

# Management dilemmas in pulmonary arterial hypertension associated with congenital heart disease

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## Abstract

There are few randomised controlled data to guide management of patients with pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD). In this clinical review, common areas of uncertainty in the management of PAH-CHD are identified, the literature is summarised and discussed and a suggested approach offered for each clinical dilemma.

## Keywords

Pulmonary arterial hypertension, Eisenmenger syndrome, congenital heart disease, management dilemmas, Down syndrome

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## Introduction

Pulmonary arterial hypertension (PAH) may complicate different forms of congenital heart disease (CHD) associated with volume and/or pressure overload of the pulmonary circulation, including simple pre- and post-tricuspid shunts, corrected shunts and more complex disease. The clinical classification of PAH associated with CHD (PAH-CHD) is summarised in Fig 1.<sup>1–3</sup>

Data from randomised controlled trials (RCTs) including patients with PAH-CHD are limited. In practice, the clinician and patient are often faced with management choices which are not supported by RCT evidence. The CHAMPION (Congenital Heart disease And pulmonary arterial hypertension: Improving Outcomes through education and research Networks) programme aims to improve the care of patients with PAH-CHD.<sup>4</sup> In this review, we discuss some of the most clinically challenging scenarios facing health care professionals who manage people with PAH-CHD.

## Methods

The CHAMPION steering committee identified clinical dilemmas related to challenging issues in PAH-CHD. Each

committee member performed a literature search on three or four dilemmas and drafted a suggested approach. The committee then held a further round-table discussion to achieve consensus.

## Management dilemmas

### 1. A patient with ES is in World Health Organisation Functional Class (FC) III and complains of progressive breathlessness. Which PAH therapy should I start?

Three large observational studies have demonstrated survival benefit in ES patients receiving PAH-specific therapy as compared to matched historical controls.<sup>5–7</sup> The BREATHE-5 study, which enrolled 54 patients in FC III, was the first multicentre RCT in ES.<sup>8</sup> Significant improvements in haemodynamics and exercise capacity were observed following 16 weeks of bosentan, with an extension study demonstrating sustained improvements at 40 weeks.<sup>9</sup> Current international guidelines therefore recommend bosentan for ES patients in FC III.<sup>2,10</sup> A number of other

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<b>A. Eisenmenger Syndrome</b>
Large congenital systemic-to-pulmonary shunt resulting in pulmonary vasculopathy, increased PVR and shunt reversal. Cyanosis and erythrocytosis present, with multi-system involvement.
<b>B. PAH associated with a predominant systemic-to-pulmonary shunt</b>
Moderate to large shunts with mild or moderately increased PVR. Not cyanotic at rest. May be correctable or non-correctable.
<b>C. PAH associated with a small defect</b>
Significantly elevated PVR in the presence of a small defect (ASD <2 cm diameter, VSD <1 cm diameter). Behaves similarly to idiopathic PAH
<b>D. PAH following a repaired defect.</b>
PAH persists after closure or develops/recurs following closure.
<b>E. Segmental PH</b>
Encompasses any condition with abnormal underlying cardiac or vascular anatomy, usually including varied sources of pulmonary blood supply, which results in distal pulmonary vascular disease that affects various lung segments to differing degrees (e.g. pulmonary atresia with hypertensive aorto-pulmonary collateral perfusion of certain areas of the lung).

**Figure 1.** Clinical classification of PAH-CHD. Current guidelines define four subgroups ((a)–(d)) while a fifth subgroup (segmental PH) can also be described.

ASD: atrial septal defect; CHD: congenital heart disease; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; VSD: ventricular septal defect.<sup>2,3</sup>

oral PAH therapies have subsequently been studied in ES (Table 1). Several small observational studies have reported improvements in clinical parameters following commencement of therapy with the newer endothelin receptor antagonists (ERA) ambrisentan and macitentan.<sup>11–13</sup> The MAESTRO study studied the effect of macitentan in 226 ES patients and has been reported in abstract form.<sup>14</sup> Although there was a significant decrease in N-terminal pro-brain type natriuretic peptide (NT-proBNP) in those patients receiving macitentan and an improvement in pulmonary vascular resistance (PVR) in the invasive substudy, no significant improvement was noted in the primary endpoint, the 6-minute walk distance (6MWD). Of note, an unexpected improvement in 6MWD (19.7m) was observed in the placebo group. Several observational studies have reported functional and haemodynamic improvements following sildenafil treatment.<sup>15–20</sup> Two small, single-centre, placebo-controlled crossover trials of phosphodiesterase-5 inhibitors (PDE5-i) have also been published.<sup>21,22</sup> Both studies demonstrated significant placebo-corrected improvements in FC, 6MWD and pulmonary haemodynamics. Although a number of observational studies have reported clinical improvement following intravenous, subcutaneous or inhaled prostanoid therapy, they are unlikely to be used as initial therapy in FC III patients because of their more complex administration.<sup>23–29</sup> Finally, the choice of initial therapy is affected by reimbursement issues, patient choice

and clinical factors such as side effects, interactions and contraindications.

**Suggested approach:** Initiation of PAH therapy in an ES patient in FC III is strongly recommended. The strongest RCT evidence is for use of bosentan; however, published data support treatment with PDE5-i (tadalafil or sildenafil), dependent on local reimbursement and patient-specific clinical factors.

## **2. A patient with ES secondary to a ventricular septal defect is functionally stable and in FC II. Should PAH-specific therapy be started?**

Although more than one-quarter of ES patients are in FC I or II at time of diagnosis or presentation to a pulmonary hypertension (PH) centre,<sup>5,32,33</sup> there are few published RCT data which have specifically investigated ES patients with FC II (Table 1).<sup>14,21,22</sup> The merits of PAH treatment in FC II PAH patients were established with the EARLY study, a placebo-controlled RCT of bosentan in FC II PAH (21% PAH associated with small septal defects or patent ductus arteriosus (PDA)).<sup>34</sup> A significant reduction in PVR and clinical worsening after six months of bosentan was observed. The mortality in ES patients in FC I or II, although lower than in those in FC III or IV, is still substantial.<sup>5</sup> Furthermore, even mildly symptomatic ES patients have significantly impaired exercise capacity: In one study, peak oxygen consumption in 20 ES patients

**Table 1.** Selected therapeutic studies in patients with Eisenmenger syndrome.

Class	First author	Year	Drug	N	FC % II/III/IV or mean	RCT	Main findings
<b>ERA</b>	<b>Galiè<sup>8</sup></b>	<b>2006</b>	<b>Bosentan</b>	<b>54</b>	<b>0/100/0</b>	<b>Yes</b>	<b>↓PVRi, ↓mPAP, ↑6MWD</b>
	Zuckerman <sup>11</sup>	2011	Ambrisentan	17	NR	No	↑6MWD
	Blok <sup>12</sup>	2017	Macitentan	40	52/48/0	No	↓FC, ↓NT-proBNP, ↔6MWD
	Herbert <sup>13</sup>	2017	Macitentan	15	NR	No	↑6MWD, ↑SaO <sub>2</sub>
	<b>Galiè<sup>14</sup></b>	<b>2017</b>	<b>Macitentan</b>	<b>226</b>	<b>60/40/0</b>	<b>Yes</b>	<b>↔6MWD, ↓NT-proBNP, ↓PVRi</b>
<b>PDE5-i</b>	Mukhopadhyay <sup>15</sup>	2006	Sildenafil	16	69/31/0	No	↑6MWD, ↑SaO <sub>2</sub> , ↓mPAP, ↓PVR
	<b>Singh<sup>22</sup></b>	<b>2006</b>	<b>Sildenafil</b>	<b>10</b>	<b>30/60/10</b>	<b>Yes</b>	<b>↓FC, ↑6MWD, ↓mPAP</b>
	Chau <sup>16</sup>	2007	Sildenafil	7	3.3 ± 0.7	No	↓FC, ↑SaO <sub>2</sub> , ↓mPAP, ↓PVR
	Garg <sup>17</sup>	2007	Sildenafil	21	46/54/0	No	↓FC, ↑6MWD, ↑SaO <sub>2</sub> , ↓mPAP, ↓PVRi
	Tay <sup>18</sup>	2011	Sildenafil	12	0/100/0	No	↓FC, ↑6MWD, ↑HRQOL
	Zhang <sup>19</sup>	2011	Sildenafil	84	52/39/8	No	↑6MWD, ↑SaO <sub>2</sub> , ↓mPAP, ↓PVRi
	<b>Mukhopadhyay<sup>21</sup></b>	<b>2011</b>	<b>Tadalafil</b>	<b>28</b>	<b>79/21/0</b>	<b>Yes</b>	<b>↓FC, ↑6MWD, ↓PVR</b>
	Sun <sup>20</sup>	2013	Sildenafil	29	NR	No	↓FC, ↑6MWD, ↓PVR
	<b>Prostanoid</b>						
<b>Prostanoid</b>	Rosenzweig <sup>23</sup>	1999	Epoprostenol (intravenous)	20	15/50/35	No	↓mPAP, ↑CI, ↓PVRi, ↑SvO <sub>2</sub>
	Fernandes <sup>24</sup>	2003	Epoprostenol (intravenous)	8	0/25/75	No	↑6MWD
	Thomas <sup>25</sup>	2013	Epoprostenol (intravenous) and treprostinil (subcutaneous)	9	12/88/0	No	↓mPAP, ↑SvO <sub>2</sub>
	Skoro-Sajer <sup>26</sup>	2018	Treprostinil (subcutaneous)	22	0/47/53	No	↓FC, ↓PVR, ↓NT-proBNP, ↑6MWD
	Yang <sup>27</sup>	2012	Iloprost (nebulised)	12	0/75/25	No	↓FC, ↑6MWD, ↑SaO <sub>2</sub>
	Cha <sup>28</sup>	2013	Iloprost (nebulised)	13	0/69/31	No	↓FC, ↑6MWD, ↑HRQOL
	Chon <sup>29</sup>	2017	Iloprost (nebulised)	11	0/64/36	No	↓FC, ↓mPAP, ↓PVR, ↑SaO <sub>2</sub> , ↑6MWD
	<b>Combination</b>						
	<b>Iversen<sup>30</sup></b>	<b>2010</b>	<b>Bosentan ± sildenafil</b>	<b>21</b>	<b>43/48/5</b>	<b>Yes</b>	<b>↔6MWD, ↑SaO<sub>2</sub></b>
	D'Alto <sup>31</sup>	2012	Bosentan and sildenafil	32	2.9 ± 0.3	No	↓FC, ↑6MWD, ↓mPAP, ↓PVR, ↓NT-proBNP

ERA: endothelin receptor antagonist; FC: functional class; HRQOL: health-related quality of life; mPAP: mean pulmonary arterial pressure; 6MWD: 6-minute walk distance; NR: not reported; NT-proBNP: N-terminal b-type brain natriuretic peptide; PDE5-i: phosphodiesterase 5 inhibitor; PVR: pulmonary vascular resistance; PVRi: pulmonary vascular resistance index; RCT: randomised controlled trial; SaO<sub>2</sub>: systemic arterial oxygen saturation; SvO<sub>2</sub>: mixed venous oxygen saturation. Randomised controlled trials in bold.

(70% in FC I or II) was only  $11.5 \pm 3.6$  ml/kg/min.<sup>35</sup> PAH is a progressive disease and delays in instituting therapy may be detrimental. FC underestimates the severity of limitation in adult congenital heart defect (ACHD) patients who have been affected since birth and are likely to have adapted their “ordinary” activities to their ability. There is, therefore, a rationale for the use of PAH therapy in ES patients in FC II but given the lack of specific evidence in this population, this cannot yet be routinely recommended. Routine assessment of ES patients should include risk stratification, either using the criteria recommended by current European Society of Cardiology guidelines, and/or ES-specific predictors or outcome including BNP, C-reactive protein, platelet count and 6MWD.<sup>2,36–38</sup> In a multicentre study of 1098 ES patients, five independent predictors of mortality were identified: age, pre-tricuspid shunt, lower systemic oxygen saturations (SaO<sub>2</sub>), presence of pericardial effusion and absence of sinus rhythm.<sup>39</sup> Patients at increased risk of death should be considered for PAH therapies, independent of FC.

**Suggested approach:** FC can be misleading as to the severity of PAH in ES. Therefore, patients with ES in WHO FC

II should be assessed further for the presence of adverse prognostic features which may support PAH therapy.

### 3. A patient with ES secondary to an unrepaired ventricular septal defect (VSD) is in FC III despite being treated with PAH-specific oral monotherapy. Should I add further therapy and if so what?

The role of combination therapy in PAH has evolved significantly over recent years. The AMBITION trial of upfront combination therapy with ambrisentan and tadalafil in 500 PAH patients (including 13 patients with previously closed defects) and the SERAPHIN study of macitentan in 742 PAH patients (including 62 patients with previously closed defects, 64% of whom were on background PDE5-i) demonstrated an improvement in time to clinical worsening and 6MWD in those receiving combination therapy (upfront or early sequential).<sup>40,41</sup> The COMPASS-2 study of 334 PAH patients on background sildenafil (including 20 patients with previously closed defects) who were given bosentan or placebo failed to demonstrate improvement in time to clinical worsening, but significant improvements in

6MWD and NT-proBNP were observed.<sup>42</sup> On the basis of these studies, current guidelines recommend upfront or sequential oral combination therapy for PAH patients in FC II or III.<sup>43</sup>

There are, however, few data to support this approach in ES. In one study, 21 ES patients were randomised to receive sildenafil or placebo in addition to background bosentan.<sup>30</sup> No significant effect on 6MWD was observed, although a significant increase in resting SaO<sub>2</sub> was noted (Table 1). In another study of 32 ES patients receiving bosentan, addition of sildenafil resulted in significant improvements in FC, 6MWD, NT-proBNP and haemodynamics (Table 1).<sup>31</sup> Diller et al. reported outcomes in 153 ES patients, 26 (17%) of whom received sequential combination therapy with bosentan and sildenafil: No difference in long-term mortality between those treated with mono- as opposed to dual therapy was observed.<sup>6</sup> Finally, the MAESTRO study randomised 226 ES patients, 61 of whom were on background PDE5-i therapy, to receive macitentan or placebo.<sup>14</sup> While the primary endpoint of change in 6MWD was not met, detailed results are awaited.

Several observational studies have reported improvement in exercise capacity and haemodynamics following intravenous, subcutaneous or inhaled prostanoid therapy (Table 1).<sup>23–29</sup> Intravenous therapy is associated with a risk of paradoxical embolic events; where available, subcutaneous treprostinil may be an attractive option. Owing to the complexities of prostanoid therapies, their role in ES is limited to patients deteriorating despite PDE5-i/ERA combination therapy, especially when they are candidates for transplantation. Currently there are no data to support the use of oral therapies acting on the prostacyclin pathway, even though PAH patients with repaired CHD were included in the GRIPHON study.<sup>44</sup>

**Suggested approach:** There are insufficient data to support routine upfront/early sequential oral combination therapy in ES. However, oral combination therapy with a PDE5-i and ERA should be considered in ES patients with markers of adverse outcome or clinical deterioration whilst on monotherapy. Prostanoid therapy should be considered in patients who fail to respond or deteriorate despite oral combination therapy.

#### 4. Should cardiac catheterisation be performed to establish the diagnosis of ES?

Current international PH guidelines recommend right heart catheterisation (RHC) to confirm a diagnosis of PAH, assess haemodynamic severity and, in cases of suspected idiopathic, heritable or drug-associated PAH, assess acute vasoreactivity.<sup>2</sup> Cardiac catheterisation, including acute vasoreactivity, is also used to assess operability in CHD patients. Therefore, all PAH patients, including ES, should in principle undergo cardiac catheterisation to establish the diagnosis of PAH.

In adult clinical practice, however, echocardiography can provide sufficient information to establish the presence of severe pulmonary artery (PA) pressures in patients with

post-tricuspid shunts (e.g. VSD, PDA, aortopulmonary window), which, together with clinical features such as hypoxaemia, clubbing and secondary erythrocytosis, are highly suggestive of ES. Cardiac catheterisation is, however, indicated in patients with pre-tricuspid shunts or those who present with left-to-right shunting and may be candidates for defect closure. Similarly, cardiac catheterisation is indicated for patients with PAH associated with small or repaired defects and those with associated lesions (e.g. pulmonary stenosis), suspected segmental PH or other complex anatomy.

**Suggested approach:** In principle, all patients should undergo cardiac catheterisation to establish the diagnosis of PAH. However, the diagnosis of ES in adults with post-tricuspid defects may be established based on echocardiographic and clinical signs.

#### 5. What is the role for oxygen therapy in patients with ES? What should I advise my patients regarding flying?

Hypoxaemia in patients with ES results not from alveolar hypoxia but rather from right-to-left shunting as a result of increased PVR. Hence, a proportion of deoxygenated blood leaving the right heart bypasses the alveolar-capillary interface. The rationale for the use of supplemental oxygen is, therefore, not immediately apparent. Early studies on the use of oxygen in patients with ES did, however, demonstrate a reduction in PVR and increase in pulmonary blood flow (Qp).<sup>45</sup> A significant improvement in SaO<sub>2</sub> was observed in 29 patients with cyanotic CHD following 10 minutes of 40% oxygen.<sup>46</sup> More recently, a significant improvement in 6MWD, heart rate recovery, dyspnoea and lower limb fatigue was seen in 30 ES patients who received acute 40% oxygen supplementation.<sup>47</sup> There was, however, no benefit after two years of nocturnal oxygen therapy on mortality, exercise capacity, erythrocytosis or quality of life in an RCT involving 23 patients with ES and a post-tricuspid defect.<sup>48</sup> The routine prescription of oxygen therapy is, thus, not supported by the current literature, and the use of oxygen should be considered on a case-by-case basis and continued only if there is clear subjective or objective benefit.

The percentage of inspired oxygen in most pressurised airlines at cruising altitude is 15% compared with 21% at sea level.<sup>49</sup> Hypoxia has the potential to cause pulmonary vasoconstriction and, thus, current PH guidelines recommend the use of supplementary oxygen in idiopathic PAH patients in FC III or IV or with a arterial oxygen pressure <8kPa.<sup>2</sup> Broberg et al. surveyed the flight history of 53 ES patients over a 10-year period.<sup>50</sup> The majority of flights were taken without supplementary oxygen and no adverse events of significance were observed. It, therefore, seems reasonable for most stable ES patients to fly without supplemental oxygen. Measures to reduce the risk of other complications around flights, such as keeping well hydrated and mobilising regularly, should be advocated.

**Suggested approach:** Long-term oxygen therapy need not be routinely prescribed in ES. A trial of ambulatory oxygen

may be considered on a case-by-case basis, providing it does not restrict patients from remaining active and mobile. Most patients with ES can fly without the administration of oxygen, although patients may choose to take oxygen on board for their first flight, or on long-haul flights.

**6. A patient with single ventricle physiology and associated Eisenmenger complex is in FC III. What is the evidence for the use of PAH-specific therapy in patients with ES due to complex defects? What about patients with segmental PAH?**

Data regarding treatment outcomes in ES associated with complex anatomy are extremely limited. Ten patients with complex anatomy received two years of bosentan therapy and demonstrated significant improvements in 6MWD and WHO FC.<sup>51</sup> Baptista et al. treated 14 patients with ES and complex anatomy (including four with truncus arteriosus, two with transposition of great arteries and five with tetralogy and pulmonary atresia) and demonstrated a significant improvement in 6MWD after six months of bosentan.<sup>52</sup> Significant improvements in WHO FC and 6MWD were seen in response to bosentan therapy in seven patients with pulmonary atresia and segmental PAH.<sup>53</sup> Yamamura et al. subsequently reported beneficial effects of bosentan on haemodynamics and BNP in two paediatric patients with surgically treated tetralogy of Fallot with pulmonary atresia and major aorto-pulmonary collaterals.<sup>54</sup> There are currently no data on the use of PAH therapies in patients with unoperated single ventricle physiology with an unprotected pulmonary circulation and Eisenmenger complex. While an increase in Qp may improve oxygenation, close monitoring of systemic ventricular function is recommended for the potential detrimental effects of the additional volume load.

**Suggested approach:** Despite the lack of strong evidence, a trial of PAH therapy may be considered in patients with ES and complex cardiac anatomy, and patients with segmental PAH.

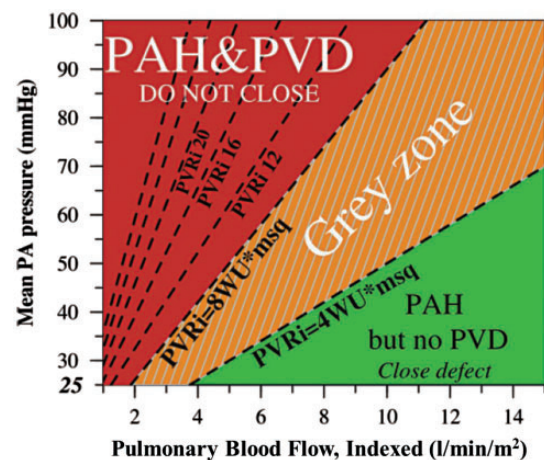
**7. My patient has PAH associated with a large secundum atrial septal defect (ASD). Which patients can have a defect safely closed, what is the role of pretreatment with PAH-specific therapy and when should a fenestrated closure device be used?**

In CHD, PH as conventionally defined (mean pulmonary arterial pressure (mPAP)  $\geq 25$  mmHg) is not synonymous with pulmonary vascular disease (PVD). A large left-to-right shunt may result in elevation of mPAP due to increased flow rather than a pulmonary vasculopathy. It is widely accepted that cardiac defects should not be closed in patients who have developed “significant” PVD.<sup>55</sup> Indeed, while the defect may have been instrumental in the development of PVD, it thereafter acts as a “relief valve” for the pressure-overloaded right ventricle (RV), which can fail acutely or over time if the defect is repaired. The above considerations become even more complex in patients with pre-tricuspid shunts, i.e. various types of ASD, in whom the

development of PVD is a rather unexpected phenomenon and suggests an intrinsic predisposition of the pulmonary vasculature towards PVD, and a phenotype resembling idiopathic PAH.

Whilst the decision to repair a congenital heart lesion should rely on the overall clinical picture, PVR is the single best indicator of the severity of PVD.<sup>10</sup> International guidelines suggest that patients with a PVR indexed (PVRi)  $< 4$  WU.m<sup>2</sup> (or PVR  $< 2.3$  WU) should be considered for repair and those with a PVRi greater than 8 WU.m<sup>2</sup> (or PVR  $> 4.6$  WU) should not (Fig. 2).<sup>2</sup> A “grey” area of patients with “borderline” haemodynamics remains; these should be considered individually in expert PAH and CHD centres. Fenestrated closure of large ASDs is recommended in borderline cases deemed suitable for repair, hence preserving a “relief valve” for the RV, whilst significantly reducing left-to-right shunting.

Data to support pretreatment of patients with borderline or prohibitive haemodynamics with PAH therapies, followed by intervention (the “treat-and-repair” approach) are lacking, with concerns persisting regarding the long-term response of the pulmonary vascular tree and RV to defect closure.<sup>6</sup> Certainly, no patients with ES (i.e. those with very high PVR and reversal of the shunt) should undergo repair, regardless of the treatment received.



**Figure 2.** The importance of calculating PVRi in assessing suitability for closure of atrial septal defects. A mean left atrial pressure of 10 mmHg is assumed in this example. Patients with a left-to-right shunt and significantly raised pulmonary blood flow may have pulmonary hypertension (mPAP  $\geq 25$  mmHg) in the absence of an increase in PVR (green zone); in these cases, defect closure is advisable. Patients with PVRi  $> 8$  WU.m<sup>2</sup> are deemed to have established PVD and the defect should not be closed. Those with PVRi  $> 4$  but  $< 8$  WU.m<sup>2</sup> are in the “grey” zone and the decision on whether to repair the defect should be taken in expert centres. PA: pulmonary artery; PAH: pulmonary arterial hypertension; PVD: pulmonary vascular disease; PVR: pulmonary vascular resistance; PVRi: pulmonary vascular resistance index; mPAP: mean pulmonary arterial pressure.

**Suggested approach:** Patients with a left-to-right shunt through a large ASD with a  $PVR_i < 4 \text{ WU.m}^2$  should be considered for closure while those with a  $PVR_i > 8 \text{ WU.m}^2$  should not. The role of PAH therapy in patients with a  $PVR_i$  between 4 and 8  $\text{WU.m}^2$ , with a view to subsequent closure, is unclear.

**8. A 35-year-old patient with suspected idiopathic PAH is found, after investigation, to have partial anomalous pulmonary venous drainage involving the right upper and middle lobes and no associated ASD (Fig. 3). RHC reveals a mean right atrial pressure (mRAP) of 8 mmHg, mPAP 30 mmHg, pulmonary arterial wedge pressure (PAWP, left upper lobe pulmonary vein) 13 mmHg,  $Q_p$  via thermodilution of  $71 \text{ l/min/m}^2$  with a  $PVR_i$  of  $2.4 \text{ WU.m}^2$ .  $Q_p$  to systemic flow ( $Q_s$ ) ratio was calculated as being 1.9:1. Is there a role for surgical correction?**

Partial anomalous pulmonary venous return of the right upper pulmonary veins to the superior vena cava (SVC) may be associated with a sinus venosus ASD, both of which are very difficult to identify on transthoracic echocardiography in adults. Pulmonary venous drainage should be, therefore, systematically evaluated on cross-sectional imaging in patients with suspected or proven PH. Cardiac catheterisation also provides an opportunity to avoid misdiagnosis, by routinely sampling  $\text{SaO}_2$  in the upper and lower SVC and identifying the “step-up” in saturations.

In this case, mean PA pressure was indeed high (30 mmHg), as was the transpulmonary gradient (17 mmHg). It can be argued that  $Q_p$  should be calculated using the direct Fick method rather than thermodilution, which is not recommended in the presence of a shunt (even though this shunt occurs proximal to the right atrium where the cold saline is injected). An indexed  $Q_p$  of  $71 \text{ l/min/m}^2$  suggests a significant left-to-right shunt, and  $PVR_i$  is estimated as  $2.4 \text{ WU.m}^2$ . Hence there is no evidence of PVD and, with a  $Q_p:Q_s$  well above 1.5 and RV dilatation, the patient should be referred for surgical repair. Transoesophageal echocardiography is

indicated to determine the presence of a sinus venous ASD or other CHD prior to surgery.

Correctly identifying an intracardiac shunt may mean the difference between a wrong diagnosis of idiopathic PAH (with years of inappropriate treatment), and cure by repairing the defect.

**Suggested approach:** Partial anomalous pulmonary venous return can be easily missed. The drainage of the pulmonary veins should be systematically evaluated on cross-sectional imaging in patients with suspected PH. RHC with serial oximetry, calculation of  $PVR_i$  and shunt fraction ( $Q_p:Q_s$ ) are essential for diagnosis and management.

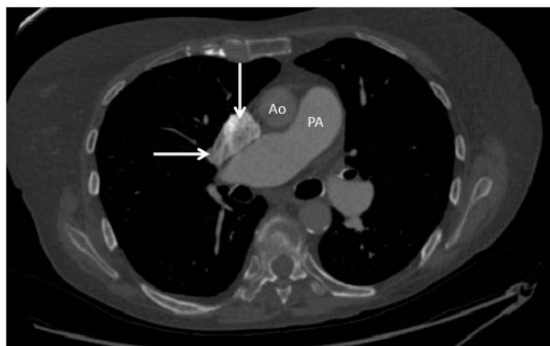
**9. A 39-year-old female underwent closure of a 2.9 cm secundum ASD three years ago with an unfenestrated device. She now complains of progressive exertional breathlessness and presyncope on strenuous efforts. RHC demonstrates significant PAH: mRAP 14 mmHg, mPAP 49 mmHg, PAWP 12 mmHg, CO  $4.21 \text{ l/min}$  and PVR  $8.8 \text{ WU}$ . What is the evidence for the use of PAH-specific therapy? Is there a potential role for atrial septostomy?**

Secundum ASDs are, in their vast majority, easily repairable through percutaneous device implantation, while others are amenable to surgery. However, no ASDs should be closed unless there is clear evidence of a normal PVR (see Case 8, Fig. 2). Closing the defect in a patient with established PVD can have detrimental effects, as the ASD may act as a “relief valve” for the RV. Adult PAH-CHD patients with previously repaired defects have the worse prognosis of all PAH-CHD (including ES), underscoring the need to avoid inappropriate CHD repair.<sup>56</sup>

This patient has severe PAH, with a severely raised PVR of  $8.8 \text{ WU}$  and significant symptoms of dyspnoea and presyncope on effort. Even though we do not know the haemodynamics before ASD closure, it is likely that PVD was pre-existent and closure of the defect (perhaps associated with progression of the PVD or other predisposing factors) has led to progressive deterioration of RV function, transforming this into a condition akin to idiopathic PAH. For this reason, patients with repaired PAH-CHD have been included in major PAH trials,<sup>41,57</sup> and this patient should be treated aggressively with PAH therapies in view of her severe symptoms. Other causes of PH should, of course, be considered and excluded.

Balloon atrial septostomy, which boosts systemic cardiac output by allowing right-to-left shunting at the expense of  $\text{SaO}_2$ , is a potential therapeutic option if the patient fails to respond to PAH therapies. Guidelines suggest avoiding septostomy if  $\text{mRAP} > 20 \text{ mmHg}$  or resting  $\text{SaO}_2$  are  $< 85\%$ .<sup>2</sup> However, it is better to avoid closing the defect in the first place if there is PVD, or at least allow a fenestration in borderline cases.

**Suggested approach:** Detailed haemodynamic assessment is essential prior to repairing defects, especially in patients with suspicion of a raised PVR. Patients with PAH following closure of a congenital shunt should be treated with PAH therapies in a manner similar to idiopathic PAH.



**Figure 3.** Computed tomography thorax demonstrating anomalous pulmonary venous connection of the right middle lobe pulmonary vein (horizontal arrow) into the superior vena cava (vertical arrow). Note the dilated pulmonary artery (PA) compared with adjacent ascending aorta (Ao).

**10. How can I estimate the expected degree of secondary erythrocytosis in patients with ES? What is the best method of assessing for iron deficiency? What is the evidence for iron replacement and what is the risk of “rebound polycythaemia”? In which patients with ES should I consider venesection?**

Chronic hypoxaemia stimulates compensatory erythrocytosis with the aim of preserving oxygen delivery ( $\text{DO}_2$ , Fig. 4). In a study on 171 ES patients, there was a significant inverse relationship between  $\text{SaO}_2$  and haemoglobin in those who were iron replete, which was weaker in those who were iron deficient.<sup>58</sup> Broberg et al. subsequently studied 65 ES patients in more detail and derived an equation to predict haemoglobin levels for a given  $\text{SaO}_2$ , in the absence of iron,  $\text{B}_{12}$  or folate deficiency:<sup>59</sup>

$$\text{Predicted haemoglobin (g/dl)} = 61 - (\text{SaO}_2/2)$$

This equation has not, however, been prospectively validated.

Iron deficiency occurs in up to one-third of ES patients and is likely multifactorial, due to reduced absorption and increased consumption due to the erythrocytosis and chronic bleeding. The most widely used parameters to assess iron status in clinical practice are transferrin saturation and serum ferritin. Importantly, microcytosis is uncommon in the iron-deficient cyanotic patient, and a normal mean cell volume cannot be used to exclude iron deficiency.<sup>60</sup>

Iron deficiency is associated with poorer survival in ES.<sup>61</sup> Three months of oral iron replacement (ferrous sulphate 200 mg three times daily, few instances of intravenous iron) given to 25 cyanotic CHD patients resulted in significant improvements in haemoglobin and iron stores, together with improved 6MWD and quality of life.<sup>62</sup> Although there were instances of symptomatic hyperviscosity in previous studies following iron replacement, no significant symptoms of hyperviscosity were observed in this study.<sup>63</sup> When patients cannot tolerate oral iron, intravenous iron replacement should be offered.

In previous decades, routine venesections were used in ES to keep the haematocrit below an arbitrary target, with the aim of reducing the risk of thrombotic events and other hyperviscosity symptoms. However, iron deficiency and venesections have been associated with an increased risk of cerebrovascular events<sup>64</sup> and venesection is, nowadays,

reserved for iron-replete patients with high haematocrit (well above 0.65) and severe symptoms of hyperviscosity (such as headaches and lethargy), in the absence of dehydration.

**Suggested approach:** Haemoglobin, ferritin and transferrin saturations should be checked regularly in ES patients, and iron supplementation given in the presence of iron deficiency, especially when haemoglobin concentration is lower than expected for the degree of cyanosis. Isovolumetric venesection should be reserved for the minority of patients with severe symptoms of hyperviscosity in the absence of other causes (dehydration, cerebral abscess, etc).

**11. What are the risks of pregnancy in patients with PAH-CHD? What are the most appropriate forms of contraception? What should the approach be to a patient who becomes pregnant?**

Pregnancy is currently contraindicated in all women with PH.<sup>2</sup> Despite major improvements in care over the last 15 years, Bedard et al. described a still prohibitive pregnancy-related mortality of ~25%.<sup>65</sup> Twenty-six pregnancies were observed in 20 patients with ES, 18 of which progressed to delivery.<sup>66</sup> Twenty-two per cent of patients developed severe heart failure, with inotropic support required in three patients, extracorporeal membrane oxygenation (ECMO) in one patient, and a mortality rate of 6%. The majority of deaths in PH tend to occur during the second trimester (during which cardiac output increases in the normal pregnancy) but especially in the peri-partum period. Moreover, cyanosis poses a risk to the foetus in terms of risk of spontaneous abortion and somatic growth. Current recommendations place PH in the highest-risk group (group IV of the WHO maternal risk classification); they strongly recommend against pregnancy and advise interruption of pregnancy if this does occur.<sup>67</sup> It is, therefore, essential that all women with child-bearing potential and PAH-CHD receive advice with regards to contraception (Table 2).

Some women with PH decide to proceed with pregnancy despite extensive counselling. Other women are first diagnosed with PH during pregnancy and choose to continue. A multidisciplinary approach to pregnancy in PH is essential, and requires a multidisciplinary team of health care professionals experienced in the management of pregnant women with PAH-CHD (PH and CHD physicians

$$\text{Oxygen delivery (DO}_2\text{)} = \text{Cardiac Output (CO)} \times \text{Systemic arterial oxygen content (CaO}_2\text{)}$$

$$\text{Where CaO}_2 = \text{oxygen saturation (SaO}_2, \%) \times \text{haemoglobin (g/dL)} \times 1.34/100.$$

**Figure 4.** Oxygen delivery is the product of cardiac output and the oxygen content of blood. In patients with hypoxaemia and impaired cardiac output, maintenance of oxygen delivery relies on a compensatory erythrocytosis. The minute amount of oxygen dissolved in plasma is not included.

**Table 2.** Contraceptive options in pulmonary arterial hypertension associated with adult congenital heart disease<sup>a</sup>.

Method	One-year failure rate: typical use (%)	One-year failure rate: perfect use (%)	Comments
Male condom	15	2	Not reliable enough in typical use
Combined oral contraceptive pill	8	0.1	Increased venous thromboembolism risk – not recommended
Desogestrel (e.g. Cerazette™)	8	0.1	Interaction with bosentan – additional method required (e.g. barrier)
Medroxyprogesterone acetate injection (e.g. Depo-Provera™)	3	0.3	Associated with increased venous thromboembolism risk compared with other nonoestrogen hormonal methods
Etonogestrel implant (e.g. Nexplanon™)	0.05	0.05	Interaction with bosentan – additional method required (e.g. barrier)
Copper coil	0.8	0.6	
Levonorgestrel coil (e.g. Mirena™)	0.1	0.1	Requires hospital admission during implantation because of risk of vasovagal events
Male sterilisation	0.2	0.1	
Female sterilisation	0.5	0.5	Requires laparotomy/mini-laparotomy (ligation) or hysteroscopy

<sup>a</sup>Adapted from Thorne et al.<sup>68</sup>

and nurses, obstetricians and midwives, anaesthetists, intensivists and access to ECMO/transplant services).<sup>69</sup> Endothelin receptor antagonists are potentially teratogenic and should be discontinued either prior to conceiving or as soon as pregnancy is confirmed.<sup>70</sup> Sildenafil appears to be safe in pregnancy, while the addition of prostanoid therapy (also safe) may be required. Close monitoring, with early elective delivery depending on the clinical status of the mother and level of maturity of the foetus, are recommended.<sup>71</sup> Close post-partum monitoring in a critical care environment is essential.

**Suggested approach:** Patients with PAH-CHD should be counselled regarding the very high risk during pregnancy and the type of contraception to use. If a patient becomes pregnant and chooses to continue with the pregnancy, sildenafil ± prostanoid therapy is recommended and the patient should be managed by a highly experienced multidisciplinary team.

## 12. My patient with ES secondary to a VSD has recurrent cholecystitis. What are the risks of surgery and what is the optimal way of managing the patient in the perioperative period?

Noncardiac surgery and anaesthesia in PAH patients is associated with a mortality of 3.5% to 18%, with the risk being higher in emergency and prolonged surgery.<sup>72–75</sup> Other predictors of outcome around surgery include the severity of PH, degree of exercise intolerance and requirement for inotropic or pressor support.<sup>72–75</sup>

Perioperative management should include measures to reduce blood loss, avoid sudden reduction in systemic vascular resistance (SVR) or rise in PVR, and minimise the

negative cardiovascular effects of airway instrumentation and positive airway pressure support.<sup>76</sup> Where possible, regional anaesthesia may be preferred, using regional nerve blocks and low-dose spinal or combined spinal/epidural techniques to minimise the drop in systemic pressure. Patients with intracardiac defects may be prone to right-to-left shunting secondary to the fall in SVR during anaesthesia, resulting in worsening hypoxaemia. Pressor agents to maintain SVR and intravenous prostanoid therapy to reduce PVR may, therefore, be required. Established PAH therapies should be continued; an intravenous formulation of sildenafil is available and preoperative commencement of intravenous prostanoid therapy may be considered. Care should be taken to reduce the risk of air emboli by using air filters and automated giving sets.

Close postoperative cardiovascular monitoring is essential. PA catheters are not routinely used because of concerns regarding complications such as PA trauma; however, noninvasive methods of cardiac output measurement may be considered.

Patients with ES commonly have few, less-effective platelets and may, therefore, have an increased requirement for platelets and clotting products. Given the importance of haemoglobin levels to maintain DO<sub>2</sub>, a higher threshold for transfusion (10–14 g/dl, depending on baseline haemoglobin concentration) should be considered. Finally, surgery is best performed in an elective manner with an experienced multidisciplinary team of anaesthetists, intensivists, surgeons, ACHD and pulmonary vascular physicians.

**Suggested approach:** When surgery is essential it should be performed, where possible, electively in experienced tertiary centres. Steps should be taken to maintain SVR

and PVR, minimise fluid shifts and reduce the risks of paradoxical air emboli.

**13. A patient with ES associated with Down syndrome (DS) is reported to have progressively worsening exercise tolerance and presyncope on efforts. What is the evidence for the use of PAH-specific therapy in patients with ES associated with DS? What are the potential complications or issues associated with different therapies in this patient group? His parents do not wish him to commence any specific PAH therapy; what should the approach be?**

CHD is present in up to 43% of people with DS, with atrio-ventricular septal defects being most common.<sup>77</sup> Historically, few people with DS were offered corrective surgery and, as a consequence, the prevalence of ES in adults with DS is currently high. While randomised data on the use of PAH therapies in DS are lacking, there are some observational data suggesting efficacy. Significant improvements in WHO FC, 6MWD, Qp and PVRi were observed in a prospective study on 18 people with DS and ES after 12 months of bosentan therapy.<sup>78</sup> Similarly, 6MWD, SaO<sub>2</sub> and pulmonary acceleration time significantly improved in seven people with DS and ES who received bosentan for more than four years.<sup>79</sup> Conversely, no improvements were observed in a study of 30 ES patients with DS following four months of bosentan, although the reproducibility of the 6MWD in patients with DS has been questioned.<sup>80,81</sup> Furthermore, the recent Sildenafil in Treatment-Naive Children, Aged 1–17 Years, with Pulmonary Arterial Hypertension (STARTS-1) dose-finding trial of sildenafil in paediatric PAH failed to demonstrate a significant haemodynamic improvement in 48 people with DS.<sup>82</sup> The choice of PAH therapy depends on various parameters. The requirement for monthly blood monitoring with bosentan therapy can be problematic for some. In these cases, PDE5-i therapy or alternative ERAs with less-intensive blood monitoring requirements can be considered. A common concern regarding PDE5-i therapy is increased frequency of erections, but in practice this rarely leads to discontinuation.

Many people with DS lack full capacity to make informed treatment decisions. Family members sometimes have concerns regarding new medications which can result in a patient being denied effective therapy. In these situations, a best-interests meeting should be held including members of the multidisciplinary team, the family, the patient and an independent advocate.

**Suggested approach:** DS patients with ES should be offered oral PAH therapy, with a similar approach to non-DS patients.

## Conclusion

The suggested approaches are based on interpretation of the published literature, guidelines and clinical experience. Management decisions in an individual patient require clinical assessment of risks and benefits.

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## Conflicts of interest

R.C. has received honoraria from Actelion, Bayer, GSK, and MSD. P.C. has received honoraria from Actelion and Bayer. K.D. has received grants and honoraria from Actelion, Bayer, GSK, MSD, and Pfizer. R.M.R.T. has received honoraria from Actelion, Abbott International, Bayer, and GSK.

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