

Clinical update

Pulmonary hypertension related to congenital heart disease: a call for action

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Pulmonary arterial hypertension related to congenital heart disease (PAH-CHD) is a common type of pulmonary arterial hypertension (PAH). Despite this, little emphasis has been given to this group of patients until recently, when compared with idiopathic PAH. This is largely because of the complexity and the wide range of underlying cardiac anatomy and physiology, with a multitude of adaptive mechanisms not fully understood. Pulmonary arterial hypertension related to congenital heart disease is, therefore, best diagnosed and managed in centres specializing in both CHD and PAH, to avoid common pitfalls and old practices and to provide state-of-the-art care. We discuss the optimal management of PAH-CHD patients in a series of actions to be taken in order to optimize short- and long-term outcome, based on current knowledge of the condition and the advent of targeted advanced therapies.

Keywords

Eisenmenger syndrome • Congenital heart disease • Pulmonary hypertension • Advanced therapies • Targeted therapies • Treat and repair • Pulmonary vascular disease

Introduction

All congenital heart defects, in which a large intra- or extracardiac communication allows unrestricted pressure and volume overload of the pulmonary circulation, can lead to the development of pulmonary arterial hypertension (PAH), unless repair takes place in early childhood.¹ Advances in paediatric cardiology and surgery in the last 5 decades have led to an improvement in early identification and treatment of such defects, therefore preventing the development of PAH in most cases. Despite this, the number of patients with PAH related to congenital heart disease (PAH-CHD) seen in specialist centres continues to increase. In the 2012 report of the UK National Pulmonary Hypertension Audit, in which all seven designated PH centres were obliged to report on their patients, the prevalence of PAH-CHD (30.2% of PAH) was equivalent to that of idiopathic PAH (33.6%) and connective tissue disease-related PAH (28.3%), much higher than previously reported in other registries.^{2,3} The prevalence of PAH within the adult CHD population remains uncertain, with recent data suggesting a prevalence of over 10% for any PAH, but likely much lower for Eisenmenger syndrome. This, we submit, is likely due to increasing awareness of this common association of PAH-CHD, better referral patterns, and closer collaboration between CHD and PAH centres.

Pulmonary hypertension can develop at any stage of a CHD patient's life and, when it does, impacts on quality of life, exercise capacity, and morbidity and mortality.^{2,3} Recent advances in surgical and percutaneous treatment of CHD have enabled repair or palliation of even complex defects, with reduced perioperative mortality. Closure of defects [i.e. atrial or ventricular septal defects or a patent ductus arteriosus (PDA)] in patients with raised pulmonary vascular resistance (PVR) may have long-term detrimental effects, even among patients responding well to PAH advanced therapies (ATs).^{4–6} Patients with residual PAH following 'successful' defect closure have, in fact, a worse long-term outlook compared with patients with more severe PAH but patent intra- or extracardiac communication, such as in patients with Eisenmenger syndrome.⁷

While pulmonary vascular disease in CHD patients does not differ in terms of pulmonary histology compared with idiopathic or other types of PAH, there are important differences with regards to the pathophysiology and management (Table 1).^{13,14} Specific expertise is clearly required in identifying and treating PAH-CHD patients, avoiding common pitfalls and inappropriate practices of the past, such as routine venesections and absolute exercise restriction. In this article, we discuss the optimal management of PAH-CHD patients in the form of a series of actions that need to be taken to optimize their care and long-term outlook, based on currently available

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Table 1 Differences between Eisenmenger syndrome and idiopathic pulmonary arterial hypertension

	Idiopathic PAH	Eisenmenger syndrome
RV response		
RV dimensions	Dilation	Typically significantly hypertrophied in post-tricuspid defects
RV function	Rapid deterioration	Often preserved (in ventricular or atrioventricular septal defect cases), quite stable over time
Cardiac output	Reduced	Supported by right–left shunting
Vasoreactivity	May have significant vasoreactivity	Minimal/no acute vasoreactivity
Prognosis without ATs	Poor, survival limited to few years after diagnosis	Not as poor, patients often survive decades after diagnosis
Cyanosis		
Prevalence	When low cardiac output or patent foramen ovale/atrial septal defect present	The rule in Eisenmenger syndrome
Severity	Rarely severe at rest	Mild–severe at rest even in stable patients, severe on effort
Haematologic effect	Rare haematologic manifestations. Iron deficiency frequent	Secondary erythrocytosis common in Eisenmenger syndrome. Frequently iron deficient. Commonly thrombocytopenic. Predisposed to bleeding and thrombosis. Little evidence on the use of anticoagulation
Systemic complications	Not common (late)	Common (renal dysfunction, gout, gallstones, etc.)
Associated genetic/ chromosomal disorders	BMPR2 mutation in <25% of iPAH, low penetrance	Common (Down's syndrome)
Perception of limitation	Normal perception of limitation	Typically underestimate the degree of limitation, as present from infancy
Coexisting left heart disease/ valve disease	Rare until tricuspid regurgitation develops	Common (e.g. atrioventricular septal defect, univentricular circulation)
Transplantation	Rapid progression, likely to benefit from transplantation	Slow progression, common systemic complications, complex cardiac disease: not ideal candidates for transplantation

knowledge of the condition and the recent advent of targeted PAH therapies.

Action 1: identify patients with pulmonary arterial hypertension related to congenital heart disease lost to follow-up and those followed in non-specialist centres

While CHD-PAH can significantly shorten life expectancy, patients may survive into their 40s, 50s, and occasionally beyond.^{8,9} The lack of specific therapies for this condition in previous decades, and gaps in the process of 'transition' from paediatric to adult services, meant that many patients were either lost to follow-up or followed in non-specialist centres.¹⁰ This has led to dilution of expertise and perhaps encouraged practices, which are now known to be detrimental. Patients with Eisenmenger syndrome, for example, are still subjected to inappropriate routine venesections with the scope of 'normalizing' haematocrit.^{11,12} Many patients are still advised to avoid any physical effort, leading to physical deconditioning with its detrimental effect on the body and psychology.¹³ This is particularly true, but not confined to patients with Down syndrome and PAH.

A further pool of PAH-CHD patients in the developed world not followed in tertiary settings are migrants from developing countries. These patients may have been lost to follow-up or the PAH-CHD diagnosis has never been made (*Figure 1*). Current ACHD and PAH clinical guidelines strongly recommend that follow-up of PAH-CHD patients should be undertaken in centres combining expertise in CHD and PAH.^{21–23} This is true for all CHD-PAH patients, not just those with complex intracardiac anatomy. Patients followed in tertiary CHD-PAH centres benefit from a multidisciplinary approach including areas such as complex electrophysiology, anaesthesia, gynaecology and high-risk obstetrics, dentistry, etc.

We call for robust, community-based studies to ascertain the exact prevalence of PAH-CHD, identify patients lost to follow-up, and facilitate their timely return to tertiary care.

Action 2: screen all congenital heart disease patients thoroughly for the presence of pulmonary arterial hypertension

An important component of the routine assessment of CHD patients is that of identifying residual and progressive haemodynamic lesions or other conditions that can cause functional deterioration and impact

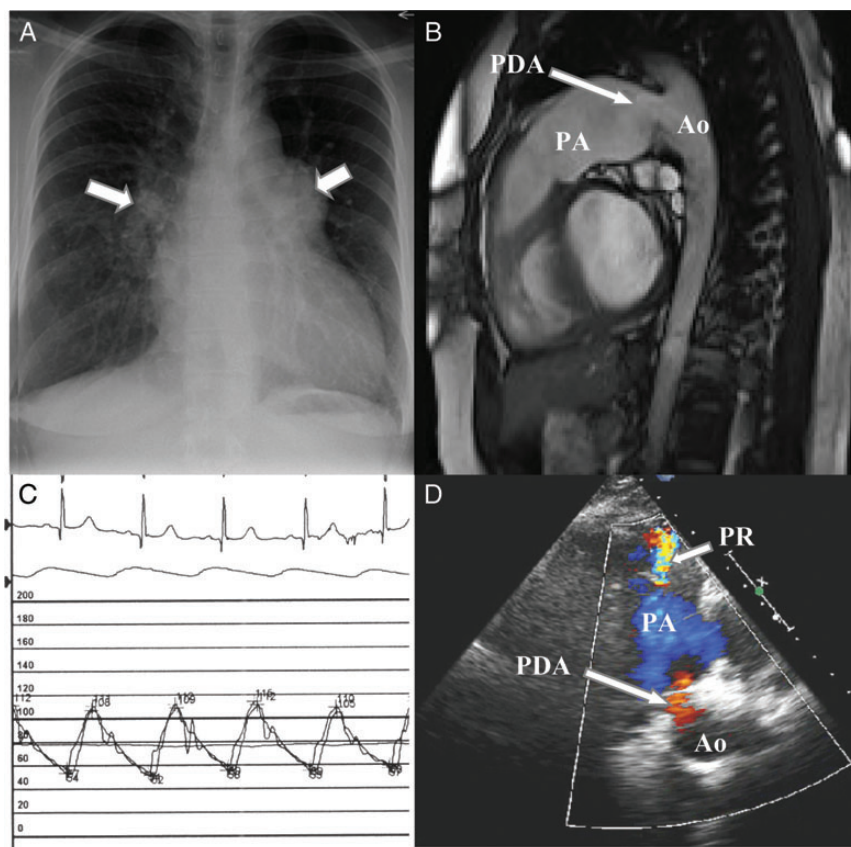


Figure 1 Late diagnosis of severe pulmonary arterial hypertension related to congenital heart disease (PAH-CHD). This is a 25-year-old woman, previously diagnosed in infancy with a ‘heart defect’ in a developing country and lost to follow-up. On referral to specialist PAH-CHD services, she is found to have prominent pulmonary arteries on the chest radiogram (A, arrows). On echocardiography and cardiac magnetic resonance (B), she was found to have a large patent ductus arteriosus (PDA). In (C), pressure traces of the pulmonary arterial and aortic pressure, demonstrating systemic levels of pulmonary hypertension. In (D), colour Doppler imaging of the PDA in the short-axis great vessels view. There is a low velocity shunt between the aorta (Ao) and the pulmonary artery (PA), suggestive of significantly raised PA pressures. There is also pulmonary regurgitation (PR) enhanced by the raised PA pressures.

on quality of life and outcome.¹⁴ Pulmonary arterial hypertension is one of these conditions and should, therefore, be sought and investigated for in every single patient with CHD. Pulmonary arterial hypertension may be present since childhood, usually the result of a large unrepaired ventricular septal defect or a large PDA. Pulmonary arterial hypertension may also be the result of late repair of a post-tricuspid defect (ventricular septal defect, aortopulmonary window, or PDA) or may indeed develop later on in life, even after timely early childhood repair of a defect, even in the absence of significant residual haemodynamic lesions.^{14,24,25} An example of ‘unexpected’ PAH-CHD developing late in life is that in patients with transposition of great arteries following early childhood atrial switch-type repair (Mustard or Senning procedure). A minority of such patients seem to develop PAH later on in life, which may be progressive and likely to compromise outcome (Figure 2, top panels). Pulmonary vascular disease may also develop unexpectedly in patients with atrial communications, both large and small; such PAH-CHD is often associated with a more aggressive clinical

phenotype than Eisenmenger syndrome, with a more rapid rate of progression and worse outlook, resembling idiopathic PAH.^{7,15}

It is not rare for CHD-PAH patients with ‘concealed’ malformations, such as PDA, sinus venosus defect, partial anomalous pulmonary venous return and aortopulmonary window, to be misdiagnosed as iPAH. While not all PAH patients need to be seen by CHD specialists, simple measures such as looking for differential cyanosis at rest and during exercise (lower oxygen saturations in the toes compared the fingers, typical of Eisenmenger patients with a PDA), detailed echocardiographic assessment with contrast injection, serial oxygen saturation sampling during right heart catheterization (including high and low superior vena cava to detect partial anomalous pulmonary venous return), will aid in the detection of CHD and prompt specialist CHD referral.

We call for close surveillance of all CHD patients for the presence of PAH, in order to ensure appropriate and timely therapy when PAH is present.

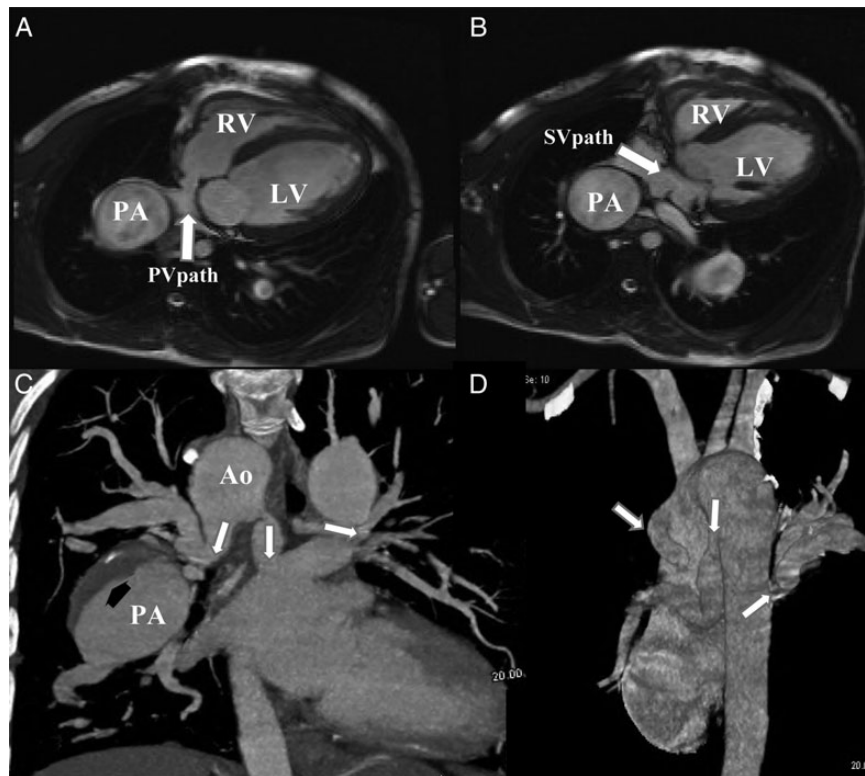


Figure 2 Pulmonary arterial hypertension in non-Eisenmenger patients. In the top panels (A and B), cardiac magnetic resonance imaging from a patient who developed severe pulmonary arterial hypertension late after timely atrial switch repair for transposition of the great arteries (Mustard procedure). Systemic right ventricles (RV) are typically severely hypertrophied and at least moderately dilated in response to the high afterload posed by the systemic circulation, whereas subpulmonary left ventricles are typically small, with good systolic function. Unexpectedly, this patient has a normal-sized right ventricle (RV) and a dilated and severely impaired left ventricle due to the presence of PAH. There is also severe dilatation of the pulmonary artery (PA), in keeping with pulmonary arterial hypertension. The pulmonary (PV path) and systemic venous pathways (SV path) are indicated with arrows. In the bottom panels (C and D), CT imaging from a patient with complex pulmonary atresia and segmental pulmonary arterial hypertension. There are multiple aorto-pulmonary collaterals (MAPCAs, arrows), arising from the aorta (Ao) and feeding segments of the pulmonary circulation. While certain lung areas may be normally perfused or hypoperfused (e.g. left upper lobe), areas supplied by large MAPCAs develop pulmonary vascular disease. In this case, large MAPCAs are feeding areas of the right lung, which is hypertensive, leading to aneurysmal dilatation of the PA, with *in situ* thrombosis (panel C, black arrow). In (D), three-dimensional reconstruction of the aorta with large MAPCAs (arrows).

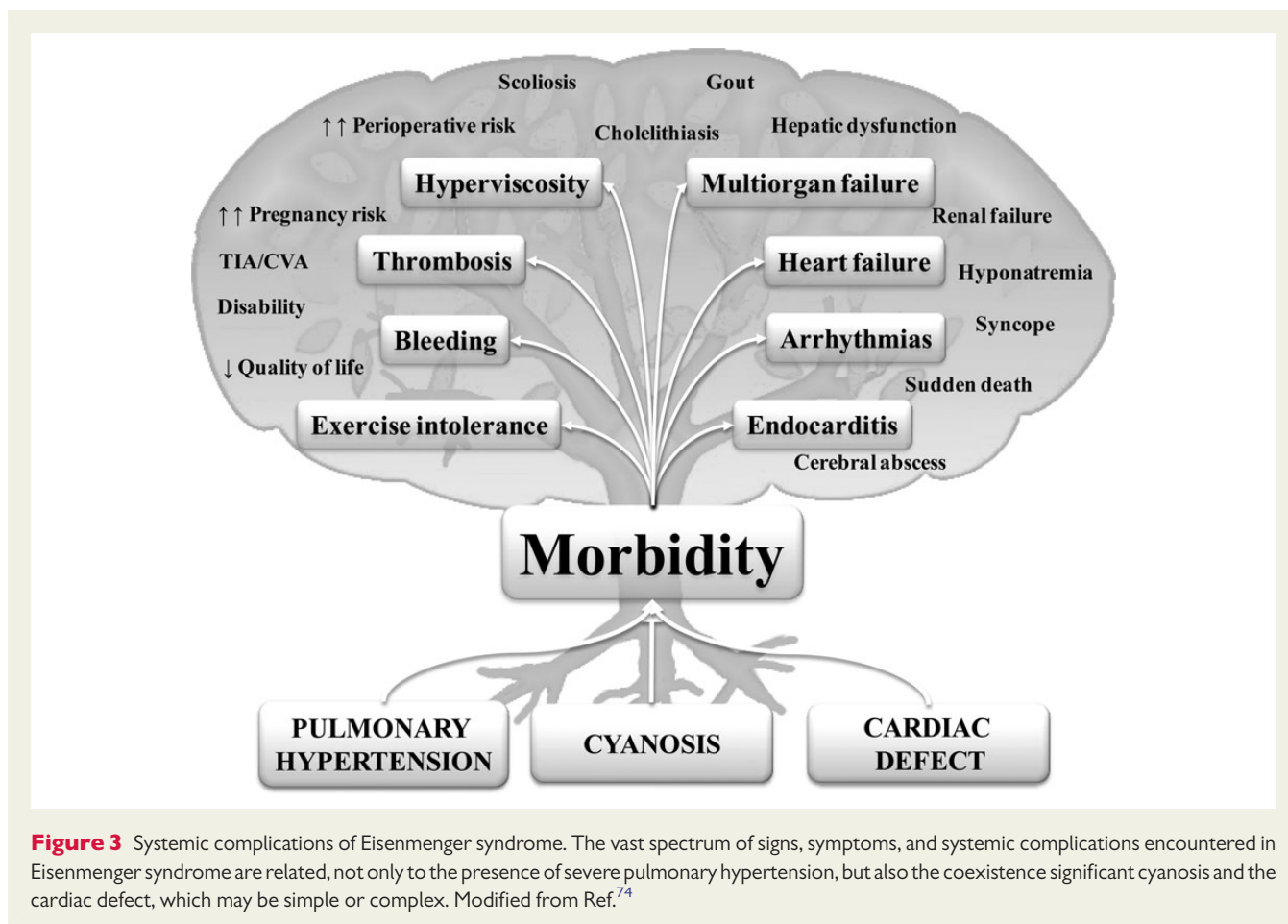
Action 3: educate cardiologists and pulmonary hypertension physicians on the distinct features of Eisenmenger syndrome

The often complex anatomic and pathophysiologic features of PAH-CHD can at times exceed the expertise of physicians who are not specifically trained in CHD, including those with a general cardiovascular background. Pulmonary arterial hypertension related to congenital heart disease, in fact, differs significantly from other types of PAH and, thus, requires significant expertise in its diagnosis and management. Table 1 lists a series of differences between Eisenmenger syndrome and idiopathic PAH.¹⁵

The most salient feature of Eisenmenger syndrome, which distinguishes it from other types of PAH, is the presence of severe long-standing cyanosis, with its array of systemic effects and potential

complications (depicted in Figure 3).^{8,16–18} Cyanosis in Eisenmenger syndrome mainly reflects right-left shunting, which occurs due to the high PVR and right ventricular pressures, but also helps maintain cardiac output during exercise.^{30,31} Cyanosis in Eisenmenger syndrome results in significant haematologic changes, including secondary erythrocytosis, thrombocytopenia, and at times leukopenia.^{27,32,33} Secondary erythrocytosis is a desirable compensatory mechanism aimed at increasing the blood's oxygen carrying capacity to maximize oxygen tissue delivery given the cyanosis.¹⁹

Chronic cyanosis in Eisenmenger syndrome also leads to significant abnormalities in coagulation, which may have implications in terms of anticoagulation. Patients with Eisenmenger syndrome are at risk of thrombosis, commonly *in situ* thrombosis within the central pulmonary arteries.^{35,36} Patients with Eisenmenger syndrome are at the same time at risk of bleeding, such as epistaxis, menorrhagia, and haemoptysis, which is often self limiting but can occasionally be life-threatening.³⁷ For this reason, there is currently no consensus



on routine anticoagulation, albeit there are often other indications for anticoagulants, namely thrombosis in the pulmonary arteries, history of paradoxical emboli, recurrent persistent arrhythmia, and/or congestive heart failure.

Another common feature among patients with Eisenmenger syndrome is Down syndrome, seen in approximately a quarter of patients in contemporary cohorts.^{5,38,39} Expertise in Down syndrome, which is associated with learning difficulties and other co-morbidities, such as thyroid dysfunction, obesity, and sleep apnoea, is important. Moreover, interaction with a multidisciplinary group of carers, including dietitians, occupational and speech therapists, specialist dentists, ophthalmologists, audiologists/ENT experts, social workers, and of course the patients' general practitioners and carers/legal guardians, can improve patient management.

The diagnosis of pulmonary vascular disease itself requires special attention and expertise in PAH-CHD. In patients with a large post-tricuspid shunt, the diagnosis of Eisenmenger syndrome can often be confirmed by echocardiography alone: in a patient with resting or exercise induced cyanosis, a low-velocity bidirectional shunt through a large ventricular septal defect, in the absence of pulmonary stenosis, may be sufficient to indicate systemic levels of pulmonary arterial pressures.⁴⁰ However, in the presence of an atrial septal defect or in patients with left-to-right shunts, cardiac catheterization is paramount in diagnosing PAH and for guiding management. When a large left-right shunt is present, accurate estimation of PVR becomes

essential, as the increase in pulmonary blood flow due to the shunt may cause a significant rise in pulmonary arterial pressure with little or no rise in PVR.⁴¹ Identifying PAH (based on a mean pulmonary arterial pressure ≥ 25 mmHg and a normal left atrial pressure) is, thus, not sufficient for establishing the diagnosis of pulmonary vascular disease in CHD (Figure 4).²⁰ In all patients with shunts, accurate estimation of pulmonary (Q_p) and systemic blood flow (Q_s) is important, not only for calculating PVR, but also for quantifying the magnitude of the shunt and for deciding operability (i.e. whether the defect should be repaired, with long-term benefit). For this purpose, the Fick principle is commonly used.²¹ Cardiac magnetic resonance can also be used in hybrid labs.²² Thermodilution or other indicator dilution methods should never be used in patients with intracardiac shunts. Finally, reversibility studies using pulmonary vasodilators such as nitric oxide should be performed in PAH-CHD patients, for the purpose of assessing operability.^{14,23,24} Acute response to nitric oxide may also convey prognostic benefits.^{25,26} There are no data on the potential benefit of calcium channel blockers in PAH-CHD, as there are in patients with idiopathic PAH.²⁰

Although desirable, it is practically impossible to provide comprehensive, day-to-day care for all PAH-CHD patients within tertiary centres for reasons of geography, cost of travel, and limitations in effort capacity. Moreover, there is occasional need for other local routine and/or emergency care.

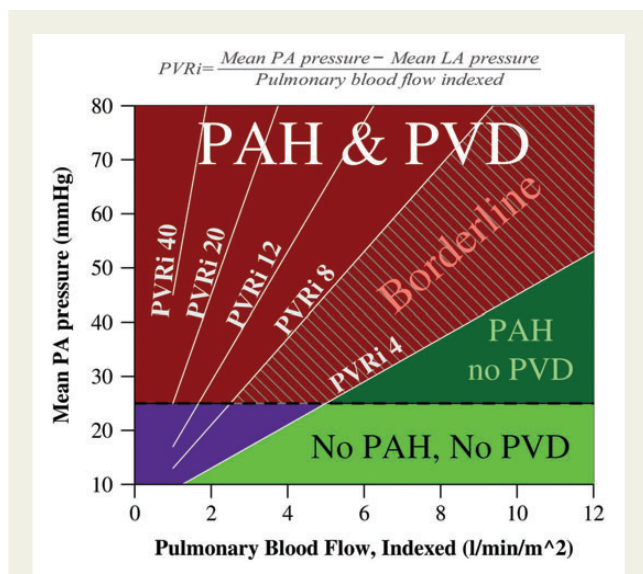


Figure 4 The importance of calculating pulmonary vascular resistance in patients with congenital heart disease. In this plot, the formula for indexed pulmonary vascular resistance (PVRi) is used to graphically represent changes in mean pulmonary arterial (PA) pressure with increasing pulmonary blood flow, for various levels of PVRi. A normal left atrial (LA) pressure of 5 mmHg is assumed. While a mean PA pressure of 25 mmHg or above with a normal LA pressure is sufficient to diagnose pulmonary arterial hypertension (PAH), this is not synonymous to pulmonary vascular disease (PVD). In fact, in patients with high pulmonary blood flow, such as those with a left–right shunt (e.g. through an atrial septal defect), mean PA pressure may be raised while maintaining a normal PVRi (dark green area to the right). In these cases, closure of a haemodynamically significant defect is advisable. Vice-versa, in patients with a very low pulmonary blood flow, including those with a Fontan-type (univentricular) circulation, there can be a rise in PVRi with no rise in mean PA pressure (bottom left purple area). Therefore, calculation of PVR is essential when assessing PAH-CHD patients. Pulmonary vascular disease is likely to be present when PVRi is 4 Wood units \times m² or above. While CHD patients with a high PVRi (>8 Wood units \times m²) are deemed inoperable and should be considered for ATs, a grey area of uncertainty remains when PVRi is 'borderline' (between 4 and 8 Wood units \times m², shaded red area).

We call for a wider engagement and education on PAH-CHD for a broader professional audience, with direct links to tertiary centres, to achieve optimal patient care in this complex area.

Action 4: standardize treatment, avoid pitfalls, and challenge old myths in Eisenmenger syndrome

Beyond ATs, a series of general management measures are essential for improving the quality of life and outcome of patients with PAH-CHD, mainly by avoiding pitfalls and abandoning old harmful practices. The myth that Eisenmenger syndrome patients are highly predisposed to catastrophic complications due to high blood

viscosity has now been seriously challenged. Unlike polycythaemia rubra vera, hyperviscosity symptoms, and embolic complications are rare in Eisenmenger syndrome, they can be avoided by and large maintaining adequate hydration, diagnosing and treating iron deficiency, and by avoiding prolonged immobilization. Venesections, aiming at restoring haemoglobin and haematocrit levels within normal (for non-cyanotic patients) levels, promote iron deficiency and seem to increase rather than decrease the risk of cerebrovascular events.⁴⁵ Cyanotic CHD patients should, in fact, be screened for iron deficiency, which is common even among venesection-naïve patients, and be provided with iron supplements accordingly.²⁷ Venesections are nowadays reserved for patients with severe hyperviscosity symptoms, in the absence of dehydration or iron deficiency, and should only be performed in experienced centres, with adequate volume replacement. All intravenous fluid and/or medication administration should be performed with great care, using air filters, to avoid paradoxical air embolism.

Pulmonary arterial hypertension significantly affects exercise capacity and, thus, quality of life.^{28,29} Moreover, strenuous or extreme isometric efforts can be dangerous and should be discouraged in PAH-CHD patients.³⁰ However, individualized rehabilitation programs have proven beneficial in PAH and should be considered for PAH-CHD patients. In general, patients should be encouraged to maintain fitness by remaining active within their own abilities, minimizing the use of wheelchairs or other aids wherever possible. Moreover, the continuous use of day and night-time oxygen is not supported by evidence and may lead to dependency and to physical deconditioning through immobilization. Most PAH-CHD patients wish to maintain an active lifestyle, including going to work and being socially active. Individualized consultation on physical activities which are safe, including those related to travel, hobbies, and sexual activities is, thus, recommended.³⁰ In patients with Down syndrome, an improvement in exercise capacity and fitness has the scope of improving quality of life by enabling participation in social activities (sports, dancing, etc.), while also aiding to combat obesity and its potential complications, such as sleep apnoea.

Air travel is not contraindicated; the majority of patients with Eisenmenger syndrome do not require supplemental oxygen during commercial flights.³¹ 'Fitness to fly' tests are difficult to interpret, as standard criteria used for patients with parenchymal lung disease (e.g. chronic obstructive pulmonary disease) do not seem to apply in cyanotic patients who are well-adjusted to oxygen saturation fluctuation even with mild physical activities.

Pregnancy carries significant risks in PAH-CHD patients (current mortality risk estimated at 1:3) and is, thus, contraindicated.^{32,33} Effective contraception is, thus, paramount; patients should be reminded that even termination of pregnancy carries significant risks. Dual contraception must be advised for patients on treatment with endothelin receptor antagonists, especially bosentan, in view of the interaction with progesterone-based compounds. Oestrogen containing compounds should be avoided due to the increased risk of thrombosis. Appropriate counselling and care, including psychological support, should be part of the routine management of all women with PAH-CHD of reproductive age.

General anaesthesia and even sedation can be dangerous for patients with PAH, especially those with Eisenmenger syndrome, and should, thus, be avoided whenever possible.^{34–36} All non-

essential surgery or other invasive diagnostic or therapeutic interventions should be avoided. When an invasive procedure is deemed essential, this should be planned carefully and performed in centres with appropriate cardiac, pulmonary hypertension, anaesthetic and intensive care expertise, to minimize complications. It is advisable that all PAH-CHD patients are monitored carefully for several hours or days after any invasive procedure in an intensive care setting.

We call for enhanced education of healthcare professionals looking after PAH-CHD patients, on appropriate care and ways of minimizing risks through adequate precautions and avoidance of pitfalls.

Action 5: do not close defects in Eisenmenger syndrome or other pulmonary arterial hypertension related to congenital heart disease with pulmonary vascular disease: 'I can close it' does not mean 'I should close it'

Progress in surgical and interventional techniques in recent decades meant that most congenital heart defects can, nowadays, be easily repaired, with low procedural risks. While in the majority of cases haemodynamically significant defects should undergo timely repair, there are circumstances where repairing the defect can be detrimental for the patient, especially long term.⁶ There is no doubt that in patients with established Eisenmenger syndrome, defects should never be closed, as they act as 'relief valves' for the right ventricle and the pulmonary vascular bed and maintain cardiac output through right-left shunting. Closing such defects with the scope of abolishing cyanosis is likely, therefore, to adversely affect prognosis by precipitating RV failure and by compromising systemic cardiac output.³⁷⁻³⁹ Patients with PAH-CHD after closure of an intracardiac defect in large registries have the worst prognosis of all types of PAH-CHD.⁷ 'Successful' closure and a good short-term outcome (i.e. a patient who is still alive and pinker) are by no means indicative of a favourable long-term prognosis, as pulmonary vascular disease and right ventricular dysfunction often progress in the weeks, months, or years after defect closure.

Deciding which patient may be suitable for and will benefit from surgical or percutaneous closure requires significant expertise. Despite efforts in recent decades, firm, evidence-based criteria for deciding on the operability of cardiac defects in patients who have developed pulmonary vascular disease remain elusive.^{23,40} Recent recommendations and expert consensus tend to err towards caution, suggesting repair of defects only in patients with no pulmonary vascular disease ($PVR_i < 4 \text{ Wood units} \times \text{m}^2$).^{14,24} When PVR_i exceeds $8 \text{ Wood units} \times \text{m}^2$, no intervention should be undertaken. Patients with 'borderline' PVR_i (between 4 and $8 \text{ Wood units} \times \text{m}^2$) are best assessed individually in ACHD centres, where the merits of operability can be assessed. In a recent study on CHD patients with PAH after repair of their defect, a baseline $PVR > 5 \text{ Wood units}$ and a PVR/SVR ratio > 0.33 were common, supporting a cautious approach.⁴¹ In borderline cases, a treat-and-repair approach has been

suggested (i.e. treat with PAH therapies and repair the defect if PVR drops to 'acceptable levels').⁶ Despite case reports supporting this approach, mainly in patients with atrial septal defects, there is no long-term evidence as yet to support this and in view of the potentially detrimental effect of defect closure on RV function, treat and repair cannot be recommended.

Patients with atrial communications in the presence of significant left ventricular systolic and/or diastolic dysfunction should also be treated with caution, as the atrial septal defect decompresses the left atrium. In such patients, total occlusion of the defect may lead to a sudden rise in pulmonary venous pressure and, thus, development of pulmonary oedema. Fenestrated closure, or even no closure may be preferable. Test occlusion of the defect with a balloon may provide further information on the true left atrial pressure.

We call for all patients who may be candidates for surgical or percutaneous closure of a cardiac defect in adulthood to be managed in expert CHD centres, where they can be thoroughly assessed for the presence of pulmonary vascular disease and other potential contraindications to closure. Cardiac defects in patients with pulmonary vascular disease should not be closed.

Action 6: use pulmonary arterial hypertension advanced therapies to improve exercise capacity, quality of life, and prognosis in Eisenmenger syndrome

Advanced PAH therapies are nowadays routinely used in Eisenmenger patients to improve exercise capacity and, as a result, quality of life. The BREATHE 5 trial demonstrated a significant improvement in PVR and 6-min-walk-test distance, with a concomitant improvement in functional class; there was no drop in oxygen saturations after 16 weeks of bosentan therapy in functional class III patients with Eisenmenger syndrome and a ventricular or atrial septal defect.⁴² The beneficial effect was maintained up to 1 year on the open-label extension study and was observed in both the active bosentan and the placebo arms.^{43,44} Other more recent randomized controlled trials in Eisenmenger syndrome with phosphodiesterase-5 inhibitors have demonstrated a similar beneficial effect on exercise capacity and haemodynamics.⁴⁵⁻⁴⁷ The beneficial effect of ATs appears to be maintained over several years, despite some initial data suggesting loss of efficacy after the first year.^{48,49} Our group has also demonstrated a survival benefit in contemporary patients receiving ATs, vs. those treated conventionally, albeit in a retrospective fashion.⁵⁰ In our single centre study of 229 patients, those on ATs had a significantly lower mortality over a median follow-up of 4 years compared with patients not receiving ATs.

The widespread use of oral ATs began in 2006, after the publication of the BREATHE-5 randomized controlled trial, with data on safety and efficacy. Eisenmenger patients on such therapies are likely to be treated for numerous years, even decades, posing both resource challenges and highlighting the need for continuous surveillance to assess the very long-term effect of this medication.

Table 2 Types of pulmonary arterial hypertension related to congenital heart disease

A. Eisenmenger syndrome	Includes all systemic-to-pulmonary shunts due to large defects leading to a severe increase in PVR and a reversed (pulmonary-to-systemic) or bidirectional shunt. Cyanosis, erythrocytosis, and multiple organ involvement are present
B. Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts	Patients with moderate to large defects, in which the increase in PVR is mild to moderate, left–right shunt is still largely present, and no cyanosis is present at rest
C. Pulmonary arterial hypertension with small defects	Patients with a clinical picture very similar to idiopathic PAH, who have (coincidental?) small defects: <ul style="list-style-type: none"> - ventricular septal defects <1 cm - atrial septal defects <2 cm
D. Pulmonary arterial hypertension after corrective cardiac surgery	Congenital heart disease has been corrected but PAH: <ul style="list-style-type: none"> - is still present immediately after surgery or - has recurred several months or years after surgery in the absence of significant post-operative residual congenital lesions or defects-sequela of previous surgery
Additional types of pulmonary vascular disease related to CHD	
- Segmental pulmonary arterial hypertension	In these cases, part of the lung vasculature develops pulmonary vascular disease, while other areas may be normally perfused or hypoperfused
- Raised PVR in Fontan patients	Patients with a previous Fontan-type operation can develop a rise in PVR, despite low pulmonary arterial pressures

We call for all patients with Eisenmenger syndrome to be seen in specialist CHD-PAH centres and those in functional class III to be offered PAH ATs.

Action 7: be inclusive of other types of pulmonary arterial hypertension related to congenital heart disease, beyond Eisenmenger syndrome

Recent pulmonary hypertension guidelines have recognized the wide spectrum of PAH-CHD by suggesting classification into four major groups (Table 2).²⁰ Each of these groups have distinct pathophysiologic features and, thus, differ in their management and overall outcome. The BREATHE-5 and other trials have mainly focused on Eisenmenger syndrome in patients with simple defects (atrial and/or ventricular septal defects). In Actions 7 and 8, we discuss other groups of PAH-CHD, and their distinct differences in relation to treatment with ATs.

Pulmonary arterial hypertension in patients with Left–Right shunt

The use of ATs in PAH-CHD group B (Table 2), even those who are deemed inoperable, remains controversial. In these patients, the persistence of an L–R shunt results in increased pulmonary blood flow compared with systemic flow. Administration of ATs with the scope of increasing pulmonary blood flow further may appear counter-intuitive and may accelerate progression of pulmonary vascular disease. Even though there is little scope in improving resting pulmonary blood flow in these patients, administration of ATs may, in theory, facilitate the response of the pulmonary circulation to effort, thus improving exercise capacity.⁷ As data are lacking, no recommendations can be made for or against ATs in this setting at present.

Pulmonary arterial hypertension in patients with a small defect and in patients after defect repair

Patients in group C (Table 2) are often described as patients with idiopathic PAH with a coexistent cardiac defect. While a potential link between the defect and the development and progression of PAH cannot be totally dismissed, these patients develop pulmonary vascular disease to a severity, which cannot be explained by the defect alone (see Action 8). The presence of an atrial communication is thought to improve survival in PAH patients by allowing right ventricular decompression, even though this has not been as yet demonstrated.^{19,51–53} Furthermore, a large right-left shunt may occur through a relatively small defect, in the presence of right ventricular hypertension; this shunt may be important in maintaining systemic cardiac output in the presence of PAH. This is the theoretical basis for recommending atrial septostomy in patients with severe PAH.²⁰ Pulmonary arterial hypertension related to congenital heart disease patients in group 3 are practically indistinguishable to idiopathic PAH patients with an atrial communication in terms of pathophysiology and prognosis. For this it is reasonable to recommend treatment with ATs, anticoagulation, avoiding closure of the defects.

Patients with a previously repaired defect and PAH (PAH-CHD group 4) were included in large randomized trials of ATs, together with idiopathic PAH and PAH related to connective tissue disease.^{54–56} Their prognosis is a kin to that of idiopathic PAH and, thus, should be treated with ATs.⁷

Eisenmenger physiology in patient with univentricular hearts

The use of ATs in Eisenmenger syndrome patients with univentricular circulation (e.g. double inlet left ventricle) has not been assessed in randomized controlled trials, as complex patients were excluded (due to difficulties in estimating PVR).⁴² In the absence of pulmonary stenosis protecting the pulmonary circulation, pulmonary vascular disease in these patient develops during infancy, limiting pulmonary

blood flow. An increase in Qp using ATs may be welcome and may, in theory, reduce peripheral cyanosis and improve oxygen tissue delivery. Significant increases in Qp can, however, result in increasing volume overload of the single ventricle, which supports both the systemic and pulmonary circulation, and may precipitate ventricular dysfunction.⁵⁷ No evidence exists to support this notion and ATs are used in selected cases on an empiric base. Accurate assessment of haemodynamics is important; invasive assessment can provide valuable information, although cardiac magnetic resonance appears to be a good alternative for assessing Qp and Qs.⁵⁸

Segmental pulmonary arterial hypertension

Pulmonary hypertension involving part, rather than the entire lung, is possible in CHD. For example, stenosis of the left or right pulmonary artery can be observed in patients with truncus arteriosus, resulting in pulmonary hypertension involving a single lung. Segmental pulmonary artery stenoses and multiple aortopulmonary collaterals of various sizes, commonly observed in complex pulmonary atresia, often result in pulmonary hypertension involving segments of the lung, while other lung areas are normally perfused or often hypoperfused (Figure 3, bottom panels). While there is little evidence supporting the use of ATs in this setting, segmental pulmonary hypertension affecting large areas of the lung contributes to cyanosis and exercise intolerance and is a target for treatment. A small case series of patients with complex pulmonary atresia treated with bosentan has reported improvement in 6-min-walk-test distance, albeit this was an intention to treat retrospective study.⁵⁷ The diagnosis of PAH in these cases requires a high degree of suspicion, with the loss of continuous murmurs in the affected areas and evidence of low velocity shunting through aortopulmonary collaterals detected on echocardiography, confirmed on cardiac catheterization, best performed in specialist CHD settings. It is important to remember that the tricuspid regurgitation jet cannot be used to estimate pulmonary arterial pressure in patients with pulmonary atresia.

The failing Fontan

In patients with a univentricular circulation, a Fontan-type operation is often performed with the scope of abolishing or minimizing cyanosis.⁵⁹ A Fontan circuit involves the creation of a right-sided circulation without the interposition of a ventricle.⁶⁰ This means that blood flow from the vena cavae to the pulmonary arteries is passive, achieved through an increase in venous pressure, the contribution of the muscle pump, and changes in intrathoracic pressures occurring during breathing. A prerequisite for this circulation is the presence of very low pulmonary arterial pressures, allowing passive flow of blood through the lungs without a significant rise in central venous pressures. Even small rises in pulmonary arterial pressures, either through a rise in PVR or a rise in post capillary (left atrial) pressure, can cause failure of the 'Fontan' circulation, with catastrophic effects (congestive heart failure, ascites, protein losing enteropathy, low cardiac output, arrhythmias, and eventually death).⁶¹ Pulmonary vascular resistance is often high in adult Fontan patients, despite a low mean pulmonary artery pressure and low trans-pulmonary gradient, because of very low pulmonary blood flow (Figure 3). As surgical options for these patients are limited, ATs with the scope of reducing

PVR appear as a possibly attractive option. Despite some promising data in a non-randomized study of acute administration of sildenafil (demonstrating an improvement in exercise haemodynamics) and in other case series, two randomized trials have failed to demonstrate an increase in exercise capacity with ATs.^{62–65} Therefore, to date, there is no evidence to suggest that PAH therapies are beneficial in patients with a failing Fontan due to raised PVR.

Call for action

We call for all specialist centres following patients with the above conditions to coordinate efforts in assessing the potential safety and efficacy of ATs and/or other interventions, and improve knowledge on pathophysiology and risk stratification for patients with PAH-CHD, beyond Eisenmenger syndrome.

Action 8: concept of a 'permissive' trait genotype in patients with large atrial septal defects who develop out-of-proportion pulmonary arterial hypertension and Eisenmenger syndrome

In the majority of cases of PAH-CHD, the presence of a large post-tricuspid defect is sufficient to explain the development of pulmonary vascular disease, through 'flooding' of lungs and a combined volume and pressure overload early in life. Some patients, however, develop an Eisenmenger phenotype earlier than expected during infancy, while others with a shunt of similar size maintain a purely left-to-right shunt and good Qp until their teens and perhaps beyond. This different response of the pulmonary vascular bed to similar haemodynamic stimuli does beg the question of a different underlying predisposition to pulmonary vascular disease relating to, as yet, unknown genetic factors. This may be further supported by the fact that patients with Down syndrome are generally prone to developing pulmonary vascular disease earlier in infancy compared with the remainder, suggesting a possible role of genetics.⁶⁶ Similarly, some patients with a pretricuspid shunt (ASD) develop severe pulmonary vascular disease despite having a lesion, which causes volume but no pressure overload to the pulmonary vascular bed. How to explain also the development of, at times severe, pulmonary hypertension in patients with transposition of great arteries even after timely atrial switch repair (Figure 2, top panels). It appears that an underlying predisposition is triggered by the presence of a shunt and may manifest years after closure of the defect.

While genetic traits causing heritable PAH are well established and are present in many patients with idiopathic PAH who present with more aggressive disease, no clear association between such traits and CHD-PAH has been observed.^{67–69} Much work is needed to understand the genetic and molecular mechanisms underlying the development of PAH, both in CHD and other types of disease, leading to a common endpoint of histologically identical disease of the pulmonary vasculature.

We call for greater collaboration between CHD and PAH physicians and geneticists/epidemiologist towards this end, with inclusion

of PAH-CHD patients in national and international registries, with detailed genotypic/phenotypic characterization.

Action 9: promote clinical research and collaboration between specialist centres on areas of controversy and lack of evidence

Despite recent advances in our understanding and management of PAH-CHD, there are still numerous questions to be addressed. Little is known for example about the natural history and appropriate management of paediatric patients with PAH-CHD, who have been reported to have a worse prognosis compared with adult patients. Research is required into understanding how to best assess patients with Down syndrome functionally, who constitute a significant proportion of the Eisenmenger syndrome cohort.⁷⁰ It is unclear whether PAH-CHD patients should be treated with a goal-oriented strategy (as has been proposed for idiopathic PAH) and what these targets are. The optimal use of antiplatelets and anticoagulants in Eisenmenger patients, who are prone to both thrombosis and bleeding, remains unknown. Furthermore, more data are urgently needed on the role of rehabilitation, iron supplementation, long-term oxygen therapy, etc. Finally, it remains unclear which clinical endpoints should be used in trials on PAH-CHD, and especially adult Eisenmenger syndrome patients.⁷¹ In fact, the relative stability of adults with Eisenmenger syndrome up to the fourth decade of life makes endpoints such as mortality or morbidity difficult to implement in such an uncommon disease.

We call for closer collaboration between CHD-PAH centres, to establish multicentre collaborations and facilitate randomized trials, overcoming limitations of sample size. All efforts should be made to obtain adequate funding from National and International bodies to support such endeavours. Finally, we call for action for the purpose of agreeing to and validating endpoints that reflect clinical changes, beyond that of improved exercise capacity, reflecting overall prognosis and quality of life.

Action 10: support care of pulmonary arterial hypertension related to congenital heart disease patients in the developing world

While progress in early diagnosis and treatment of CHD has reduced the number of CHD patients developing PAH in western countries, this is often not so in developing countries. There is still paucity of data on the prevalence of congenital malformations at birth in developing countries.⁷² This is due to limitations in diagnostic capabilities, poor epidemiological data, and the lack of birth defect registries. Congenital heart disease is often not given high enough priority in the allocation of resources in developing countries, resulting in late diagnosis; this, in conjunction with the lack of expertise for timely repair of cardiac defects, allows for the development of PAH. Late diagnosis is also attributable to late presentation due to high level of illiteracy in many of these populations and the lack of access to

basic medical care. Finally, there is ignorance about CHD even among health workers, leading to frequent non-diagnosis or incorrect diagnosis, followed by inappropriate counselling and/or wrong treatment.⁷³

Identification of PAH-CHD in developing countries may be achieved through improvements in education of healthcare providers, in order to increase knowledge and the degree of suspicion when assessing patients with potential PAH-CHD. Availability of expensive ATs remains limited, but may become easier with the collaboration of Industry and, in the future, with generic preparations. However, enhancing local expertise in the identification and management of PAH-CHD should be the thrust of any effort, as general management principles and avoidance of pitfall are as important as ATs therapies in these patients.

We call for a coordinated effort in support of PAH-CHD in developing countries, through greater allocation of resources and the collaboration of international bodies and the PAH-CHD community world-wide, aiming at better awareness and improved diagnosis, followed by wider availability of therapy.

Conclusions

As our understanding of PAH-CHD improves, it is important that action is taken to ensure that all such patients receive appropriate care in expert ACHD-PAH centres. Close collaboration between tertiary specialist centres and local non-specialist services in a shared care model improves patient care further and accounts for geography. Education of the profession, patients, and the public may assist in earlier diagnosis and, in turn, better management of PAH-CHD, avoiding common pitfalls. We invite professional bodies, health providers, patient associations, and the public to implement our call for action points outlined herewith to improve the outlook for every single patient with CHD at risk of developing, or already suffering from PAH anywhere in the world.

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