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Core Curriculum

Assessment of Operability of Congenital Cardiac Shunts With Increased Pulmonary Vascular Resistance

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Patients with large left to right shunts as a result of congenital heart disease can develop changes in pulmonary vasculature that are initially reversible. It is critical in these patients to determine whether closure of the defect would reverse some of the changes in the pulmonary vasculature. A comprehensive clinical and noninvasive evaluation often allows classification in the extremes of the spectrum, but for borderline situations, cardiac catheterization is traditionally undertaken. It is important to obtain invasive data meticulously and efficiently recognizing that the numbers only offer a snapshot and may not be representative of the usual physiologic state of the patient. There are, in addition, several caveats that need to be considered while calculating flows and resistances in these patients. Currently a holistic approach that combines clinical, noninvasive, and invasive data may be the only realistic way of making a decision regarding operability in this challenging group of patients with shunt lesions and elevated pulmonary vascular resistance. © 2008 Wiley-Liss, Inc.

Key words: congenital heart disease; pulmonary vascular obstructive disease; surgery; catheter intervention

INTRODUCTION

Infants with large post-tricuspid left to right shunts are often symptomatic with failure to thrive and may succumb to heart failure and pneumonia if correction is delayed [1]. A proportion of these infants however survive infancy without surgery and may even show transient symptomatic improvement because of an increase in the pulmonary arteriolar wall thickness and an associated reduction in pulmonary blood flow. In the long-term however this process often becomes progressive leading to the development of pulmonary vascular occlusive disease (PVOD) with right to left shunting and cyanosis.

For a variable period of time after pulmonary vascular resistance (PVR) starts to increase, changes in lung vasculature may still be reversible following correction of the defect (operable situation). However once irreversible PVOD is established, closure of the defect may actually worsen the natural history (inoperable situation). The question of operability most commonly arises in older children and adults with large post-tricuspid shunts [ventricular septal defects (VSD) or patent ductus arteriosus (PDA)] and selected patients (mostly adults) with shunts at the atrial level (pretricuspid) who develop increased PVR. The mechanism and histological changes of PVOD in the setting of increased pulmonary blood flow have been extensively described [2]. Exposure to high blood flow results in impaired endothelium-mediated relaxation and increased vasomotor tone accompanied by histological changes in the vessel wall.

The response of the pulmonary vasculature to high pulmonary blood flow is however not uniform and does not occur in a predictable fashion [1]. This results in difficulties in decision-making regarding operability of these defects particularly in patients who present beyond infancy and early childhood. There appears to be a spectrum in the development of pulmonary vascu-

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lar disease with a subset of patients with high PVR and advanced PVOD in early infancy at one end of the spectrum [3] and adults who remain operable with large left to right shunts at the other [4].

The two main factors that affect patient outcome after closure of large left to right shunts have been identified as the age at repair and the preoperative PVR [5]. The rapid evolution of pediatric cardiac surgery and cardiology in recent decades has lead to early corrective surgery in much of the developed world. However, progression to inoperability, a feared complication of large left to right shunts still remains a reality particularly in the "developing world."

There remains a striking paucity of management guidelines regarding operability in "borderline" patients with left to right shunts and pulmonary hypertension who usually present beyond infancy and early childhood. Early studies performed in the catheter laboratory were limited by small numbers and limited follow up and failed to establish clear cut-offs for operability [1,6]. The 1980s saw the advent and rapid refinement of two dimensional and colour Doppler echocardiography which allowed clear anatomic definition of most forms of CHD virtually eliminating the need for cardiac angiography for anatomic definition [7]. For the majority of the world's children, however, correction of heart defects in early infancy is not realistic because of a paucity of resources and deficiencies in health awareness and infrastructure that do not allow timely detection of CHD [8]. With improving human development in many parts of the world, cardiac surgical centers now have to deal with a large population of untreated older children with CHD including several with "simple" shunt lesions and varying degrees of elevated PVR. There is therefore an urgent need to evolve management guidelines for these patients in whom assessment of operability remains a challenge.

In this review, we propose to provide a framework for decision-making using clinical, noninvasive, and invasive investigations by answering typical questions that are asked while managing a patient with large left to right shunts.

WHAT IS THE CORRELATION BETWEEN PREOPERATIVE HEMODYNAMICS AND LUNG BIOPSY FINDINGS AND CLINICAL OUTCOMES?

Several studies have identified a period of reversibility of pulmonary hypertension in patients with left to right shunts before the development of Eisenmenger syndrome. The quest for a relatively noninvasive index to help differentiate between reversible and irreversible pulmonary hypertension has been ongoing since the 1950s with early recognition that higher preoperative pulmonary/systemic arterial pressure (Pp/Ps) and resistance (PVR/SVR) ratios are associated with more advanced stages of pulmonary vascular disease on lung biopsy and a higher incidence of early and late postoperative pulmonary hypertension [9]. This relationship however is neither constant nor predictable and the degree of individual variability makes it difficult to apply a single cut-off to determine operability in these patients. Studies comparing hemodynamic data with lung biopsy findings as a "gold standard" are further limited by the questionable reliability of lung biopsy in determining operability in these situations [10]. This is especially true for younger patients (<2 years of age) who are often operable in spite of seemingly advanced changes on lung biopsy.

Despite these caveats, a PVR index value of 6–8 Woods units (m^2) is widely accepted as a cut-off for operability in children with large VSDs or PDAs. In addition, corollaries have been proposed using vasodilators including 100% oxygen, tolazoline, and nitric oxide (NO) [11]. These arbitrary boundaries are however constantly being challenged with the increasing use of postoperative pulmonary vasodilators and the advent of innovative surgical strategies. Although initial reports related the preoperative hemodynamic data with postoperative outcomes, recent studies have failed to demonstrate a significant association between preoperative PVR and PVR/SVR ratio and outcomes [12].

Patients with atrial septal defects form a distinct subgroup and there remains much debate regarding the nature and underlying etiopathogenesis of pulmonary hypertension in this context [13]. Studies have demonstrated poorer outcomes with both medical and surgical therapy in patients with higher PVR. A total pulmonary resistance greater than 15 Woods units (m^2) was associated with poor outcome following surgery in one retrospective analysis [14].

WHY IS IT IMPORTANT TO ASSESS HEMODYNAMICS IN LEFT TO RIGHT SHUNTS?

There are important clinical, radiological, electrocardiographic, and echocardiographic correlates of changes in the pulmonary vasculature that aid the clinician in decision-making regarding operability. Early in the course of the disease, when the shunt is still operable, there is often clear evidence of increased pulmonary blood flow. With the onset of PVOD, 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

TABLE I. Sources of Error in Flow and Resistance Calculations in the Cardiac Catheterization Laboratory

Category	Examples
Sampling errors	Obtaining samples in different physiologic states, streaming, partial wedging of catheter (pulmonary artery), nonrepresentative sampling (pulmonary veins)
Measurement errors	Diluted samples, air bubble in the syringe, delay in sending samples, nonstandardized equipment, using blood gas samples to estimate saturations, failure to account for dissolved oxygen
Assumptions	Oxygen consumption, pulmonary venous saturation
Approximations	Mixed venous samples (e.g., Using superior vena caval samples alone may amount to an approximation in measurement of the mixed venous oxygen content)

TABLE II. Conditions that are known to Elevate Pulmonary Vascular Resistance

Mechanism	Examples
Reduced oxygen content in inhaled air	Chronic exposure to high altitude
Upper airway obstruction	Enlarged adenoids, Sedation, Tracheomalacia
Hypo-ventilation	Deep sedation, neuromuscular disorders
Restrictive lung physiology	Chest wall and spinal deformities, interstitial lung disease
Lower airway obstruction	Bronchiolitis, asthma and similar conditions
Parenchymal lung disease	Consolidation, collapse, interstitial edema (pulmonary venous hypertension)

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 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.

In the context of transcatheter closure, hemodynamic assessment aids in appropriate device selection. 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 raised PVR. Similarly, the ASD or VSD device has been used in patients with PDA and pulmonary hypertension where using an Amplatzer PDA plug has the potential for embolization to the aorta because of absence of a retention disc on the pulmonary arterial end.

WHAT IS REQUIRED FOR ACCURATE HEMODYNAMIC ASSESSMENT IN THE CARDIAC CATHETERIZATION LABORATORY?

Hemodynamic studies to calculate flows and resistances in the pulmonary and systemic circulations should be done meticulously and efficiently such that saturation and pressure measurements are obtained under more or less identical physiological conditions. A detailed discussion of hemodynamic calculation is available in standard textbooks along with oxygen consumption tables adjusted for age, sex, and heart rate [15]. Several caveats and sources of error need to be considered (Table I). PVR can be influenced by a number of conditions which need to be carefully considered while interpreting the hemodynamic data (Table II).

WHAT IS THE ROLE OF REVERSIBILITY TESTING WITH NITRIC OXIDE OR OXYGEN IN ASSESSMENT OF OPERABILITY AND PREDICTION OF POSTOPERATIVE OUTCOME?

Hundred percent of oxygen has been conventionally used to assess the degree of "reversibility." Despite early reports of its usefulness, the role of oxygen in outcome prediction remains questionable [16]. In addition, the assumptions regarding oxygen consumption and oxygen content that are routinely employed in hemodynamic calculations become inaccurate in 100% FiO_2 (inspired oxygen).

NO is well-established as a short acting pulmonary vasodilator in the management of patients with severe postoperative pulmonary hypertension. Its role in predicting mid to long-term postoperative outcomes in patients with left to right shunts and pulmonary hypertension is however less certain. Although there is some data that suggests that the response to NO may aid in risk stratification and decision-making regarding timing of lung transplantation in patients with advanced pulmonary vascular disease [17], this cannot be extrapolated to borderline situations where corrective surgery is being considered.

A recent multicenter hemodynamic study of patients with congenital heart disease and pulmonary hypertension concluded that the overall reliability of preoperative hemodynamic evaluation was limited despite the use of vasodilators [18].

Studies that examine the role of preoperative testing with NO are limited by the lack of standardization in the concentration and duration of administration of NO. Also, most studies have looked at immediate postoperative outcomes without any data on long-term survival and morbidity. This is an important consideration in a condition that would normally allow survival into the third or fourth decade of life without any intervention. Thus, vasodilator testing does not seem to add

significantly to the baseline hemodynamic data and also introduces scope for errors in calculation.

HOW USEFUL IS IT TO STUDY THE EFFECTS OF TEMPORARY SHUNT OCCLUSION?

Direct occlusion of a defect to eliminate the left to right shunt has been applied during hemodynamic evaluation to eliminate flow related pulmonary hypertension.

Small case series have been published on the use of this potentially valuable technique in the assessment of operability particularly in adult patients with sizable PDA where complete occlusion of the duct is feasible [19,20]. Occlusion of septal defects particularly VSDs can however be technically challenging and ensuring complete occlusion is often difficult. In a recent series [20] of 29 patients with PDA and pulmonary hypertension, successful device closure was achieved in 20 patients following trial occlusion. The mean pulmonary artery (PA) pressures (with range in brackets) before and after occlusion in these patients were 78 mm Hg (50–125 mm Hg) and 41 mm Hg (23–77 mm Hg) respectively. Five out of the remaining nine patients who were deemed unsuitable for device closure showed increase in PA pressures and two had worsening of symptoms.

We analyzed our own series of 21 patients (median age 6 years) with a large PDA and pulmonary hypertension in whom we performed temporary balloon occlusion before deciding on suitability for surgical or catheter based treatment. Patients with definite clinical evidence of a large left to right shunt or with evidence of irreversible pulmonary vascular disease (lower limb saturations $<80\%$) were excluded from this series. We defined "responders" as having a $\geq 25\%$ fall in PA pressures on balloon occlusion or a $\geq 50\%$ fall in the ratio between pulmonary and aortic diastolic pressures (Fig. 1).

By this definition we identified 16 responders and 5 nonresponders. All 16 responders underwent either surgical (5) or catheter based (11) treatment of their PDA. Of the responders two patients continued to have elevated PA pressures or RV systolic pressure on follow up. Of the nonresponders, one patient was operated elsewhere despite medical advice against surgery and on follow up had supra-systemic PA pressures. The rest of the nonresponders showed definite symptomatic worsening over time with further fall in saturations. We noticed that some patients with a high baseline PVR and low Qp/Qs ratio still responded favorably to balloon occlusion and tolerated duct occlusion with normalization of PA pressures. The data available on balloon occlusion as a means of identifying patients who would benefit from closure of their PDA remains inconclusive and further clarification by studies with larger numbers is warranted.

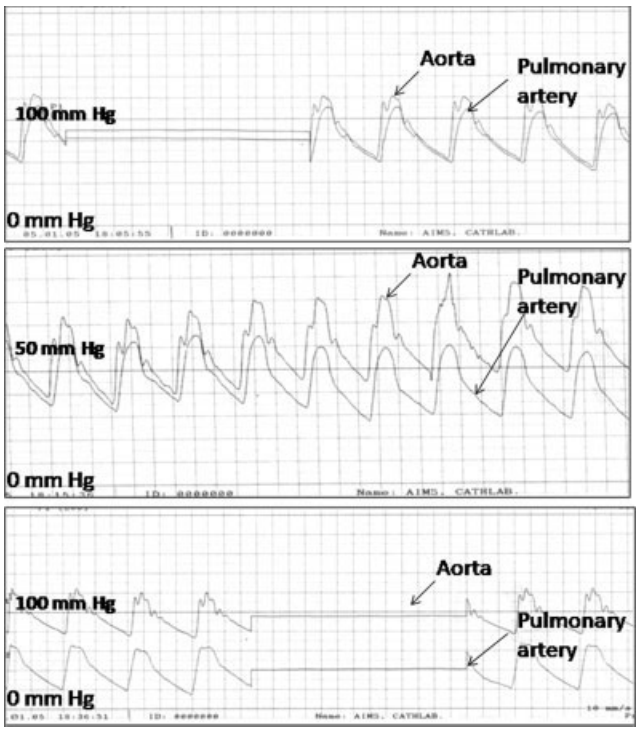

Fig. 1. The effect of balloon occlusion on pulmonary artery (PA) pressure in a patient with a large patent arterial duct. The demonstration of a substantial fall, especially of the PA diastolic pressure suggests operability.

WHAT IS THE ROLE OF CLINICAL EXAMINATION AND NONINVASIVE ASSESSMENT?

The importance of clinical clues in these borderline situations cannot be over-emphasised. Serial assessment by multiple experienced clinicians improves the reliability of clinical examination as a tool in determining operability. Considerable importance is given to history, physical examination, chest X-ray (Fig. 2), arterial blood gas (ABG) estimation, ECG, and echocardiography (Table III). These modalities provide independent useful information on the status of the pulmonary vasculature. There are occasions when despite equivocal cardiac catheterization data, defects have been successfully corrected based on a comprehensive clinical and noninvasive evaluation.

The direction of shunting across the defect is a useful tool with predominantly left to right shunting favouring operability. The ventricular septal configuration in end systole (in patients without a large VSD), the Doppler flow pattern and gradient across the defect

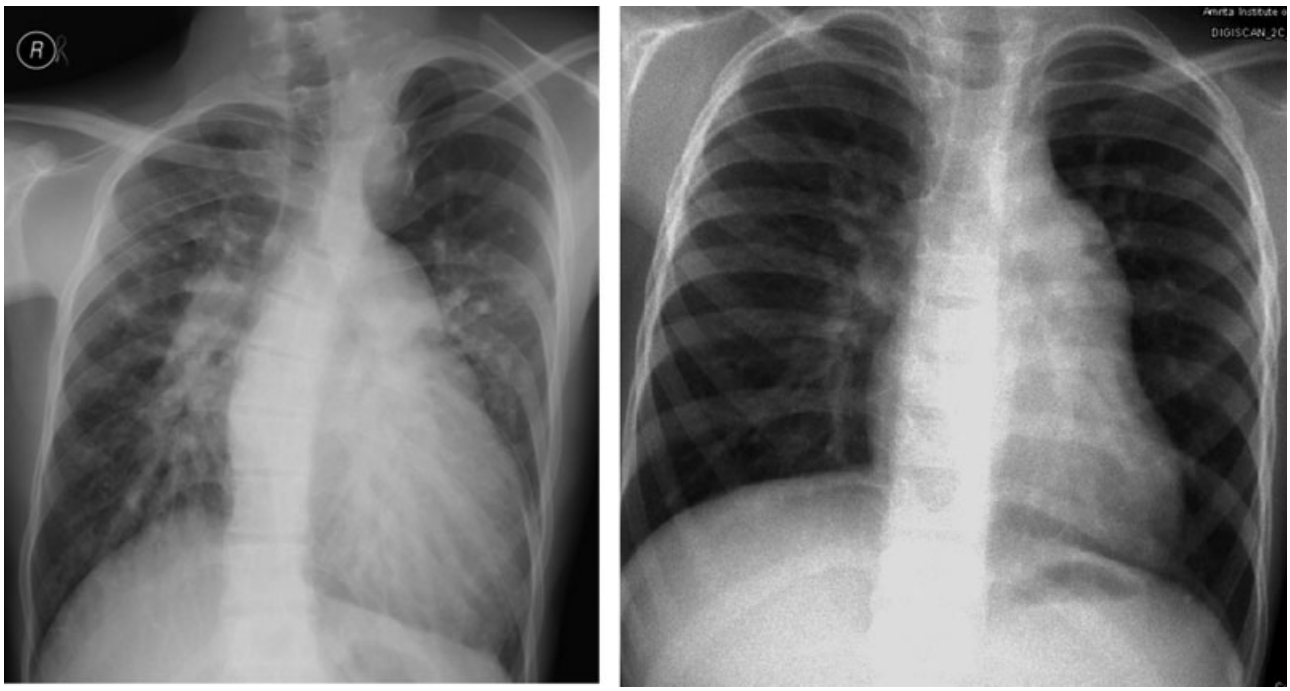

Fig. 2. Two representative X-rays from older patients with large ventricular septal defects VSD). The X-ray on the left is from a 17-year-old patient with clinical evidence of a large shunt and "operable" hemodynamics. This was in spite of kyphoscoliosis of the spine and restrictive lung physiology. On the right is an X-ray from a 16-year-old boy with VSD and Eisenmenger syndrome. This X-ray shows a typically reduced lung vasculature, prominent central pulmonary arteries, and absence of cardiac enlargement.

TABLE III. Clinical Assessment of Hemodynamics in Left to Right Shunts

Modality	Clues suggesting operability	Clues suggesting inoperability
History	Feeding difficulty, failure to thrive, tachypnea and frequent respiratory infections in infancy	Absence of symptoms or "improvement" in status as suggested by improved feeding, weight gain, and resolution of tachypnea.
Physical examination	Increased precordial activity, laboured respiratory efforts (sub-costal and intercostal recession), split second heart sound (S2), mid-diastolic "flow" murmurs	Visible cyanosis, quiet precordium, loud single S2, absence of flow murmurs, early diastolic murmur of pulmonary regurgitation
Oxygen saturation[a]	Normal (>95%)	Reduced (<90–95%)
Chest X-ray	Cardiac enlargement, increased vascularity suggested by prominent end-on vessels, visible vascularity in the peripheral lung fields	Normal heart size, normal or reduced vascularity, evidence of pruning with dilated hilar pulmonary artery and rapid decline in vessel size
ECG	Prominent left ventricular forces, q waves in lateral precordial leads	Right ventricular dominance, absence of q waves in lateral precordial leads

[a]Oxygen saturations cut-offs may not be absolute. For example, patients with ventricular septal defects with significant aortic override may have some resting desaturation at rest. However, saturations below 90% are seldom compatible with operation in simple shunt lesions. For patent ducts oxygen saturation should be estimated in the lower limbs.

give further information about the pulmonary arterial pressure.

In our experience the presence of clinical cyanosis or saturations <90% is a strong predictor of inoperability whereas the clear detection of a mid diastolic murmur on serial assessment strongly favours operability. In our institution the majority of our patients who present beyond infancy with large left to right post-tricuspid shunts are assessed and operability status determined purely on the basis of clinical examination, chest X-ray, ECG, and echocardiography. It is only a small minority that have required cardiac catheterization to obtain hemodynamic data.

The role of ABG measurement has not been adequately investigated in these situations. A decline in arterial PO_2 after exercise may suggest fixed PVR as the fall in systemic vascular resistance during exercise is not balanced by a corresponding fall in PVR

allowing for increased right to left shunting across the defect and increased hypoxia on the blood gas. In addition, blood gas analysis also allows assessment of respiratory function and the presence of hypercarbia should alert the clinician to look for restrictive or obstructive pulmonary disease as a contributory factor to the pulmonary hypertension.

CONCLUSIONS

Determining operability is important in patients with left to right shunts who present late. Although, a number of unresolved issues exist with currently available methods, a comprehensive assessment that incorporates clinical evaluation, noninvasive investigations and in selected cases, cardiac catheterization with calculation of flows and resistances allows classification of the vast majority of patients. Efforts to evolve clear guidelines through careful prospective studies need to be undertaken as a number of patients with congenital heart defects in the developing world continue to present late with pulmonary hypertension.

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