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Mechanism of disease

Pulmonary hypertension related to congenital heart disease: A comprehensive review

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a serious complication of congenital heart disease, causing an increase in morbidity and mortality. The progressive and irreversible pulmonary vascular disease is more often the consequence of a significant, uncorrected, left-to-right shunt. The rise in pulmonary vascular resistance may lead to the reversal of the shunt and cyanosis, condition known as Eisenmenger syndrome. The management of this population is challenging and requires specific expertise both for diagnosis and follow-up. The progress in the understanding of the underlying pathophysiology of this condition has promoted recent pharmacological trials. New therapeutic options are now available that could improve the long-term prognosis and the quality of life of these patients, but several controversial points still remain and need to be addressed.

Keywords: pulmonary hypertension, congenital heart disease, Eisenmenger syndrome

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a potential complication of congenital heart disease (CHD), particularly when a significant left-to-right (L-R, systemic-to-pulmonary) shunt remains uncorrected. Longstanding exposure of the pulmonary bed to increased blood flow and pressure can result in vascular remodeling and dysfunction. This may lead to a rise in pulmonary vascular resistance (PVR) and, if severe enough, may cause reversal of the shunt. In 1897 Victor Eisenmenger¹ first described a typical example of this condition. About 60 years later, Paul Wood defined Eisenmenger's syndrome (ES) as "Pulmonary hypertension at systemic level due to high PVR, with reversed or bidirectional blood flow through a septal defect".²

Pulmonary vascular disease in CHD patients is associated with increased mortality and morbidity.^{3,4} Despite growing evidence on the survival benefits of PAH-specific therapies in the PAH-CHD population, their outcome remains poor. Moreover, many questions still need to be addressed, such as the management of the more complex subgroups of patients (e.g. those with complex cardiac anatomy, Fontan circulation or coexisting conditions such as Down syndrome) or the decision-making in highly controversial conditions (e.g. in patients with still net left-to-right shunt and raised PVR, those with "segmental PH" and patients electing to become pregnant).

This article is a comprehensive review about the main features and issues of pulmonary hypertension (PH) in CHD patients.

EPIDEMIOLOGY AND CLINICAL CLASSIFICATION

The estimated prevalence of CHD is approximately 6–10 per 1,000 live births^{5,6} and between 4–15% of patients with CHD will go on to develop PAH⁷, depending on the size and location of the shunt. PH due to CHD includes a wide spectrum of conditions. Cases with PAH-CHD (precapillary PH) are included in group 1 of the PH classification according to the latest World PH symposium in Nice⁸ (Table 1).

Table 1. Updated classification of pulmonary hypertension - 5th World Symposium PH Nice 2013. PH-CHD patients can be classified in the highlighted groups according to the underlying pathophysiology. BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

1. Pulmonary arterial hypertension

- 1.1 Idiopathic PAH
 - 1.2 Heritable PAH
 - 1.2.1 BMPR2
 - 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
 - 1.2.3 Unknown
 - 1.3 Drug and toxin induced
 - 1.4 Associated with:
 - 1.4.1 Connective tissue disease
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 *Congenital heart diseases*
 - 1.4.5 Schistosomiasis
- 1'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1". Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension due to left heart disease

- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 *Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies*

3. Pulmonary hypertension due to lung diseases and/or hypoxia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms

- 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, *segmental PH*

However, cases with post-capillary PH due to left-sided congenital lesions, such as obstructive cor triatriatum, congenital aortic or mitral stenosis and aortic coarctation, are included in group 2 of the PH classification. Finally, “segmental pulmonary hypertension” has been included in group 5 (miscellaneous causes). This refers to conditions in which pulmonary perfusion is not homogeneous throughout the lungs (e.g. pulmonary atresia with a ventricular septal defect, VSD and multiple aortopulmonary collaterals, MAPCAs), resulting in areas of hyperperfused lung, which may over time develop pulmonary vascular disease.

Within PAH-CHD, 4 different clinical conditions can be defined⁸ (Table 2): Eisenmenger syndrome, left-to-right shunt, PAH with coincidental congenital heart disease and post-operative PH. It is important to correctly classify patients into one of the above pathophysiologic groups, as this should affect their management and has implications in terms of short and long-term outcome.

Table 2. Epidemiology and clinical classification of CHD-PH. A-D: group 1 PH (PAH); E: group 2 PH; F: group 5 PH; G: not PH. Modified from: Lowe BS, Therrien J, Ionescu-Iltu R, Pilote L, Martucci G, Marelli AJ. Diagnosis of pulmonary hypertension in the congenital heart disease adult population impact on outcomes. J Am Coll Cardiol. 2011;58:538–546.

| <i>Common types of CHD-PAH</i> | |
|--|--|
| A. Eisenmenger syndrome | Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of pulmonary vascular resistance (PVR) and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis and multiple organ |
| B. Left-to-right shunts | - Correctable - Non-correctable Include moderate to large defects; PVR is mildly to moderately increased systemic-to-pulmonary shunting is still prevalent, whereas cyanosis is not a feature. |
| C. Pulmonary arterial hypertension (PAH) with coincidental congenital heart disease | Marked elevation in PVR in the presence of small cardiac defects, which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. To close the defects in contraindicated. |
| D. Post-operative PAH | Congenital heart disease is repaired but PAH either persists immediately after surgery or recurs/develops months or years after surgery in the absence of significant postoperative hemodynamic lesions. The clinical phenotype is often aggressive. |
| <i>Additional types of pulmonary hypertension or pulmonary vascular disease in patients with CHD</i> | |
| E. Congenital or acquired left heart inflow/outflow obstructive lesions and congenital cardiomyopathies | Conditions with elevated pulmonary capillary wedge pressure (> 15 mmHg). Included in group 2 in the Nice recommendations. |
| F. Segmental pulmonary arterial hypertension | Part of the lung vasculature develops pulmonary vascular disease, while other areas may be normally or hypoperfused. Included in group 5 in the Nice recommendations. |
| G. Pulmonary vascular disease in Fontan patients | Patients with a Fontan-type circulation do not fulfill criteria for PAH but can develop a rise in PVR, despite low pulmonary arterial pressures (low pulmonary blood flow). |

PATHOPHYSIOLOGY

Heath and Edwards in 1958 first described a histological classification for pulmonary vascular disease, referring especially to PAH-CHD.⁹ The histopathological features of PAH include progressive endothelial dysfunction, medial hypertrophy with hyperplasia of smooth muscle cells, increased connective tissue and elastic fibers, intimal and adventitial thickening and rarefaction of the pulmonary arterial tree (Figure 1).^{10,11,12,13} The pathogenesis of these changes seems to be multifactorial, driven by progressive endothelial dysfunction of the pulmonary arterial tree caused by flow and pressure overload.

The rate of progression of pulmonary vascular disease (PVD) generally depends on the type and size of the defect. Large post-tricuspid defects (e.g. VSDs and patent ductus arteriosus, PDAs) typically result in significant PVD developing in early childhood. The rate of progression of the PVD differs from patient to patient, but individuals with Down syndrome are generally prone to developing PVD much earlier than expected.^{14,15} A minority of individuals with large VSDs presents in adult life with significant

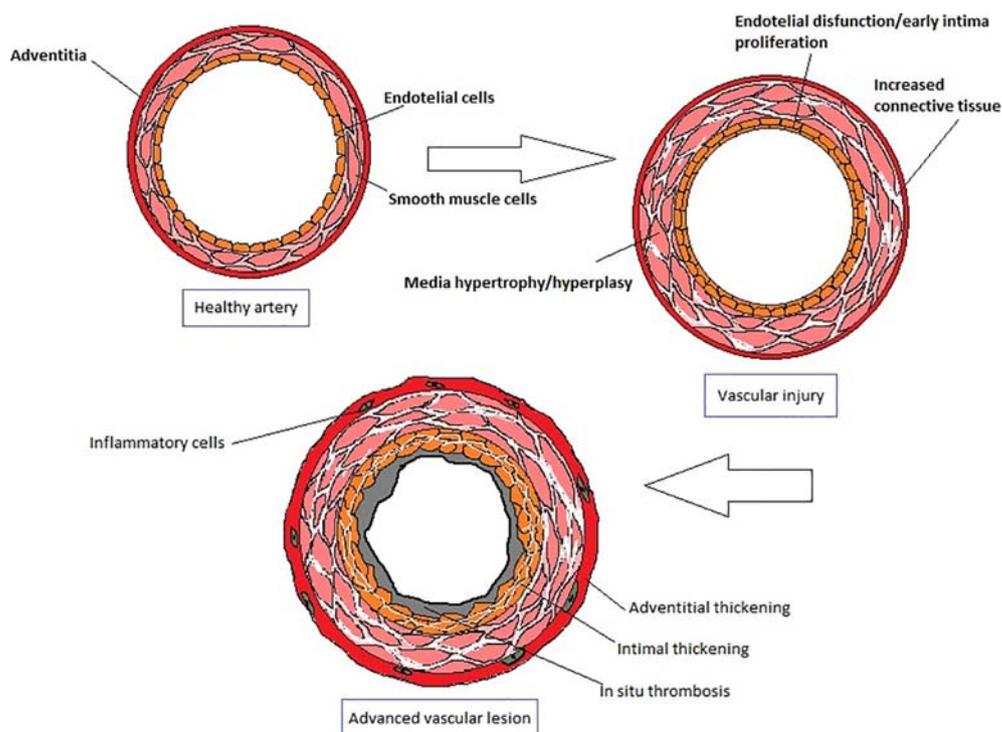


Figure 1. Progression of arteriolar pulmonary lesion in PAH. The picture shows the main modifications in arteriolar vessels structure in the different phases of pulmonary vascular disease, according to Heath, Edwards et al.⁹ The initial stage of vascular disease includes progressive endothelial dysfunction, medial hypertrophy with hyperplasia of smooth muscle cells and increased connective tissue and elastic fibres deposition. In the later stages, there is a more marked adventitial and intimal thickening, massive fibrosis of the media and in situ thrombosis. In the final stages arterioles are massively remodelled and occluded by thrombi deposition, forming complex, glomerular structures called “plexiform lesions”.

L-R shunting and little or no cyanosis. This condition is suggestive of pulmonary vasculature, which is still “compliant” for reasons that yet remain unknown.

CHD-PAH and Eisenmenger patients reaching adulthood are a “prevalent” cohort of survivors who is likely to experience a long period of relative stability. They have a lower mortality compared to other types of PAH (i.e. idiopathic PAH), and many are expected to live beyond the 4th or 5th decade of life.¹⁶ This phenomenon has been mainly attributed to two mechanisms. The first is optimal adaptation of the right ventricle (RV) to severely raised pulmonary resistance in PAH-CHD. It has been suggested that patients developing PAH early in life maintain a “fetal” RV phenotype with significant hypertrophy, more likely to tolerate high pulmonary pressures for longer periods.¹⁷ The second postulated mechanism is the “relief valve” action of right-to-left shunt, especially when post-tricuspid. The shunt allows “decompression” of the heart modifying LV afterload and contributes to maintaining systemic cardiac output at the expense of cyanosis (Figure 2).¹⁸ Recently, this principle has been used for improving the outcome of idiopathic pulmonary arterial hypertension (iPAH) patients by creating a Potts shunt, which is equivalent to a large PDA. This shunt is, in fact, a side-by-side anastomosis of the left pulmonary artery to the descending aorta, introduced as a novel surgical strategy in the management of children with idiopathic PAH and supra-systemic pulmonary pressure in 2004 by Blanc et al. (Figure 3).^{19,20} An obvious advantage over balloon atrial septostomy is that the Potts shunt it “unloads” the RV whilst only causing lower body desaturation. Other authors^{21,22} used a similar approach by transcatheter means in patients with a small PDAs. A remarkable improvement in functional status, effort capacity and echocardiographic parameters was observed soon after stenting of the ductus arteriosus.

The severity of cyanosis in Eisenmenger patients can be a marker of disease severity and progression. Cyanosis leads to exercise intolerance and a range of potential problems, including erythrocytosis, hyperviscosity, abnormal haemostasis, cerebral abscess, stroke and endocarditis.²³ Hyperviscosity symptoms include headache, dizziness, lightheadedness, fatigue, visual disturbances, tinnitus, irritability, slow mentation, dissociation, lethargy, paresthesias (lips/toes) and myalgia.²⁴ Chronic hypoxia associated with ES has other systemic effects, including gout, joint and long bone pain

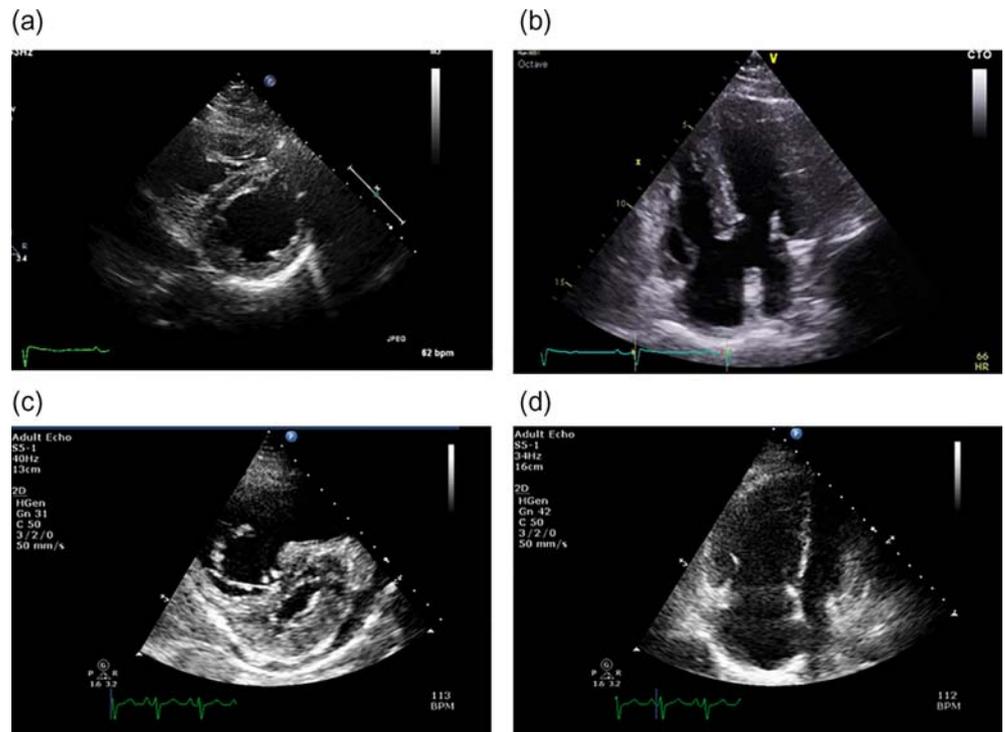


Figure 2. Ventricular interaction in Eisenmenger syndrome vs primary pulmonary hypertension. Difference in right ventricular adaptation between an Eisenmenger patient (a, b) and an idiopathic PAH (c, d). In the ES patient, the RV is hypertrophied but not dilated and has a preserved systolic function despite decades of systemic levels of PAH (a, b). The RV of the patient with severe iPAH, on the other hand, is severely dilated and impaired, also impacting on LV filling. This results in a low cardiac output and more adverse outcome (c, d).

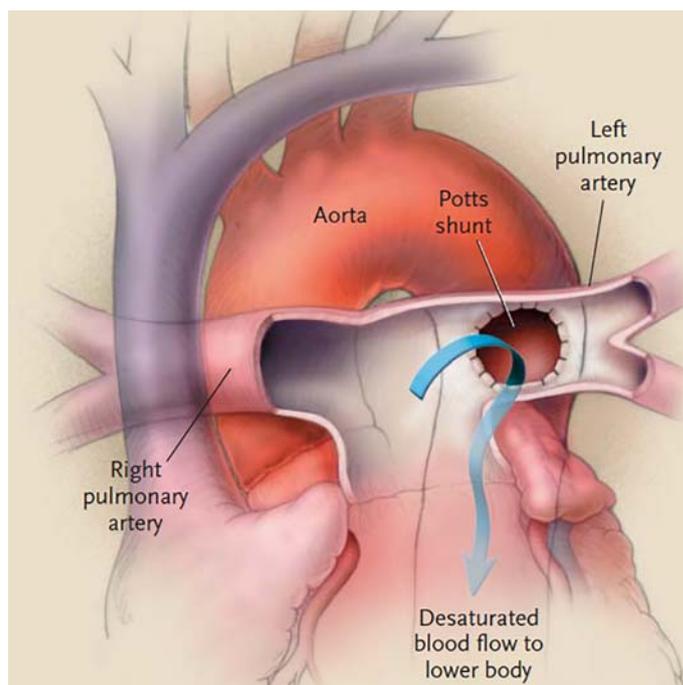


Figure 3. The Potts Shunt Procedure. The left pulmonary artery is anastomosed to the descending aorta, allowing the desaturated blood to go from the left pulmonary artery to the lower part of the body (arrow). The right pulmonary artery passes in front of the ascending aorta because an arterial-switch procedure has been performed. From ¹⁹.

(hypertrophic osteoarthropathy), hemoptysis and thrombosis. Cyanosis, together with PAH and a chronic low cardiac output state, is likely to contribute to systemic effects of PAH-CHD, including multiorgan failure.

Coagulation is a complex issue in ES patients. Cyanosis causes a paradoxical state of both increased risk of bleeding (e.g. hemoptysis or epistaxis) and thrombosis (e.g. pulmonary arterial thrombosis).^{25,26} The predisposition to bleeding has been attributed to the drop in platelet count, acquired von Willebrand syndrome, primary fibrinolysis or disseminated intravascular coagulation, liver dysfunction, increased sensitivity to activated protein C and suppression of the thrombomodulin-protein C-protein and S pathway.^{27,28} The risk of bleeding should be kept in mind when considering surgery, together with the high risks related to general anesthesia in PAH. So far, there are few data on the use of anticoagulants in ES patients. Recent data from a large European registry²⁹ discourages the routine use of anticoagulants in ES. Anticoagulation should be, instead, considered in patients with persistent arrhythmia, embolic or thrombotic phenomena, severe congestive heart failure and *in situ* pulmonary arterial thrombosis, in the absence of previous major bleeding (i.e. moderate-to-severe haemoptysis).³⁰

Embolic phenomena resulting in major clinical events are relatively rare in cyanotic PAH-CHD, even though paradoxical embolism should be part of the differential diagnosis for any neurological event in this group.³¹ Neurological signs and symptoms may be caused by air embolism (during intravenous infusion of drugs or fluids), hyperviscosity symptoms, or infective emboli. The latter can have devastating effects, with cerebral abscesses carrying a high mortality and morbidity. For this reason, European and American endocarditis guidelines strongly recommend antibiotic prophylaxis in cyanotic CHD.^{32,33}

DIAGNOSIS OF PAH AND PULMONARY VASCULAR DISEASE IN CHD

The clinical diagnosis of ES is relatively straightforward: cyanosis at rest or minimal effort in the presence of a large uncorrected shunt. Cyanosis is typically (but not always) associated with digital clubbing (Figure 4). Rarely, cyanosis may only be present in the lower body (toes) due to a



Figure 4. Nail clubbing. Nail clubbing (also known as “drumstick fingers and watch-glass nails”) is a deformity of the fingers and fingernails associated with cyanosis and Eisenmenger syndrome.

patent ductus arteriosus, in which the shunt occurs at the level of the proximal descending aorta. Detecting PH in non-Eisenmenger patients may be less straightforward. Electrocardiographic signs of right ventricular hypertrophy and right atrial dilatation should raise the suspicion of PAH in patients with CHD (Figure 5). Chest x-ray typically reveals prominent dilated pulmonary artery, decreased peripheral lung vascular markings (pruning) and right ventricular enlargement (Figure 6).³⁴

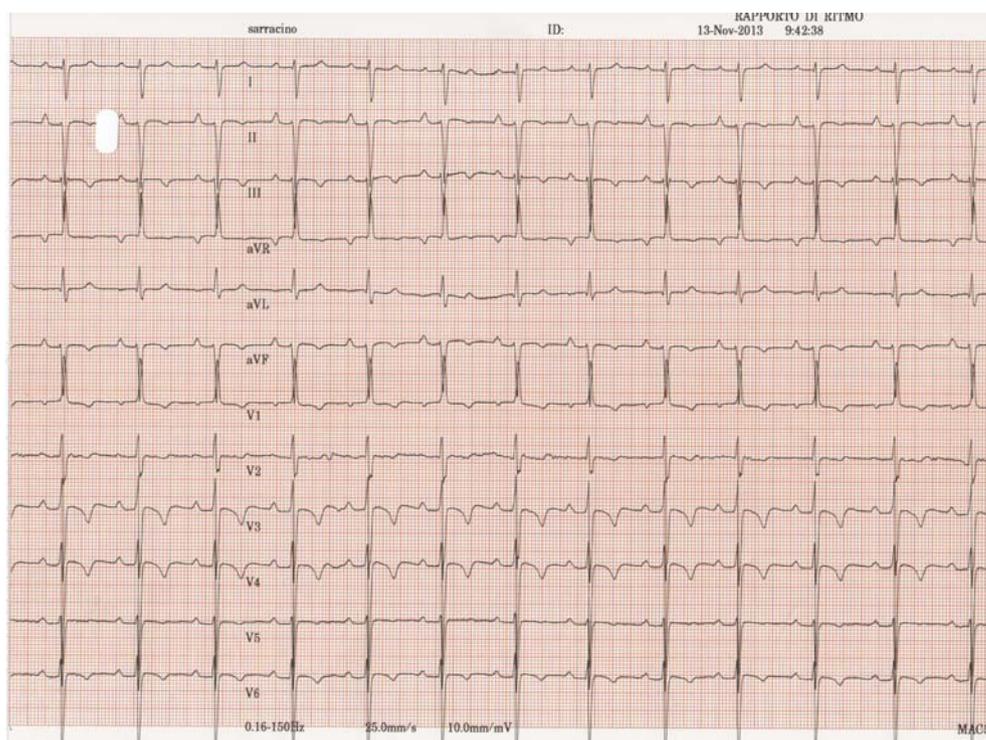


Figure 5. ECG in ES patients. Typical ECG from a patient with Eisenmenger Syndrome due to uncorrected complete AV canal showing left axis deviation and right atrial and right ventricular strain.

Echocardiography plays a key role in diagnosing PAH in CHD. In ES patients, echocardiographic demonstration of a large defect with low velocity bidirectional shunting is reliable evidence of near equalization of systemic and pulmonary pressures (Figure 7). Nevertheless, echocardiography cannot replace cardiac catheterization, especially in cases with moderately increased PVR and persistent left-to-right shunts (group B of clinical classification or “Left-to-right shunts” patients), pretricuspid shunts or no residual defects (Group D).^{35,36} Echocardiography also provides prognostic information in CHD-PAH and Eisenmenger patients.³⁷ Cardiac magnetic resonance is invaluable in defining cardiac and extracardiac anatomy and has become the gold standard for assessing right ventricular size and function. Computed tomography is also very useful in defining complex extracardiac anatomy, such as defining the location and size of MAPCAs in pulmonary atresia, as well as the patency of palliative shunts (Figure 8).

Cardiac catheterization is the gold-standard for diagnosing PAH, especially in CHD patients. Currently, international guidelines define PAH as a mean PAP (mPAP) ≥ 25 mmHg in the presence of a normal PWP (≤ 15 mmHg) and high PVR (>3 Wood Units).⁸ While a raised mPAP is likely to be associated with PVD in non-CHD patients, this may not be the case in CHD. mPAP may, in fact, be raised in the presence of normal PVR due to a significant systemic-to-pulmonary shunt with high pulmonary blood flow (so called “high-flow pulmonary hypertension”: high mPAP, high QP/QS, normal/low PVR, absence of PVD). Reversibility testing is only used for the purpose of assessing operability (i.e. estimating the severity and reversibility of PVD), or for prognostication.^{38,39}

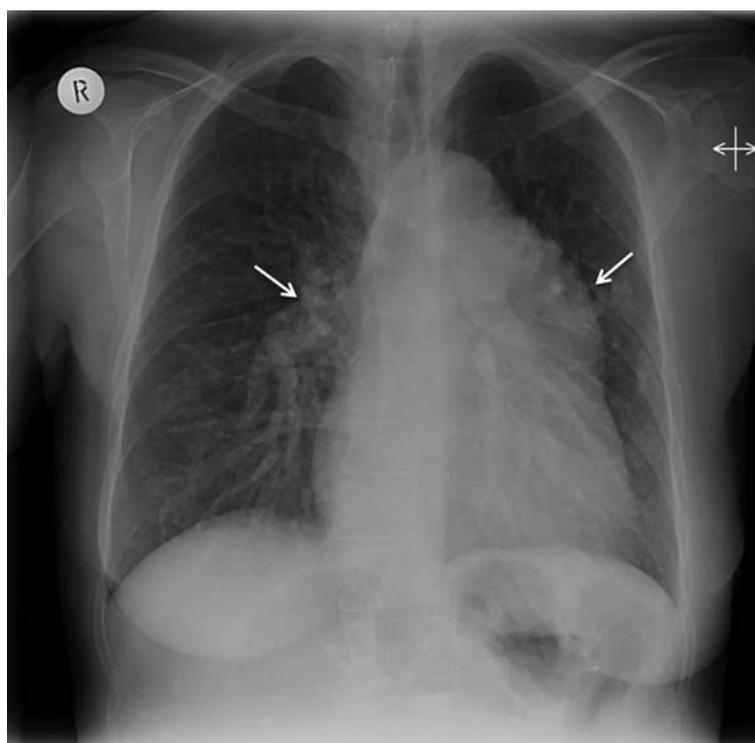


Figure 6. Chest x-ray in Eisenmenger syndrome due to a complete AVSD. Prominent pulmonary arteries are visible bilaterally (arrows). There is significant cardiomegaly (CTR = 0.56).

TREATMENT FOR CHD-PAH

Supportive measures: tips and trick for avoiding common pitfalls

In Eisenmenger patients, screening and treatment for iron deficiency is important and should be screened for at least yearly.^{40,41} Iron supplementation, both oral and intravenous, is performed on an

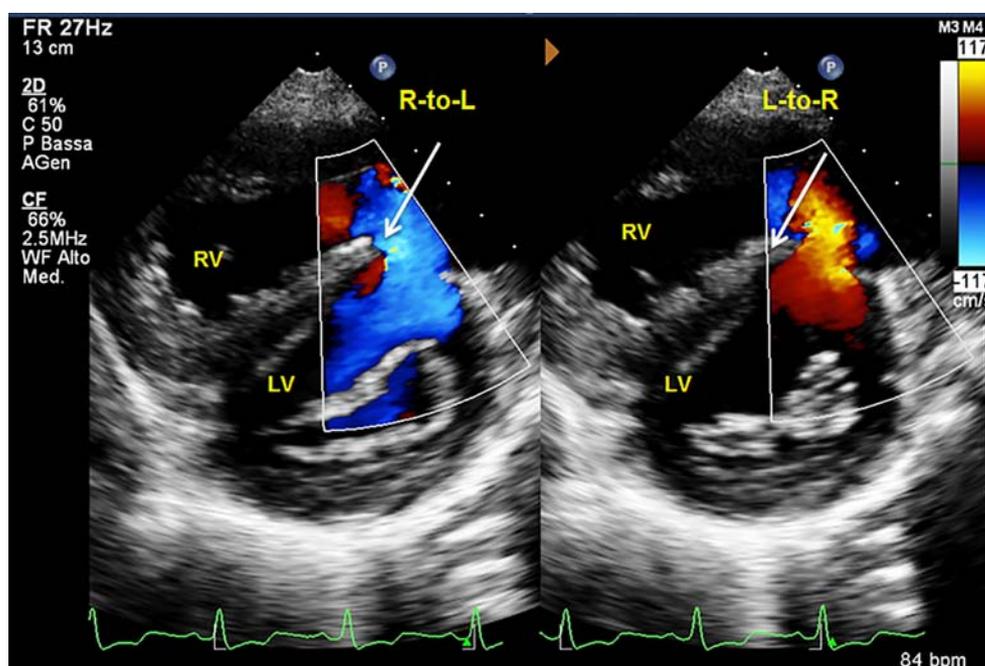


Figure 7. Echocardiographic short axis view of interventricular septal defect with bidirectional shunt. LV: left ventricle; RV: right ventricle; R-to-L: right-to-left shunt; L-to-R: left-to-right shunt.

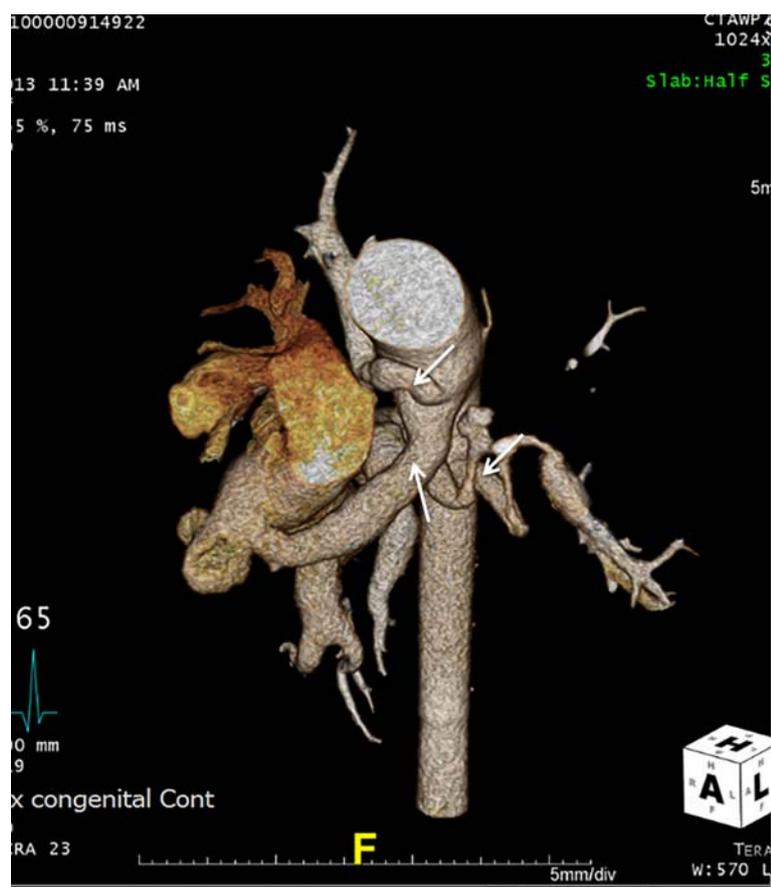


Figure 8. 3D CT-scan reconstruction of MAPCAs in a patient with pulmonary atresia and segmental pulmonary hypertension. The arrows point to the multiple anomalous vessels originating from the descending aorta and perfusing the lungs.

empirical basis, monitoring hemoglobin levels and iron profile carefully. In a study of 25 patients with cyanotic heart disease (the vast majority with Eisenmenger syndrome), gentle iron supplementation was efficient in improving exercise capacity and quality of life at 3 months of treatment, even though many of the patients were still iron deficient at the end of the study. Routine venesections in cyanotic patients with erythrocytosis has been abandoned. This procedure is a ‘double-edged sword’ since erythropoietin level increases due to iron removal and may stimulate the bone marrow to produce more red cells. Moreover, phlebotomies promote iron deficiency and can be detrimental, with evidence to suggest that they may promote cerebrovascular events.^{27,42} Venesection with removal of small volumes of blood (250–500 ml over 30–60 min) and adequate volume replacement, is justified only in patients with severe hyperviscosity symptoms (headache, tinnitus, dizziness, visual disturbances, paresthesias, absence, poor concentration) and a hematocrit >65% in the absence of dehydration or severe iron deficiency. Venesection has also been advocated prior to surgery to boost platelet levels, but there is little evidence to support this practice.⁴³

General anesthesia and sedation carry significant risks of hemodynamic complications in all PAH-CHD.²⁶ Non-essential surgery should be avoided and, when any intervention under general anesthesia or sedation becomes essential, this should be performed in tertiary expert centers with anesthesiologists and intensivists expert in PAH-CHD.

Optimal dental and skin hygiene are paramount for reducing the risk of endocarditis. Patients with cyanotic heart disease are felt by European and American endocarditis guidelines to be at high risk of complications from endocarditis and, hence, prophylactic dental procedures are still advocated.^{33,35} A cerebral abscess should always be suspected in cyanotic CHD patients presenting with neurological signs and symptoms, including syncope or headache, even in the absence of overt signs of sepsis or endocarditis.²⁶

Hemoptysis is common in PAH-CHD, especially Eisenmenger patients.^{16,25,26} Patients presenting with hemoptysis should be monitored for hemodynamic deterioration, airway compromise or significant anemization. Causes or facilitators of hemoptysis, such as anticoagulation, chest infections, strenuous efforts or progression of PAH, should be addressed.

PULMONARY ARTERIAL HYPERTENSION THERAPIES

Small trials of PAH-therapies have been conducted in Eisenmenger syndrome, including a single industry-run randomized controlled trial⁴⁴ and several smaller investigator-led trials.⁴⁵

Endothelin receptor antagonists

BREATHE-5 is so far the only industry-run randomized clinical trial performed in adults with Eisenmenger syndrome, assessing the safety and efficacy of bosentan, an endothelin receptor antagonist (ERA).⁴⁴ This trial demonstrated no significant drop in oxygen saturation and a significant improvement in PVR and 6 minute walking test (6MWT) distance after 16 week. The one year open label extension demonstrated a sustained effect of bosentan,⁴⁶ which is currently felt to be the PAH-therapy with the strongest evidence in Eisenmenger syndrome.^{36,47} There is little evidence on the use of other ERAs in PAH-CHD.^{48,49}

PDE-5 inhibitors

Phosphodiesterase-5 (PDE-5) inhibitors are widely used in clinical practice for the treatment of PAH-CHD, despite no large randomized trials. Sildenafil has been shown to be safe and effective in small randomized and longitudinal studies in patients with Eisenmenger syndrome, improving exercise capacity, functional class and hemodynamics.^{41,50,51,52} An investigator-led randomized cross-over trial of tadalafil in 28 adult Eisenmenger patients demonstrated a significant increase in 6MWT distance, a decrease in PVR, and an improvement in pulmonary blood flow, oxygen saturations and functional class.⁵³



Figure 9. Epoprostenol infusion pump.

Prostanoids

Limited evidence exists on the use of prostanoids in adults with PAH-CHD. Prostanoid therapy is reserved for patients presenting in functional class (FC) IV or FC III with poor hemodynamics, either as a 1st line therapy or when oral therapies fail (Figure 9). Concerns with regard to the risk of endocarditis and embolic phenomena have not been substantiated.⁵⁴

Combination therapy and effect on survival

While PAH therapies are often used in combination in PAH-CHD, there is little evidence to support their use. One non-randomized study on 32 adult Eisenmenger patients reported that addition of sildenafil on bosentan was safe and improved clinical status, exercise tolerance, saturations and haemodynamics.⁵⁵ A small randomized trial did assess the efficacy of sildenafil on adult Eisenmenger patients treated with bosentan:⁵⁶ the addition of sildenafil did not lead to significant improvements beyond a minor increase in oxygen saturations.

No trials in PAH-CHD have been designed or powered to assess the effect of PAH therapies on survival. Nevertheless, a retrospective study on a large cohort of Eisenmenger patients using propensity score analysis has demonstrated a clear survival advantage conferred by PAH-therapies in Eisenmenger patients, after accounting for numerous potential clinical and demographic confounders.⁵⁷ Heart-lung transplantation is a potential treatment option for patients with PAH-CHD.⁵⁸ As many Eisenmenger patients who reach adulthood experience long periods of relative stability, referral to transplantation is usually deferred.⁵⁸ In others, decades of significant cyanosis and low cardiac output may result in end-organ damage (e.g. renal or hepatic dysfunction) eventually precluding transplantation.

How to evaluate the prognosis in CHD-PAH

A modification of the widely used ESC/ERS guidelines table on severity, stability and prognostic parameters in PAH⁸, has been recently proposed by Gatzoulis et al. (Table 3).⁵⁹ Considering the complex pathophysiology of Eisenmenger syndrome, it is not surprising that several different prognostic factors have been reported in this population (Table 4). D'Alto et al.²⁶ observed that complex anatomy, non-cardiac surgery, pregnancy, renal failure, younger age at presentation and overt right ventricular dysfunction were predictors of mortality. The most frequent cause of death was sudden unexpected death (29.5%), followed by heart failure (22.9%) and massive hemoptysis (11.4%), mainly due to pulmonary artery rupture. Cantor et al.⁶⁰ found that younger age at presentation, complex anatomy, supraventricular arrhythmias and voltage evidence of right ventricular hypertrophy were

Table 3. Monitoring and prognosis in adult patients with Eisenmenger syndrome (modified from Gatzoulis et al. 2014).

| Better prognosis | Determinants of prognosis | Worse prognosis |
|------------------------------------|-----------------------------------|------------------------------------|
| No | Right ventricular failure | Yes |
| No | Syncope | Uncertain* |
| I, II | WHO functional class | III, IV |
| > 350 m | 6MWD | < 300 |
| > 85% | Oxygen saturation | < 85% or a drop of > 2%/year |
| Transferrin sat \geq 20% | Iron deficiency | Transferrin saturation < 20% |
| Normal/near normal | BNP plasma levels | Elevated |
| TAPSE \geq 15 cm | Echocardiographic findings | TAPSE < 1.5 cm |
| RA area < 25 cm ² | | RA area \geq 25 cm ² |
| RA/LA < 1.5 | | RA/LA \geq 1.5 |
| RAP < 8 mmHg | Haemodynamics** | RAP > 15 mm Hg |
| CI \geq 2.5 l/min/m ² | | CI \leq 2.0 L/min/m ² |

BNP, brain natriuretic peptide; CI, cardiac index; LA, left atrium; RA, right atrium; RAP, right atrial pressure; 6MWD, 6-minute walk distance; TAPSE, tricuspid annular plane systolic excursion; WHO, World Health Organization.

* Syncope in patients with ES and chronic cyanosis can be vasovagal, due to autonomic nervous dysfunction; therefore, if syncope is present, its prognostic value is assumed to be uncertain.

** Acute vasoreactivity studies during baseline haemodynamic assessment may convey prognostic information (From: Post MC, Janssens S, Van de Werf F, Budts W. Responsiveness to inhaled nitric oxide is a predictor for mid-term survival in adult patients with congenital heart defects and pulmonary arterial hypertension. *Eur Heart J* 2004;25(18):1651–6; D'Alto M, Romeo E, Argiento P, Santoro G, Sarubbi B, Gaio G, Mélot C, Russo MG, Naeije R, Calabrò R. Pulmonary vasoreactivity predicts long-term outcome in patients with Eisenmenger syndrome receiving bosentan therapy. *Heart* 2010;96:1475-79).

Table 4. Factors relating to deterioration and death and their strength according to literature. Data (modified from D'Alto et al. 2014).

| Factors relating to deterioration and death | Strength |
|---|----------|
| Advanced functional class | *** |
| Complex anatomy | *** |
| Right ventricular dysfunction | *** |
| Renal failure | *** |
| Younger age at presentation | *** |
| Iron deficiency | *** |
| Non-cardiac surgery | ** |
| Pregnancy | ** |
| Syncope/pre-syncope | ** |
| Bleeding (haemoptysis) | ** |
| Arrhythmias | ** |
| Poor/absent vasoreactivity | * |
| Brain natriuretic peptide levels | * |
| ECG signs of hypertrophy and/or QTc abnormalities | * |
| Low serum albumin and potassium levels | * |

*Low, **medium, ***high.

Ref: D'Alto M, Diller GP. Pulmonary hypertension in adults with congenital heart disease and Eisenmenger syndrome: current advanced management strategies. Heart 2014.

associated with increased mortality. Diller et al.⁶¹ assessed the risk factors for mortality in 171 Eisenmenger patients for a median follow-up of 67 months. Similar to previous studies, functional class, signs of heart failure and a history of clinical arrhythmias were found to be predictors of mortality. In addition, several ECG features (for example QRS duration and QTc interval) and low serum albumin and potassium levels were shown to have a prognostic impact on survival.

More recently, in a population of 229 Eisenmenger patients, the same group⁵⁷ observed that treatment with specific drugs for PAH resulted in a significant reduction in mortality, even after adjustment for baseline clinical differences. The authors concluded that specific drugs for PAH in a large contemporary cohort of adult patients with Eisenmenger syndrome were associated with a lower risk of death.

UNSOLVED QUESTIONS IN CHD-PAH

1) Patients with PAH-CHD and a left-to-right shunt: to treat or not to treat?

A proportion of patients with left-to-right shunts are not recognized until later in their life and, by this time, may have developed PAH. While the decision to repair (or not) is relatively straightforward in cases with no or extreme rise in PVR, there remains a “grey” area in-between where patients with medium-to-large defects, net left-to-right shunt and mild-moderate increase in PVR lie. A recent retrospective study⁶² assessed hemodynamics in a consecutive cohort of patients developing PAH after shunt closure. This showed that many of the patients had a preoperative PVR ≥ 5 Wood units (WU), PVR index (PVRi) ≥ 6 WU \cdot m² and/or PVR/systemic vascular resistance (SVR) ≥ 0.33 . Recent recommendations from the 5th World Symposium on Pulmonary Hypertension suggest a very cautious approach to patients with cardiac shunt and pulmonary hypertension. In particular, novel criteria for closing cardiac shunts in CHD patients with net left to right shunting (QP/QS > 1.5) have been proposed.⁸ A PVR value < 2.3 WU (PVRi < 4 WU \cdot m²) has been suggested as safe limit for shunt closure. Conversely, PVR > 4.6 WU (PVRi > 8 WU \cdot m²) should be the upper-limit for considering operability. There remains a proportion of patients with PVR between 2.3 and 4.6 WU (PVRi 4-8 WU \cdot m²) that represents a management dilemma. On one hand, shunt closure may abort right-to-left shunting, reduce cerebrovascular events, prevent cyanosis and its devastating consequences, and protect the pulmonary circulation. On the other hand, should pulmonary vascular disease progress after closure of the defect, the right ventricle will have lost its “relief valve”, becoming idiopathic PAH-like (i.e. dilated and impaired), with a poorer prognosis than patients with uncorrected PAH-CHD.⁶³ Even with the use of PAH-specific therapies, the so-called “treat-and-repair” strategy, the benefits and long-term risks of closure of the defect remain unknown. Some authors have recently suggested a partial surgical⁶⁴ or percutaneous⁶⁵ closure of the shunt (valved patches or fenestrated devices), aimed to allow a small defect as a “relief” valve, in case of excessive post-repair rise in PVR.

2) Pregnancy and contraception

Pregnancy carries significant risks in PAH-CHD patients and is, therefore, contraindicated (WHO risk IV, ESC Guidelines on the management of cardiovascular diseases during pregnancy).⁶⁶ A systematic review of pregnancies in patients with different forms of pulmonary hypertension published between 1997 and 2007⁴⁴ showed that 72% of patients with idiopathic PAH were receiving advanced therapies, compared with 52% of CHD-PAH and 47% of obliterative pulmonary hypertension (oPH). Maternal death occurred mainly in the last trimester of pregnancy and the first months after delivery due to pulmonary hypertensive crises, pulmonary thrombosis, or refractory heart failure. Moreover, maternal cyanosis poses a significant risk to the fetus: if resting oxygen saturation is <85%, the likelihood of a live birth is very low (<12%).⁶⁷

Dual contraception should be advised for patients on treatment with ERAs, especially bosentan, in view of the interaction with progesterone-based compounds. Estrogen-containing compounds should be avoided due to the increased risk of thrombosis. Intrauterine devices are effective and are often used, despite some yet unfounded concerns about infection and endocarditis. Appropriate counseling and care, including psychological support, should be part of the routine management of all women with PAH-CHD of reproductive age.

Women with PAH-CHD who do become pregnant despite extensive consultation, require multidisciplinary management.^{31,67} During pregnancy, ERAs and warfarin must be discontinued due to the high potential for fetal toxicity. PDE-5i, prostanoids and low-molecular-weight heparin (if anticoagulation is required) should be considered. Inhaled nitric oxide may be used in the intensive care unit if a pulmonary hypertensive crisis occurs, in particular in the peripartum period.

Pulmonary hypertension in patients with Down syndrome: challenging diagnosis, prognosis and treatment

Down's syndrome (trisomy 21) is the most common chromosomal abnormality, with an estimated incidence of approximately 1.1 per 1,000 live births.⁶⁸ The prevalence of CHD in the Down's population is 40–60%, atrioventricular septal defects being the most commonly occurring type of CHD (~30–50%).⁶⁹ Moreover, Down's syndrome patients tend to develop pulmonary vascular disease earlier than their non-Down's counterparts with similar congenital heart defects, perhaps due to intrinsic endothelial dysfunction.⁷⁰ In addition, upper airway obstruction resulting from a range of pathologies, including macroglossia, tracheal stenosis and nasopharyngeal, oropharyngeal and subglottic compromise, are common findings in patients with Down's syndrome, and may contribute to the high prevalence of other forms of pulmonary hypertension in Down patients (group 3 hypoxia-related).⁷¹

There are no randomized clinical trials to date on the efficacy of PAH-specific therapies in patients with CHD-PAH and Down's syndrome. Two recent non-randomized papers^{72,73} suggested that oral bosentan therapy is safe and well tolerated in adult patients with CHD-related PAH and Down's syndrome. More recently, D'Alto et al.⁷⁴ assessed the safety and long-term effects of oral bosentan in adult patients with CHD-PAH with and without Down's syndrome. The authors reported that bosentan was safe and clinical status and exercise tolerance. Pulmonary hemodynamics improved during 12 months of treatment, regardless of the presence of Down's syndrome.

SEGMENTAL PULMONARY HYPERTENSION

Segmental pulmonary hypertension describes conditions in which pulmonary perfusion is not homogeneous. In this situation there are areas of "hyperperfused" lung, which may over time develop PVD. In these cases, PVD may involve one part rather than the entire lung vasculature, resulting in "segmental pulmonary hypertension" (i.e. pulmonary vascular disease involving a single lung or specific segments of the lungs). Segmental pulmonary hypertension has recently been included in Group 5 of the international PH classification (PH with unclear multifactorial mechanisms).⁸

Typical examples of conditions inducing segmental pulmonary hypertension are truncus arteriosus type 2 with stenosis of the left or right pulmonary artery or complex pulmonary atresia with multiple major aortopulmonary collateral arteries (MAPCAs) and/or peripheral pulmonary artery stenoses.³¹ To date, there is little known on the use of specific therapy for PAH in this setting. A very small retrospective case series of seven patients with complex pulmonary atresia treated with oral bosentan

reported significant improvement in functional class and exercise capacity in patients having segmental PAH.⁷⁵

PULMONARY VASCULAR DISEASE IN PATIENTS WITH A FONTAN-TYPE CIRCULATION

A Fontan circuit (atrio- or cavo-pulmonary connection), is commonly used for palliating patients with “univentricular” hearts. It involves the creation of a right-sided circulation without the interposition of a ventricle in the subpulmonary position. Such a circuit relies on very low PVR, allowing passive flow of blood through the lungs with, ideally, a mild rise in central venous pressures. Patients with a Fontan circulation could never meet criteria for the diagnosis PH (mPAP \geq 25 mmHg), as such a pressure rise would result in a very low cardiac output. However, rises in PVR are possible despite relatively low pulmonary pressures in the presence of low pulmonary blood flow, and can promote failure of the ‘Fontan’ circulation, with devastating effects: congestive heart failure, ascites, protein losing enteropathy, low cardiac output, arrhythmias, and eventually death. In such patients, there is an obvious theoretical advantage in lowering PVR with the purpose of increasing pulmonary blood flow and thereby preload reserve, improving cardiac output. Despite initial evidence of potential clinical response to specific PAH therapies using oral sildenafil or bosentan,^{76,77} two randomized trials have failed to demonstrate a meaningful increase in exercise capacity with PAH drugs.^{78,79} Therefore, to date, there is insufficient evidence to support the use of PAH therapies in the setting of the failing Fontan circulation.

CONCLUSION

All CHD patients should receive “timely” repair of the defect, hence avoiding the development of PAH, which is associated with increased morbidity and mortality. Despite this, a sizeable proportion of CHD patients do develop PAH and can benefit from PAH-specific therapy, now routinely used in specialist centers. There is urgent need for further improvement in management by promoting specialist follow-up for all patients, while establishing close collaboration between tertiary specialist centers and local non-specialist services in a shared care model.

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