Hemodynamic assessment of congenital heart defects with left to right shunts and pulmonary hypertension

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INTRODUCTION

Shunts at the level of ventricles or great arteries (also known as post-tricuspid shunts) often have symptoms and fail to thrive during infancy, and may result in death from heart failure and pneumonia, if correction is delayed.[1–4] Ventricular septal defects and patent ductus arteriosus (PDA) are common examples of post-tricuspid shunts. A proportion of infants with large post-tricuspid shunts, however, survive infancy without surgery and may even show transient reduction in pulmonary blood flow. However in the long-term, this process often becomes progressive leading to the development of pulmonary vascular occlusive disease with right to left shunting and cyanosis.

Eisenmenger in 1897 initially wrote a description of a 32-year-old man with cyanosis and hemoptysis who was found after death to have a large ventricular septal defect (VSD).[5] Paul Woods in 1958 coined the term Eisenmenger syndrome to describe situations where high pulmonary blood flow due to left to right shunts results in pulmonary vascular occlusive disease and shunt reversal.[6] Although patients with atrial septal defects (ASD) usually do not present in early infancy, they may be associated with pulmonary vascular obstructive disease (PVOD) in adulthood. For a variable period of time after pulmonary vascular resistance (PVR) starts to increase, the change in lung vasculature may still be reversible following correction of the defect (operable situation). Once 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 and selected patients (mostly adults) with shunts at the atrial level (pre-tricuspid) who develop increased PVR. The clinical and management implications of elevated PVR in this group of patients remains unclear and has been the subject of intense debate.[7]

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The mechanism and histological changes of pulmonary vascular occlusive disease in the setting of increased pulmonary blood flow have been extensively described.[8,9] The reduced availability of endogenous nitric oxide (NO) and increased production of vasoconstrictor prostanoids in response to high pulmonary blood flow result in impaired endothelium-mediated relaxation and increased vasomotor tone.[10,11] Studies in rats with an experimentally created aortocaval shunt have demonstrated changes in the morphology and vaso-reactivity of the pulmonary arterial wall with an increase in the thickness of the internal elastic lamina and basement membrane, and a widening of the sub-endothelial space due to exposure to high blood flow. Protein quantification carried out using Western blot analysis and scanning densitometry demonstrated increased levels of endothelial nitric oxide synthase (Enos) and cyclo-oxygenase 2 (COX-2) in the pulmonary arterial wall. Cyclic GMP levels measured by radioimmunoassay are reduced accounting for the decreased biological activity of endogenous nitric oxide.[12] The imbalance between COX-2 mediated vasoconstrictor prostanoids and endogenous nitric oxide in response to high pulmonary blood flow results in increased pulmonary arterial vaso-reactivity. Table 1 summarizes the various mechanisms responsible for development of increased PVR.

The response of the pulmonary vasculature to high pulmonary blood flow is, however, not uniform and does not occur in a predictable fashion.[3,4] 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 vascular disease with a subset of patients with high PVR and advanced PVOD in early infancy at one end of the spectrum[13] and adults who remain operable with large left to right shunts at the other.[14]

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 pre-operative PVR.[5,15–17] The rapid evolution of pediatric cardiac surgery and cardiology in recent decades has led to early correction in these patients in much of the developed world. The high mortality associated with infant cardiac surgery during the 1960s,[12,13] has dramatically declined with excellent results now being achieved at minimal risk in early infancy. 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 patients with left to right shunts and pulmonary hypertension presenting beyond infancy and early childhood. The rare infant who presents with left to right shunts and elevated PVR can also be challenging. Some hemodynamic information is available from early studies of patients with large left to right shunts in the catheter laboratory.[3,4,18,19] These were performed in the era when cardiac surgery was only realistic in relatively older children. These studies were limited by small numbers of patients included and limited follow-up duration, and could not generate unambiguous guidelines for decision making and could not establish clear cut-offs for operability. Once infant heart surgery was well established in the 1980s, there was no impetus for refinement of these guidelines

Table 1 Mechanisms that contribute to development of increased pulmonary vascular resistance in congenital heart defects associated with increased pulmonary blood flow.

Broad category	Specific consequences
Loss of endothelial barrier function resulting from high flow and pressure	Degradation of extracellular matrix, release of growth factors, smooth muscle hypertrophy and proliferation, extension of smooth muscle into peripheral pulmonary arteries, smooth muscle migration with neo-intima formation
	Adherence and activation of platelets, activation of coagulation pathways and thrombosis
Activation of the endothelin system	Vasoconstriction and unfavorable vascular remodeling
Decreased production of prostacycline	Shift of balance in favor of arteriolar vasoconstriction
Decreased production of nitric oxide	Shift of balance in favor of arteriolar vasoconstriction, reduction in antiproliferative stimuli
Increased turnover of serotonin	Pulmonary arteriolar vasoconstriction
Altered expression of pulmonary potassium channels	Accentuated response to hypoxia
Mutations in bone morphogenetic protein receptor (type 2) and activin-like kinase (type 1)	May account for rapid development of pulmonary vascular disease in selected patients. BMP receptor type 2 mutations have been identified in 6% of patients associated with PAH

because almost all patients were operated well before establishment of irreversible PVOD. The 1980s also saw the advent of two-dimensional and color echocardiography. Rapid refinements in this modality allowed clear anatomic definition[20] of most forms of CHD virtually eliminating the need for cardiac angiography for anatomic definition. By 1990s, most institutions had stopped performing diagnostic cardiac catheterization for most forms of CHD.

For the majority of the world's children, correction of heart defects in early infancy is not realistic. This is due to a number of reasons that include a paucity of resources and deficiencies in the health infrastructure that do not allow timely detection of CHD. With improving human development in many parts of the world, new centers with congenital heart surgery expertise are being established. These centers have to deal with a large population of untreated older children with CHD including several with simple shunt lesions (such as ventricular septal defects) many of whom have varying degrees of elevation of PVR. There is an urgent need to evolve management guidelines for these patients. The key question that needs to be answered relates to whether or not the lesion is operable (or correctable, if catheter intervention is feasible).

OBJECTIVES OF THE REVIEW

1. To provide a framework for decision making on operability in common left to right shunts using clinical, non-invasive and invasive investigations.
2. To suggest indications for diagnostic catheterization for shunt lesions.
3. To identify the sources of error in hemodynamic assessment: shunt quantification and resistance calculations.

Correlating Pre-operative Hemodynamics with Lung Biopsy Findings and Clinical Outcomes

Several studies have identified a period of reversibility of pulmonary hypertension in patients with left to right shunts prior to the development of Eisenmenger syndrome and it is important to identify this subset of patients who would still benefit from the abolition of the left to right shunt. The quest for a relatively less invasive index to help differentiate between reversible and irreversible pulmonary hypertension has been ongoing since the 1950s with early recognition that higher pre-operative 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.[21,22] 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 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.[7,23] Classical teaching that defines irreversible pulmonary vascular disease as having at least Grade 3 histological changes[9] has been questioned with studies reporting patients deemed operable by histological grading to have suffered adverse outcomes with postoperative hypertension.[24,25] Conversely, patients with evidence of irreversible pulmonary vascular disease on lung biopsy have undergone successful surgery with no correlation between pre- and postoperative hemodynamic data and lung biopsy findings.[7] Despite these caveats, a PVR index value of 6–8 Woods units/sq meter is widely accepted as a cut-off for operability in children with large post-tricuspid left to right shunts. In addition, corollaries have been proposed using vasodilators including 100% oxygen, tolazoline and nitric oxide.[26] These arbitrary boundaries are, however, constantly being challenged with the increasing use of postoperative pulmonary vasodilators and the advent of innovative surgical strategies.[27,28] Although initial reports related the pre-operative hemodynamic data with postoperative outcomes, recent studies have failed to demonstrate a significant association between pre-operative PVR and PVR/SVR ratio and outcomes.[7,29]