. There were no cases of aortic/atrial erosion, device thrombosis or atrioventricular valve interferences. This study indicated that intracardiac echocardiography-guided interatrial

shunt transcatheter closure is safe and effective and appears to have excellent long-term results, potentially minimizing the complications resulting from incorrect device selection and sizing[58]. Bartel *et al*. also found that Intracardiac echocardiography is superior to conventional monitoring for guiding device closure of interatrial communications[59].

(6). Opioid use in CHD surgery: There is a commonly held belief that short-acting opioids possess more beneficial hemodynamic profiles and may help patient recovery. However, Akpek *et al*. did not find any difference regarding the effects of remifentanil and fentanyl on hemodynamics and respiration intraoperatively or 24 hours postoperatively in pediatric patients aged from 3 months to 6 years old with CHD[60].

Postoperative management

1. Postoperative monitoring: Postoperatively patients with left-to-right shunt or other CHD should be continuously monitoring hemodynamically, until major vital signs, metabolic status, and vital organ functions return to normal levels.

2. Postoperative Pain Control: Adequate postoperative analgesia enhances deep breathing and minimizes respiratory complications after thoracotomy. In recent years, the use of regional techniques in cardiothoracic anesthesia have gained significant popularity and improved cardiac surgery outcomes. Ultrasound guided epidural placement is one such example of a technique that reduces postoperative pain and discomfort. Continuous infusion epidurals have led to shorter ICU stays, decreased occurrence of postoperative emesis, earlier oral feedings, and overall shorter hospital stays[61]. Opioid agent use in patients with left-to-right shunt can have potential benefits because it lowers systemic MAP, and SVR. The drop in MAP and SVR may decrease left-to-right shunt and decrease the ratio of Qp/Qs.

Summary

More and more children with left-to-right CHD now survive into adulthood. These patients with CHD typically will need surgical care for their original cardiac defect(s) or other non-cardiac medical conditions. Commonly encountered CHD with left-to-right shunt include ASD, VSD, ECD and PDA. The key pathological change is the increased pulmonary vascular resistance due to arterial wall thickening, increased tonicity and impaired relaxation secondary to increased blood flow from the left-to-right shunt. Increasing PVR will lead to PAH and the reversed direction of flow through the cardiac defect (Eisenmenger Syndrome). The main causes of death are heart failure and dysrhythmia. To prevent permanent PAH and Eisenmenger Syndrome, cardiac defects with left-to-right shunt generally require surgical repair at an early age. However, some patients may survive into adult life even without repair. Surgical care for those patients with un-repaired left-to-right shunt poses many challenges for the anesthesiologist due to alterations in cardiopulmonary physiology. For this reason, it is imperative that the anesthesiologist maintain a thorough understanding of pathophyiological changes and possess up-to-date strategies of managing these patients.

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