The Right Heart and Pulmonary Circulation (X)

# Pulmonary Hypertension in Congenital Shunts

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Pulmonary arterial hypertension frequently arises in patients with congenital heart disease. The vast majority present with congenital cardiac shunts. Initially these may manifest as left-to-right (i.e. systemic-to-pulmonary) shunts. The natural history of disease progression involves vascular remodeling and dysfunction that lead to increased pulmonary vascular resistance and, finally, to the development of Eisenmenger's syndrome, which is the most advanced form. The anatomical, pathological and structural abnormalities occurring in the pulmonary circulation of these patients are, to some extent, similar to those observed in other forms of pulmonary arterial hypertension. This understanding has recently led to significant changes in the management of Eisenmenger's syndrome, with the introduction of treatment specifically targeting pulmonary vascular disease.

Early closure of the cardiac shunt remains the best way of preventing pulmonary vascular lesions. However, it is still not clear which preoperative parameters predict safe and successful repair, though hemodynamic evaluation is still routinely used for assessment. Postoperative pulmonary hypertension, both in the immediate period after surgical repair and during long-term follow-up, remains a real therapeutic challenge. The clinical situation of a single ventricle with Fontan circulation also presents difficulties when pulmonary vascular lesions are present. This article reviews pulmonary hypertension associated with congenital shunts and discusses a number of the specific problems encountered.

**Key words:** *Congenital heart disease. Congenital shunts. Pulmonary hypertension.*

## Hipertensión pulmonar en los cortocircuitos congénitos

La hipertensión arterial pulmonar aparece con frecuencia en los pacientes con cardiopatías congénitas. La inmensa mayoría de ellos presentan cortocircuitos cardiacos congénitos. Inicialmente pueden mostrar un cortocircuito izquierda-derecha (sistémico-pulmonar). Su evolución natural muestra que, a medida que progresa la enfermedad, el remodelado y la disfunción vasculares dan lugar a aumentos de la resistencia vascular pulmonar y finalmente se desarrolla un síndrome de Eisenmenger, que es la forma más avanzada. Las anomalías anatomopatológicas y estructurales que se producen en la circulación pulmonar de estos pacientes son, en cierta medida, similares a las que se observan en otras formas de hipertensión arterial pulmonar. Basándose en este conocimiento, el tratamiento del síndrome de Eisenmenger ha sufrido cambios significativos recientemente, con la introducción de los tratamientos dirigidos a abordar las lesiones vasculares pulmonares.

El cierre más temprano de la comunicación cardiaca continúa siendo la mejor prevención de la lesión vascular pulmonar. Sin embargo, los parámetros preoperatorios que indican que una reparación será segura y eficaz continúan sin estar claros, aun cuando la hemodinámica siga siendo la evaluación habitual. La hipertensión pulmonar postoperatoria, tanto en el periodo inmediato tras la reparación quirúrgica como en la evolución a largo plazo, aún es un verdadero reto para el tratamiento. La situación concreta de los ventrículos únicos y la circulación de Fontan plantea también dificultades en presencia de lesiones vasculares pulmonares. Algunos de estos problemas se comentan en este artículo de revisión de la hipertensión pulmonar asociada a cortocircuitos congénitos.

**Palabras clave:** *Cardiopatía congénita. Cortocircuitos congénitos. Hipertensión pulmonar.*

## INTRODUCTION

Pulmonary hypertension complicates the course of many children and adults with congenital heart diseases (CHD). The increase in pulmonary pressure associated with CHD is either secondary to increased pulmonary blood flow or to increased post-capillary pressures. Pulmonary arterial hypertension (PAH)

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ABBREVIATIONS

CEC: circulating endothelial cell
CHD: congenital heart disease
ES: Eisenmenger's syndrome
HLT: heart and lung transplantation
PAH: pulmonary arterial hypertension
PAP: pulmonary arterial pressure
PVD: pulmonary vascular disease
PVR: pulmonary vascular resistance

is in the vast majority associated to congenital shunts.

Despite major advances in the understanding of the regulation of the pulmonary vascular bed and the pulmonary endothelial lesions leading to pulmonary vascular disease, despite the advances in surgical repair and the discovery of potential therapies in the pre and postoperative period, pulmonary hypertension still carries a significant mortality and morbidity in patients with CHD.

One of the most important aspects that needs to be defined is the exact wording used to define the disease in the setting of PAH associated with CHD. Based on hemodynamic definition of PAH (mean pulmonary arterial pressure [PAP] >25 mmHg)[1] almost all patients present with pulmonary hypertension in the presence of a large unrestricted left to right shunt, but what is important in this setting is the degree of pulmonary vascular lesions and what would be called pulmonary vascular disease (PVD). Indeed, a patient with high pulmonary blood flow and low pulmonary vascular resistance (PVR) will fulfil the requirements for a diagnosis of PAH but can be definitely treated with surgical closure of the shunt. On the contrary, a patient with low pulmonary blood flow, cyanosis with reverted shunt (right to left) and high PVR, and the so called Eisenmenger's syndrome (ES) will not benefit from surgical closure and this is even contraindicated, but will potentially benefit from new targeted therapies for PAH.

The recent introduction of targeted therapies in other forms of PAH has led to a renewed interest in pulmonary hypertension associated with CHD and this particularly for the most advanced form, the ES.[2]

The particular setting of the single ventricle physiology is also of major interest as even a minimal increase in pulmonary vascular resistance may either preclude Fontan surgery or lead to failure of this circulation.[3]

This review summarizes the current knowledge on pulmonary hypertension associated with CHD characterized by congenital shunts. Specific discussions will be dedicated to pre and postoperative PAH, ES management and the particular setting of the Fontan circulation.

## EPIDEMIOLOGY AND CLASSIFICATION

A wide range of CHD can lead to PAH but the most important group is left-to-right shunts lesions. This group includes many different defects that have different evolutions and this is of importance.

Advances in pediatric cardiology and surgery have increased the number of CHD patients surviving into adulthood, and helped to prevent the onset of ES in many patients in the western world, resulting in a reduction of approximately 50% in prevalence over the past 50 years. Around 5% of adults with CHD will develop PAH.[4] The prevalence of PAH in CHD has been estimated between 1.6 and 12.5 million of adults, with 25-50% presenting with ES.[5] However, still a growing number of patients present with malformations characterized by a so-called single ventricle physiology requiring a particular surgical approach (partial or total cavopulmonary anastomosis). Although they do not present pulmonary hypertension as per the classical definition, these patients may have pulmonary vascular lesions that either preclude surgery or carry a high risk of morbidity and mortality.

Structural changes in the pulmonary vasculature in all forms of PAH, including ES, are qualitatively similar, although there is some variation in the distribution and prevalence of pathological changes with different underlying etiologies. According to the classification, pulmonary hypertension resulting from CHD is grouped with idiopathic/heritable PAH, drug-related PAH, PAH associated with connective tissue diseases and HIV-related PAH.[6] However, CHD is, as mentioned above, a complex group of pathologies that may differ from other forms of PAH with regards to cardiac anatomy, hemodynamic and natural history.[7, 8] This is one of the reasons why experts have tried progressively to develop a sub-classification to better define PAH-CHD patients.[8-10] Sub-classifications have taken into account several factors important to better describe the lesions but also factors important in the development of PVD such as type and size of defects, hemodynamic, presence of extra cardiac anomalies and the status of the repair (unrepaired, palliated or repaired). Based on these suggestions and further understanding

TABLE 1. **Clinical classification of congenital systemic-to-pulmonary shunts associated to PAH**

| | |
|---|---|
| Eisenmenger syndrome | Includes all systemic-to-pulmonary shunts due to large defects, leading to a severe increase of PVR and resulting in a reversed (pulmonary-to-systemic) or bi-directional shunt. Cyanosis, erythrocytosis and multiple organs involvement are présent |
| PAH associated with systemic-to-pulmonary shunts | In patients with moderate to large septal defects the increase of PVR is mild to moderate, systemic-to-pulmonary shunt is still largely prevalent and no cyanosis is present at rest |
| PAH with small septal defects | Small defects (usually ventricular septal defects <1 cm and atrial septal defect <2 cm of effective diameter assessed by echo); clinical picture similar to IPAH |
| PAH after corrective cardiac surgery | CHD has been corrected but PAH either is still present immediately after surgery or has recurred several months or years after surgery in the absence of significant immediate postoperative residual lesions |

CHD: Congenital Heart Defect, IPAH: Idiopathic Pulmonary Arterial Hypertension, PVR: Pulmonary Vascular Resistance.
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of the disease, several modifications have been introduced at the last world meeting on pulmonary hypertension allowing for an updated pathologic and physiopathology classification that should satisfy both the CHD expert and non expert.[6]

For clinical practice use, four distinct phenotypes have been recognised, differing in their management and responses to treatment (Table 1). The first group is composed of patients with ES, at the final stage of PAH-CHD but beneficiating from the emerging therapies. The second cluster encompasses patients with PAH associated with systemic-to-pulmonary shunts, at earlier stages of the disease. These pre-Eisenmenger patients have a mildly or moderately increased PVR. Unlike ES patients, they are not often enlisted in studies and their management is consequently challenging.

The third group includes patients with a small cardiac shunt that is not thought to be the cause of PAH. They are very similar to idiopathic PAH patients.

The last group is composed of patients with a persistent or recurrent PAH after successful surgical correction of the cardiac defect. Their very poor prognosis emphasizes the need for more accurate operability criteria.

These different groups require separate management strategies, and have different responses to treatment.

A pathological-pathophysiological classification of congenital systemic-to-pulmonary shunts associated with PAH has also been proposed to better describe the type of congenital shunts (Table 2).

## NATURAL HISTORY-EISENMENGER SYNDROME

### Surgical Correction/Operability

Advances in pediatric cardiac surgery now enable corrective surgery for CHD that are associated with increased pulmonary blood flow to take place in very early infancy. These procedures aim to prevent a whole plethora of sequelae, including the development of PAH and PVD. However, in some individuals with left to right shunts, such defects may pass undetected until childhood or even adulthood and are diagnosed late when pulmonary vascular lesions have developed. In developing countries, due to a previous lack of opportunity to close defects during infancy, PAH in children with CHD is common. This situation is now becoming a very real issue, as healthcare in these countries is starting to improve.[11] Therefore, there is a real need for guidance concerning complete surgical repair or palliative surgery of CHD in patients that, as a result of their condition, develop some degree of PVD.

How can patients with a high risk of persistent PAH after surgery be identified with accuracy? Physicians currently use to base their decision on different criteria on whether a patient is a suitable surgical candidate. There is no overall consensus and recommendations rather than definitive guidance can only be given.[12]

Surgical repair in patients with high PVR and established PAH is risky. If PVR remains high post-operatively and PAH persists then prognosis

TABLE 2. **Pathological-Pathophysiological classification of congenital systemic-to-pulmonary shunts associated with PAH**

| |
|---|
| 1. Type |
| 1.1 Simple Pre-tricuspid Shunts |
| 1.1.1 Atrial septal defect (ASD) |
| 1.1.1.1 Ostium stecundum |
| 1.1.1.2 Sinus venosus |
| 1.1.2 Total or partial unobstructed anomalous pulmonary venous return |
| 1.2 Simple Post-tricuspid Shunts |
| 1.2.1 Ventricular septal defect (VSD) |
| 1.2.2 Patent ductus arteriosus |
| 1.3 Combined Shunts. Describe combination and define predominant defect |
| 1.4 Complex CHD |
| 1.4.1 Atrioventricular septal defects |
| 1.4.1.1 Partial (Ostium primum ASD) |
| 1.4.1.2 Complete |
| 1.4.2 Truncus arteriosus |
| 1.4.3 Single ventricle physiology with unobstructed pulmonary blood flow |
| 1.4.4 Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent ductus arteriosus |
| 1.4.5 Other |
| 2. Dimension (specify for each defect if more than one congenital heart defect) |
| 2.1 Hemodynamic |
| 2.1.1 Restrictive (pressure gradient across the defect) |
| 2.1.2 Non-restrictive |
| 2.2 Anatomic |
| 2.2.1 Small to moderate (ASD ≤ 2.0 cm and VSD ≤ 1.0 cm) |
| 2.2.2 Large (ASD > 2.0 cm and VSD >1.0 cm) |
| 3. Direction of shunt |
| 3.1 Predominantly systemic-to-pulmonary |
| 3.2 Predominantly pulmonary-to-systemic |
| 3.3 Bidirectional |
| 4. Associated extracardiac abnormalities |
| 5. Repair status |
| 5.1 Unoperated |
| 5.2 Palliated (specify type of operation/s, age at surgery) |
| 5.3 Repaired (specify type of operation/s, age at surgery) |

ASD: Atrial septal defect, PAH: pulmonary arterial hypertension, VSD: Ventricular septal defect
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is poor.[13] In a 5-year retrospective study of children with PAH in the United Kingdom, the subpopulation with post-operative CHD-PAH fared far worse than those with PAH associated with complex (un-operated) CHD and ES. Almost one quarter of these children died (11/47).[13] Children with ES had a greater cumulative survival time by 1.3 years indicating that surgical repair is not necessarily always the best option.

There are several examinations and criteria that are used to inform the decision on whether a patient with PAH related to CHD is suitable for surgery and ascertain the best possible outcomes that can be attained: clinical examination for signs of congestive heart failure and oxygen saturation; echocardiography for signs of pulmonary over-circulation (Figure 1 and 2); and the current gold standard of right heart catheterisation measurements of hemodynamic parameters and vasoreactivity (Figure 3).[11,14]

For some time examination of histopathological changes of the pulmonary vasculature by means of lung biopsy was used to assess operability.[15] At present, the reliability of the results is not considered sufficient to justify the invasive nature and risks involved in obtaining a tissue sample.[16] Moreover biopsy may not represent the all lung disease but just a random part. Patients without intimal thickening of the pulmonary arteries and so considered to have reversible PVD can still develop irreversible postoperative PAH. Moreover, younger children (<2 years) are often

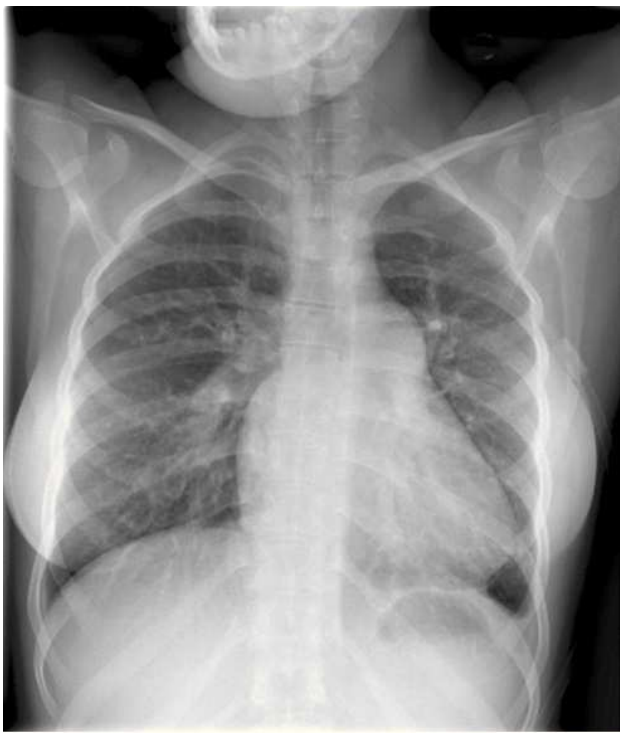

**Figure 1.** Chest radiograph of a patient with Eisenmenger syndrome showing mild cardiomegaly, enlarged pulmonary arteries and decreased peripheral pulmonary vascular markings. These signs prelude the possibility of surgical repair.

operable despite advanced changes on lung biopsy.[15] However, in light of new information correlating apoptotic markers to morphological changes in lung tissue and the development of irreversible post-operative PAH,[9] lung biopsies do and should continue to play an important role in clinical and basic research. A better understanding of the pathophysiology of the pulmonary vasculature in PAH-CHD is still required in order to fully examine the effects drugs and treatments available now and in the future. See Viswanathan and Kumar,[11] Lopes and O'Leary,[12] and Giglia and Humpl[14] for comprehensive reviews on invasive and non-invasive assessments for determining operability in PAH-CHD patients.

At present, empirical means using hemodynamic data from right heart catheterisation and vasoreactivity are principally used to best predict which patients would have a positive or negative surgical outcome. In a recent paper, Lopes and O'Leary, from available literature and by seeking expert opinion from recognised centres of excellence, specified hemodynamic criteria based on both PVR and the ratio of pulmonary to systemic resistance and the way these values change during acute vasodilator challenge. It was determined that[12]:

*1.* A baseline PVR index <6 Woods units/m$^2$ associated with a resistance ratio of <0.3 without a vasoreactivity test is interpreted as indicative of a favourable outcome following operations resulting in a biventricular circulation.

*2.* Acute vasodilator challenge using oxygen/nitric oxide has been strongly encouraged if baseline PVR index is between 6 and 9 Wood units/m$^2$ in the presence of a resistance ratio from around 0.3-0.5. Although there is no absolute consensus, operability with a favourable outcome is considered likely if the following criteria are met:

– A decrease of 20% in the PVR index.

– A decrease of around 20% in the ratio of pulmonary to systemic vascular resistance.

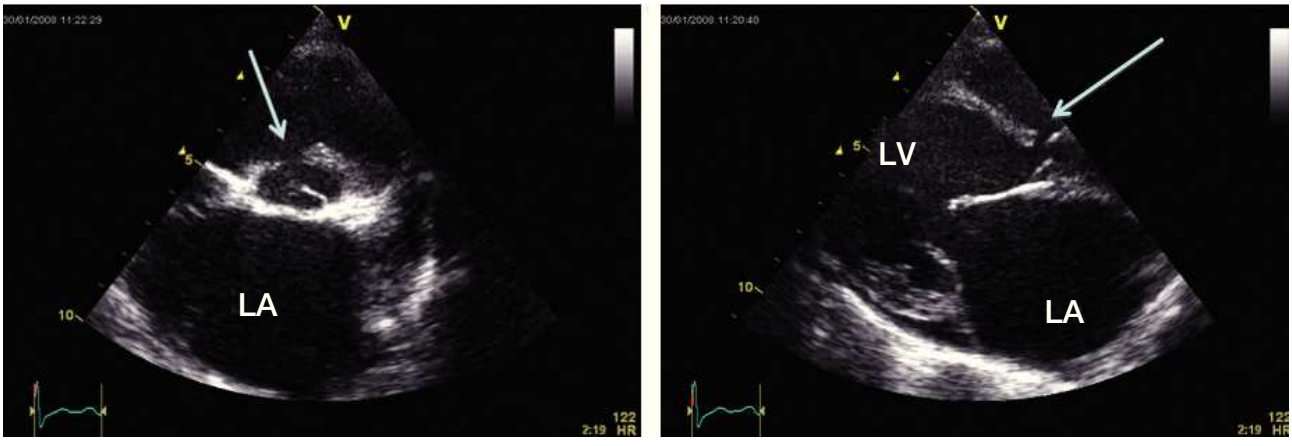


**Figure 2.** Echocardiography of a patient with a ventricular septal defects and signs of pulmonary overcirculation attesting for low pulmonary vascular resistance and high pulmonary blood flow. These pictures are usually allows for surgical repair with performing catheterization. Left pannel shows a short axis view with the ventricular septal defect defect (arrow) and in particular a dilated left atrium (LA). Right panel shows a long axis view with a dilated left ventricle (LV) and LA attesting pulmonary overcirculation in presence of a shunt.

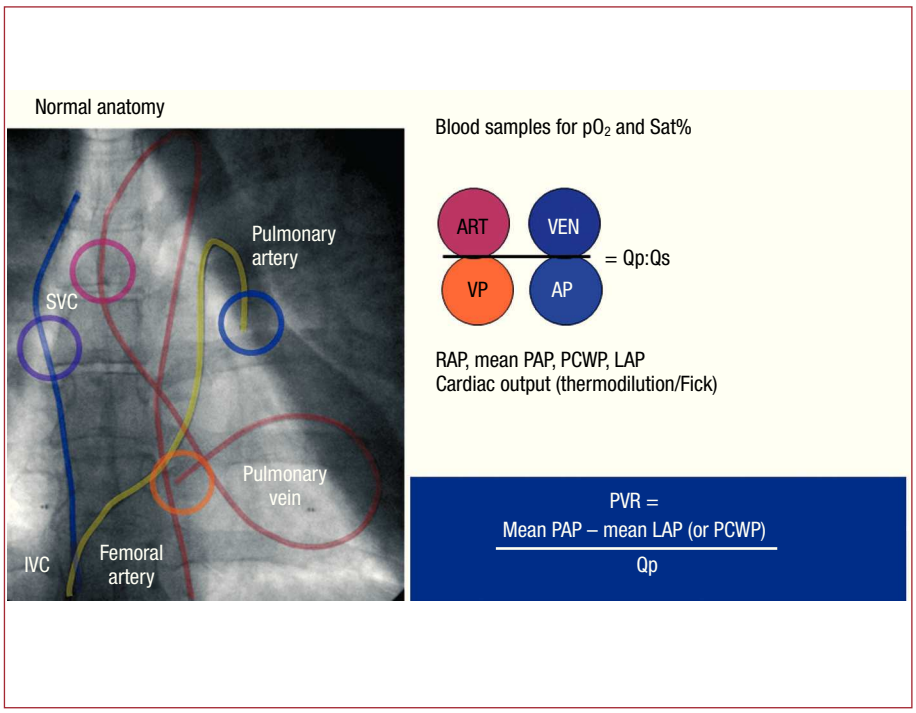


**Figure 3.** Ideal cardiac catheterization with catheters measuring simultaneously s oxygen saturation and pressures in all cavities and vessels simultaneously to avoid time sampling bias. It describe the formula to calculate Qp/Qs in congenital shunts which is the ration of pulmonary blood flow (Qp) over systemic blood flow (Qs), Cardiac output can be measured by thermodilution in absence of shunt or with the Fick formula in presence of intra or extracardiac shunts. LAP indicates mean left atrial pressure; PAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; RAP, mean right atrial pressure. (Courtesy of Ingram Schulze Neick National & UK Centre for Pulmonary Hypertension in Children, Great Ormond Street Hospital, London, United Kingdom).

– A final PVR index of <6 Woods units/$m^2$.
– A final ratio of resistance of <0.3.

These are very conservative numbers that may be adapted in the future. Acute vasodilator testing, regardless of whether nitric oxide alone or in an admixture with oxygen, is the gold standard measure of the reactivity of the pulmonary vascular bed.[17,18] In idiopathic PAH, vasodilator testing is done in order to determine whether a patient will respond to therapy with calcium channel antagonists. However, when to assess the operability of a patient with a CHD and high PVR, it is an open question on whether it is accurate enough to completely discriminate between patients who will or won't have a good surgical outcome. In addition, technical difficulties leading to calculation errors and other medical conditions need to be considered when undertaking vasodilator testing.[11] It remains unclear which preoperative pulmonary hemodynamic parameter correlate with the best outcomes. How individual patient factors such as cardiac lesion type and genetic predisposition influence the outcome is also not completely understood.

It should be noted that the above criteria do not apply to patients with single ventricle physiology who are being assessed for the creation of a Fontan circulation. These patients should ideally have near normal levels of PVR and certainly no more than 3 Woods unit per $m^2$. Moreover, obtaining accurate hemodynamic measurements can be even more difficult in patients with single ventricle physiology.[14]

Although right heart catheterisation measurement of hemodynamics are helpful, and indeed the best tools available at present, they are not failsafe. Patients that fall within the ranges deemed appropriate for determining a good operable outcome may still present with persistent post-operative PAH. Better, more accurate and preferably less invasive evaluation tools are needed, and especially in patients considered borderline for operability due to their hemodynamic profile. Recently, Lévy et al have made some promising advances to develop new tools to assess operability.[19-21]

Patients with similar hemodynamics prior to operation were stratified into two groups post-operatively depending on the presence of persistent postoperative hypertension. In lung biopsies, although increases in pulmonary arterial wall thickness were apparent for all patients, 10/11 of those with irreversible pulmonary hypertension also had pronounced thickening of the intimal layer. Coupled with this was the exclusive expression of Bcl-2, an antiapoptotic marker, by the endothelial cells from arteries with severe intimal fibrosis. There was no difference between the expression of apoptotic markers, capsase-3 and p53, in the endothelial cells of the groups. These data suggest that proliferation of apoptotic-

resistant endothelial cells may be a causative factor of intimal thickening. Experimental evidence from animal models of PAH supports a hypothesis that a triggering event leading to initial apoptosis of endothelial cells could promote subsequent proliferation and emergence of apoptotic resistant endothelial cells.

Recognising that lung biopsy is an invasive tool and less than ideal in general clinical practice, Smadja et al set out to determine whether circulating endothelial cells (CEC)—already recognised as a non-invasive marker of vascular damage, remodelling and dysfunction—would be a suitable biomarker that could identify patients at high risk of developing irreversible PAH after repair of a CHD. Patients with irreversible PAH, in addition to showing pulmonary arterial intimal thickening and a corresponding high expression of blc-2 in the endothelial cells on lung biopsy, also had significantly higher peripheral blood CEC levels than those with reversible PAH.[20] In contrast to CEC, other biomarkers of endothelial activation, regeneration and injury have not been able to discriminate between reversible and irreversible PAH following surgery.

## Non-operable preEisenmenger

As mentioned above the second group of the subclassification includes patient with PVR considered too high for surgical repair but they do not reach the diagnosis of ES. So far, the therapeutic approach of this group is to watch and see and wait for the development of ES. However, with the upcoming new targeted therapies use to treat pulmonary hypertension in several settings, the concept of treat and repair as emerged, with more questions than answers![22]

In the past 10 years prostacyclin analogues, endothelin receptor antagonists and phosphodiesterase type-5 (PDE-5) inhibitors have all shown to be effective in treating PAH, in part via vasodilatory actions.[23] It is proposed that endothelin receptor antagonists in particular may have additional actions such preventing endothelial cell growth and fibrosis and have a remodelling effect on the pulmonary vascular bed. Indeed, their vasodilatory actions are of lesser interest in the discussion of the potential ability to prepare PAH-CHD patients for operability; it is their antiproliferative actions and potential to induce lesion regression that is of greater importance.

The dual endothelin receptor antagonist bosentan, has been extensively tested in idiopathic PAH and there is also good evidence that it is effective in treating PAH associated with CHD.[24] Unlike idiopathic PAH, the cause of PAH in CHD patients with large defects is partially known; it is thought that the pressure and volume load on the pulmonary vascular bed leads to pulmonary vascular remodelling and lesions. While in idiopathic PAH patients always have defined lesions, this may not always be the case for CHD patients where lesions may be less extensive. So by reducing PVR in patients where vascular lesions are not extensive, the possibility arises that pre-treatment with vasodilators can be used to improve a patient's condition and an inoperable case could be considered operable (Figure 4). This may not, however, always be the case in patients where lesions are extensive and PVD is established. Although drugs can reduce PVR in these patients, PAH could remain post operatively and a worse prognosis could result.

One problem that may arise by decreasing PVR with PAH-targeted therapies is that an increase in pulmonary blood flow, due to an increase in shunt pressure, re-establishes the propensity towards lesion occurrence. Thus, paradoxically, the reversal of vascular remodelling and lesion formation, leading to an initial decrease in PVR could actually result in pulmonary vascular damage later on. One solution would be to apply a pulmonary artery band once PVR decreases, thereby reducing blood flow to the pulmonary vascular bed and preventing further damage.

In addition to vasodilatory actions, bosentan also has anti-fibrotic, anti-proliferative and anti-inflammatory actions. Prostacyclin analogues inhibit platelet aggregation and smooth muscle cell growth. The additional properties of these drugs may also have a role in preventing or slowing vascular remodelling. There have been several case reports of pre-treatment with prostacyclins or bosentan being used prior to CHD surgery to prepare borderline or "inoperable patients."[25-28] These reports suggest an advantage to using prostacyclin analogues or endothelin receptor antagonists to improve hemodynamic and make conditions more favourable for repair. However, there are several very important elements that need to be considered. Most patients had simple atrial septal defects (ASDs). Assessment of operability may be questionable. For most of these case reports the follow-up time of the patients when outcomes were reported was short—1 year or less—. To confidently declare a successful outcome, data over a minimum of several years would be required. While these isolated cases show success with pre-treatment prior to operability, we do not know how many cases have failed and not been reported. A retrospective analysis of national registries on this type of data would be required in order to gain a complete picture.

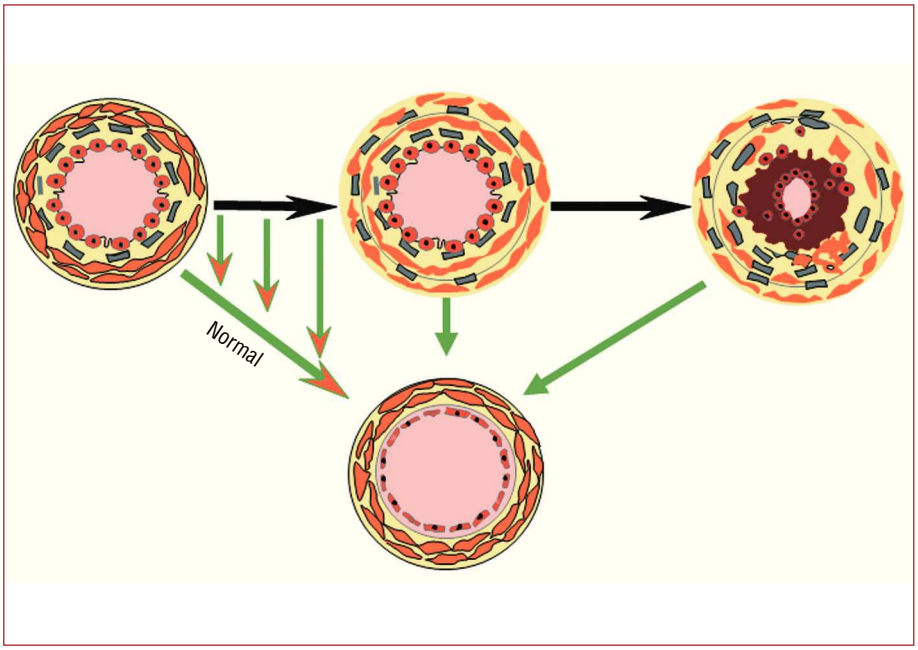


**Figure 4.** Treat and repair? The upper part shows the progression of lesions in presence of a left to right shunt. The arrows represent the opportunity to see the lesions to regress to normal or near normal. This raises the opportunity to treat patients with increased pulmonary vascular resistance that contraindicates surgery in order to remodel the vascular bed and possible to allow complete correction of the underlying anatomical lesion.

## PERSISTENT PULMONARY HYPERTENSION LATE AFTER SURGICAL REPAIR

The functional and structural state of the pulmonary vascular bed plays a pivotal role in the presentation and outcome of the child with congenital cardiovascular disease. It is in the immediate postoperative period that the child is most vulnerable to a sudden or sustained increase in pulmonary vascular resistance. Following surgery for congenital cardiac disease, pulmonary vascular reactivity is heightened, and vasospastic stimuli may result in sudden increases in PAP and resistance, resulting in acute right-sided cardiac failure, tricuspid regurgitation, systemic hypotension, myocardial ischemia, and increased resistance in the airways.[29] These episodes, called pulmonary hypertensive crises, may be lethal events. Mildly stimulating events can precipitate similar crises, and the crises tend to last longer and cluster.

However, with improved postoperative care and the introduction of new therapies, acute pulmonary hypertensive crisis can, in most cases, be treated.

The incidence of postoperative pulmonary hypertensive events decreased from 31% in the period from 1980 through 1984, to 6.8% before the routine use of inhaled nitric oxide.[30] Series reflective of contemporary practice suggest that pulmonary hypertension complicates 2% of patients undergoing congenital cardiac surgery, with crises occurring in 0.75%.[7] The mortality in those suffering a crisis, nonetheless, remains high at 20%, and pulmonary vascular disease is identified as a major contributor to length of stay in hospital, and the need for prolonged mechanical ventilation (see a recent review by Adatia and Beghetti for further detail, as this is not the scope of this review.[29])

However, acute treatment and survival in the immediate postoperative period does not mean that pulmonary hypertension resolves and the patient may present persistent PAH after surgical repair but in the absence of a shunt. Little is known about this particular group, as literature remains scarce. This group has been included in the subclassification of CHD-PAH (group 4 of the clinical subclassification).[6] The hemodynamic presented by this group is very similar to idiopathic PAH and thus prognosis seems to be poor based on recent data.[13] This underscores the importance of accurate decision for operability and survival could even be better with an open shunt and ES than with a closed shunt and right ventricular failure.[31]

## EISENMENGER SYNDROME MANAGEMENT

ES represents the most advanced form of PAH associated with CHD. The signs and symptoms of ES usually result from low blood oxygen saturation

and include dyspnoea, cyanosis, fatigue, dizziness, syncope, and arrhythmia. Symptoms may not arise until childhood or early adulthood. In general, patients with ES have reduced life expectancy, although many survive into their third or fourth decade,[32] with some even surviving into their seventh decade with appropriate management.[32,33] Of all patients with CHD, those with ES are the most severely compromised in terms of exercise intolerance.[34] Exercise intolerance in these patients has been identified as a predictor of hospitalisation or death independent of age, gender, functional class or underlying cardiac defect.[34] Anecdotal evidence suggests that patients with ES adapt their lifestyle around their exercise capabilities, and that they tend to under-report their limitations. Despite this, ES clearly and severely affects a patient's exercise capacity and so decreases their quality of life.

## Conventional Management

Recent publications have extensively described the management of ES.[2,5,35] As mentioned earlier, treatment options for patients with ES were historically limited to palliative measures and heart-lung transplantation. Treatment most commonly involved the use of digitalis, diuretics, antiarrhythmics, and/or anticoagulants. However, none of these classes of drugs significantly modifies survival or significantly affects the risk of deterioration in ES. Digoxin has been used in palliative therapy for right heart failure in ES, although available evidence supporting its use is particularly weak.[36] The use of anticoagulation in patients with ES is controversial, as ES patients have a high incidence of pulmonary artery thrombosis, haemoptysis, stroke and an increased risk of haemorrhage.[36] One recent study estimated the prevalent pulmonary artery thrombosis in ES to be 20%, with risk correlating with increasing age, biventricular dysfunction, dilatation of the pulmonary arteries, and concomitantly decreased pulmonary flow velocity.[37] Although evidence suggests a benefit of such treatment in patients with idiopatic PAH, no data exist in ES, and the haemorrhage associated risks of treatment in these patients may outweigh potential benefits. To date, no prospective studies have addressed the value of anticoagulation in the prevention of either thrombosis or haemoptysis, and a great need exists for such data.[38]

The efficacy of calcium channel blockers in patients with ES is neither proven nor generally recommended, as their use can result in an acute decrease in systemic arterial pressure and increased right-to-left shunting, which may lead to syncope and sudden death.[39] Long-term oxygen therapy at home for a minimum of 12–15 hours per day may improve symptoms, but has not been shown to modify survival.[36]

Patient education, behavioural modifications and awareness of potential medical risk factors are all important aspects of management. Patients with ES are at particular risk during cardiac and non-cardiac surgery and anaesthesia, and as a result of dehydration, chest infections, high altitude and intravenous lines. It is also recommended to avoid strenuous exercise and not to participate in competitive sports.

Pregnancy is associated with high risk to both mother and foetus. Spontaneous abortion rates are high and only around 25% of pregnancies continue to term. For those infants who survive, around one third have evidence of intrauterine growth retardation, and perinatal mortality is high. Maternal mortality is around 45% in ES patients, and death usually occurs during delivery or within the first week postpartum, mostly as a result of thromboembolism, hypovolaemia, or preeclampsia . Pregnancy is therefore contraindicated in patients with ES.[40,41]

## Targeted Therapies

As discussed, the endothelin-1 system clearly plays a major role in the structural and functional abnormalities in the pulmonary vasculature and the progression of PAH in all forms of the condition, including PAH-CHD. Given that treatment with endothelin receptor antagonists has been successful in treating patients with idiopathic PAH and PAH-CTD,[42-44] they would be expected to have similarly beneficial effects in patients with PAH-CHD. The first randomised, double-blind, placebo-controlled study in patients with ES was BREATHE-5 (Bosentan Randomised Trial of Endothelin Antagonist-5) which investigated the efficacy of the dual endothelin receptor antagonist, bosentan, in 54 adult patients with ES. During this 16-week study, bosentan significantly reduced PVR and mean PAP and improved exercise capacity compared with the placebo group, without adversely affecting systemic arterial oxygen saturation.[45] This safety finding is of particular importance in patients with ES given the potential for aggravation of the overall shunt due to the possibility of a fall in systemic resistance in response to vasodilatory therapies. Longer follow-up data from the open-label follow-up study of patients enrolled in the original 16-week double-blind trial showed that improvements in exercise capacity continued over a further 24 weeks of treatment.[46] Functional class also improved over this period, and treatment was well tolerated.

These findings are supported by a number of small-scale, open-label studies, which also demonstrate improvements in functional class, oxygen saturation, clinical status and pulmonary hemodynamic in paediatric and adult patients with ES.[47-50] Long-term data suggest that improvements are maintained for as long as two years of treatment, without safety or tolerability issues[51,52] but other have shown that the effect may decrease with time.[53] The findings from these studies challenge the dogma that pulmonary vascular disease in patients with ES is not amenable to treatment. On the other hand, ES is not a stable disease as has been assumed, but progressive deterioration occurs, as demonstrated by the increase in PVR seen in patients from the placebo arm of the BREATHE-5 study.[45]

Data from the BREATHE-5 study also suggest that the location of the septal defect does not influence short-term hemodynamic and functional improvements to bosentan treatment. As the evolution of pulmonary vascular disease differs markedly between ES patients with ASDs and ventricular septal defects (VSDs), they could respond differently to medical treatment. In a post hoc analysis of the BREATHE-5 trial, the effects of bosentan and placebo in patients with ASD and patients with either VSD or both defects (VSD/ASD+VSD) were compared.[54] In both subgroups, no changes in systemic pulse oximetry were observed between treatment groups, and placebo-corrected treatment effects on indexed PVR, exercise capacity and mean PAP were also comparable.

Data with other endothelin receptor antagonists in PAH-CHD are still awaited but it would be expected to see similar results as with other forms of PAH.

## Phosphodiesterase Type 5 Inhibitors

To date, there are limited data regarding the use of the PDE-5 inhibitors in patients with ES. After six months of treatment, World Health Organization (WHO) functional class, oxygen saturation, mean and systolic PAP and PVR were significantly improved in seven patients with ES who participated in a prospective, open-label trial of sildenafil, but although there was a trend towards improvement, changes in 6 minute walk distance did not reach significance.[55] There were few significant side effects, and, although there was a theoretical possibility of reduced pulmonary blood flow due to reduced systemic vascular resistance, cyanosis actually improved in these patients. Functional class, exercise capacity and pulmonary hemodynamic also improved without significant side effects in 21 patients with ES treated with sildenafil in a prospective, non-randomised, uncontrolled, dose-response trial.[56]

These findings are supported by other small studies of PDE-5 inhibitors, alone and in combination with prostanoids, which also showed improvements in exercise capacity, functional class and some hemodynamic parameters without safety issues.[57-60] Recently, Tay et al showed that 3 months sildenafil was well tolerated in 12 adult ES and associated with a significant improvement in quality of life and exercise capacity.[61] Results with regard to efficacy, although encouraging, need validation in large randomised, placebo-controlled trials. Such a trial—to investigate the effects of sildenafil on exercise capacity and cardiopulmonary hemodynamic in patients with ES—is currently recruiting participants in Germany. In addition, long-term effects and effectiveness in ES patients with more complex underlying defects remain to be established.

## Prostacyclin and Prostacyclin Analogues

Overall, there are few data and no large trials concerning the use of prostanoids in ES. Long-term intravenous prostacyclin improved hemodynamic and functional class in 20 patients with PAH associated with a range of CHD, although none of the patients had an acute hemodynamic response.[62] Continuous intravenous epoprostenol significantly improved functional class, arterial saturation and 6-minute walk distance, and decreased PVR in eight patients with ES after three months of therapy.[63] However, in an earlier series, treatment of patients with epoprostenol resulted in adverse events including increase in systemic vascular resistance, increased PVR and low arterial oxygen in eight out of 10 patients.[64] In addition, a number of adverse events have been recorded, including cerebrovascular accidents which probably resulted from the use of a central venous catheter in the presence of a right-to-left shunt.[63] Given the relatively longer median survival in patients with ES relative to those with idiopatic PAH, the potential risks of long-term catheter use is especially important when analysing the risk-to-benefit ratio of treatment. Data on other forms of prostanoid therapy including inhaled and intravenous iloprost, and oral beraprost in ES are limited to case reports, case studies, and small series. Inhaled and oral prostanoids offer obvious advantages over epoprostenol in terms of the safety of long-term administration, but their efficacy and safety has not yet been fully studied in this patient population.

A recent report of Dimopoulos et al shows improved survival in ES using different type of

targeted therapies and confirms the potential of this approach in ES.[65]

## Thoracic Organ Transplantation

Ultimately, transplantation, preferably heart-lung transplantation (HLT), is an option only for a small, selected subgroup of patients, and is severely limited by the availability of donor organs. The success of transplantation varies depending on the underlying cause of ES, and appears to be most beneficial for patients with VSD or multiple congenital abnormalities.[66] Overall, transplantation in patients with ES is associated with high perioperative mortality.[67] However, studies suggest that, although the postoperative course tends to be complicated in these patients, short- and long-term survival rates following HLT are similar to those reported in non-ES recipients.[68] One-year survival rates of approximately 70% after HLT, and 55% after lung transplantation, have been achieved. Five- and 10-year survival rates are 51% and 28%, respectively, after HLT.[66,68]

Given the paucity of suitable donor organs, the small number of suitable recipients and the poor prognosis following HLT, any means to delay the need for HLT in ES patents would be very welcome. One recent retrospective analysis suggests that ES patients who received novel, advanced therapies including prostacyclin analogues and endothelin receptor antagonists may benefit from significantly longer mean times to death or inscription on the active waiting list, by comparison with patients without.[69] Given the lack of benefit of conventional therapy in ES, and the limited surgical options once the disease has developed, a clear unmet medical need exists for patients with ES, which may be addressed by targeted therapies.

## The Fontan Circulation

Since its first description over three decades ago, the Fontan operation and its variations have become the procedures of choice in the management of patients with congenital heart disease with a single anatomical or functional ventricle. The aim of Fontan surgery is to use this single ventricle to drive the systemic circulation while the pulmonary circulation is primarily driven by the negative intrathoracic pressure.

Currently there is no satisfactory general medical treatment for failing Fontan. Management has involved treating specific manifestations such as ventricular dysfunction, protein loosing enteropathy and increased PVR. Treatment of ventricular dysfunction in Fontan patients has been attempted using a variety of agents, but there are few supportive data, and there is evidence that these generally have little or no benefits due to lack of impact on reduced preload.[70] Angiotensin-converting enzyme inhibitors have no effect on exercise capacity, systemic vascular resistance, resting cardiac index, or diastolic function in Fontan patients.[71] Despite this lack of evidence, however, many long-term Fontan patients are treated.

Low cardiac output, excessive hypoxemia, or protein loosing enteropathy may all be clinical manifestations of increased PVR; therefore, its prevention or management is potentially of critical importance. In the acute, post-operative phase, patients with increased PVR are treated with nitric oxide and supplemental oxygen. Inhaled nitric oxide reduces central venous pressure,[72] mean PAP and transpulmonary pressure gradient. Prostacyclins have been rarely used in perioperative Fontan patients, and there are few data available. Beraprost reduces mean PAP and PVR in pre-operative Fontan candidates with mild pulmonary hypertension,[73] and epoprostenol has been shown to prevent the rebound effect after inhaled nitric oxide cessation in the early post-operative phase.[74] When oral administration becomes possible, sildenafil, a PDE-5 inhibitor which acts as a vasodilator, is often used in the post-operative period as it is perceived as safe, with fast onset and good effectiveness. However, sildenafil is not approved for this use and there are no published data to support its efficacy or safety in this indication.

In the treatment of patients with failing Fontan, there have been few observations published to date describing the effects of PVR-lowering drugs. Treatment of late Fontan patients with inhaled nitric oxide reduces PVR, although it has no significant effect on cardiac index.[75] NO-dependent, cyclic guanosine monophosphate (cGMP)-mediated pulmonary vasodilatation can also be enhanced using sildenafil. A single dose of sildenafil has been shown to improve exercise capacity and hemodynamic response to exercise in late, non-failing Fontan patients.[76] There are also single case studies showing improvement in a patient with plastic bronchitis and a patient with protein loosing enteropathy folllowing sildenafil.[77,78] The effect of sildenafil on exercise tolerance, ventricular function and quality of life is currently under investigation in children who have undergone the Fontan procedure. There are currently no data on the effectiveness of prostanoid therapy in the failing Fontan.

The dual endothelin receptor antagonist bosentan has been shown to improve exercise capacity, functional class, quality of life and hemodynamic parameters including PVR and PAP in patients

with PAH. Long-term treatment with bosentan improved symptoms and aortic oxygen saturation, WHO functional class, maximal and sub-maximal exercise capacity, Borg dyspnoea index, mean PAP, pulmonary blood flow and PVR in a patient with plastic bronchitis following Fontan.[79] In a recent small study, oxygen saturation improved in 5/9 patients during a 16-week treatment period with bosentan.[80] The single endothelin receptor antagonists ambrisentan and sitaxentan are also used in the management of PAH; however, no data are available describing their use in Fontan patients.

Given the important role of the pulmonary vascular circulation in Fontan physiology, the demonstrated increase in PAP with age, and the current lack of data there is a major requirement for clinical studies on the efficacy and safety of potential therapies for failing Fontan on which to base much needed management recommendations.

## CONCLUSIONS

In conclusion, improvements in diagnosis and surgical and medical management have changed the long-term survival prospects for patients with PAH-CHD, resulting in a significant increase in the number of patients surviving to adulthood. Although there are some differences in aetiology, treatment response and survival, pediatric and adult patients with PAH-CHD have essentially the same disease; a complex condition with a natural history that varies depending on the underlying cardiac defect and multiorgan chronic adaptation to it. Short-term benefits of novel targeted therapies in PAH-CHD are increasingly clear, but long-term investigation in PAH-CHD populations is required. Of increasing interest is the management of patients with complex congenital defects, and the timing and operability of patients to optimize outcomes, each of which warrants further investigation. In particular the role of targeted therapies and the potential treat and repair concept requires further studies. Another challenge is the Fontan physiology that does not fulfil the diagnosis of PAH but where the role of the pulmonary circulation is central. Even, if progress has occurred, still a lot of work is required to better understand this problem in order to better address PAH in this population.

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