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Scientific Update™

Management of Pulmonary Hypertension Associated with Congenital Heart Disease

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Pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) is an increasingly common and complex disease with multiple treatment algorithms owing in part to a host of underlying disease processes. PAH-CHD is usually the result of a large systemic-to-pulmonary shunt, and often leads to right ventricular failure and early death. The newly updated and condensed European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines[1] include an expanded classification of PAH-CHD with respect to its clinical and anatomical-pathophysiological picture in an attempt to more accurately define individual patients. The objective of this issue of *Cardiology Scientific Update* is to place the current knowledge and current guidelines regarding PAH-CHD into clinical practice perspectives. A discussion of the evolution of Eisenmenger physiology (EP) and the clinical classification of patients with PAH-CHD is followed by an examination of the available evidence supporting the therapeutic interventions in these patients.

PAH-CHD was once predominantly a pediatric disease. However, with the advances in the surgical management of CHD, significantly greater numbers of patients survive into adulthood, and PAH-CHD has now become a disease of both adults as well as children. In their analysis of a Dutch registry of CHD patients, Duffels et al[2] determined the prevalence of PAH to be 4.2%. Humbert et al[3] showed that 11.3% of adults with PAH also had CHD, and the prevalence of CHD in children with PAH was as high as 50%.[4]

New Classifications of PAH-CHD

Among all of the PAH subpopulations, PAH-CHD patients represent a particularly complex group due to the underlying disease. The latest ESC/ERS guidelines divide PAH-CHD into 4 clinical groups, depending on the underlying defect and/or the direction of the shunt (Table 1). The first group, Eisenmenger syndrome, represents the most advanced form of PAH-CHD; this group is described in more detail below. The second group, PAH associated with left-to-right (systemic-to-pulmonary) shunts, includes patients with moderate to large defects, with a mild to moderate increase in pulmonary vascular resistance. The third group comprises PAH patients who have small defects (usually ventricular and atrial septal defects of <1 cm and <2 cm, respectively). For these patients, the defect may not necessarily be the underlying cause of PAH.[5] The fourth group comprises PAH that develops after corrective heart surgery, despite normalization of the underlying defect.

Of the 4 clinical groups described in the guidelines, the most severely compromised patients are those who have developed EP.[6] In EP, the initial systemic-to-pulmonary shunt is reversed as pulmonary vascular resistance increases above systemic resistance (Figure 1). EP includes all patients with an initial left-to-right shunt that has completely reversed to a right-to-left shunt.[5] The greater pulmonary blood flow caused by the initial left-to-right shunt induces shear stress and circumferential stretch, which lead to vascular remodelling and a progressive rise in pulmonary vascular resistance (PVR). Shunt reversal occurs once PVR exceeds systemic resistance. The right-to-left shunt reduces arterial oxygen capacity, leading to hypoxic damage and multi-organ disease. Cyanosis and secondary erythrocytosis are typical features encountered in EP.[7] Patients with EP have a particularly poor quality of life and most experience impaired exercise tolerance and dyspnea on exertion.[7] Although mortality is generally lower in EP than in idiopathic PAH,[5] therapeutic intervention is still warranted to further improve prognosis and importantly improve the quality of life for this population.

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Table 1: Clinical Classification of Congenital, Systemic-to-pulmonary Shunts Associated With PAH[1]	
Eisenmenger syndrome	Eisenmenger syndrome includes all left-to-right shunts due to large defects leading to a severe increase in PVR and resulting in a reversed right-to-left or bidirectional shunt. Cyanosis, erythrocytosis, and multiple organ involvement are present.
PAH associated with systemic-to-pulmonary shunts	In these patients with moderate to large defects, the increase in PVR is mild to moderate, left-to-right shunt is still largely present, and no cyanosis is present at rest.
PAH with small defects	In cases with small defects (usually VSD <1 cm and ASD <2 cm of effective diameter assessed by echocardiography) the clinical picture is very similar to idiopathic PAH.
PAH after corrective cardiac surgery	CHD has been corrected but PAH is either 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 that originate as a sequela to previous surgery.

PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; VSD = ventricular septal defect; ASD = atrial septal defect; CHD = congenital heart disease.

What is the Evidence for Managing Patients with PAH-CHD?

The management of patients with PAH-CHD involves both surgical and pharmacological options, and optimal timing for each intervention is critical.

Surgery

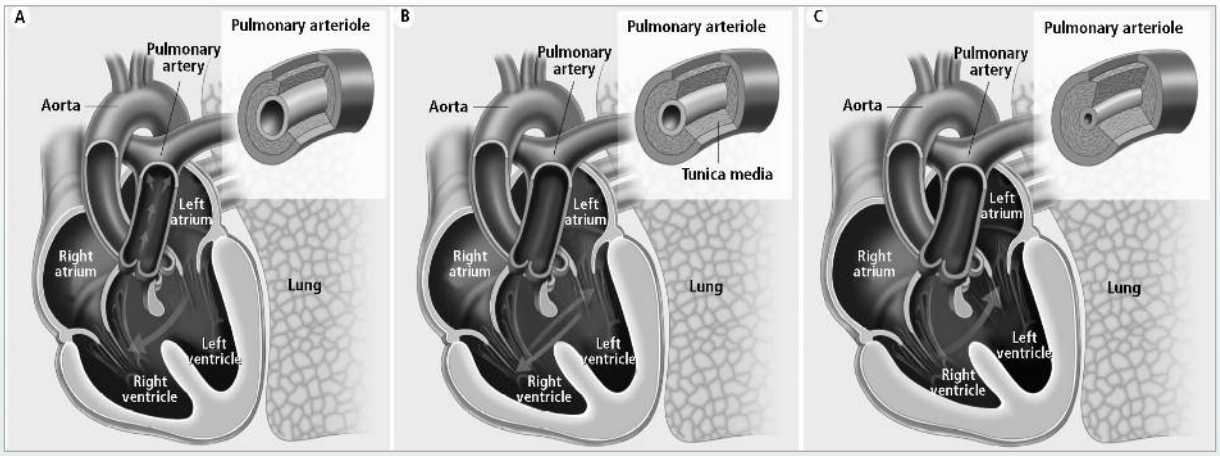
Surgical correction of the underlying defect in PAH-CHD is the appropriate intervention and should be done as soon as feasible. Patients with left-to-right shunts, high pulmonary blood flow and low PVR are most likely to still be operable.[5] Timely surgical intervention prior to the onset of high PVR may allow reversal of PAH once the defect is repaired. However, once PVR rises above a critical level, a "point of no return" is reached. Surgical intervention should be avoided at this stage because of the risk of acute right-heart failure following the operation. These patients are at increased post-surgical risk of developing shunt reversal, leading to EP. In patients who develop EP, therefore, surgery is contraindicated.[5]

Pharmacotherapy

For patients with inoperable PAH-CHD, therapeutic intervention with targeted PAH therapy is the preferred course of action. Clinical benefits of PAH-specific therapies in PAH-CHD patients have been demonstrated for the prostacyclin analogues, phosphodiesterase-5 inhibitors, and endothelin-receptor antagonists.[5] Initial open-label studies with prostacyclin analogues in PAH-CHD patients demonstrated improvements in functional capacity, oxygen saturation, and hemodynamics.[8,9] Beneficial effects of the phosphodiesterase-

Figure 1: Evolution of Eisenmenger Physiology

A. An atrial septal, ventricular septal, or complex defect increases pulmonary blood flow via left-to-right shunt. B. Pulmonary resistance rises, resulting in bi-directional flow. C. Right-to-left reversal of shunt flow leads to Eisenmenger physiology.

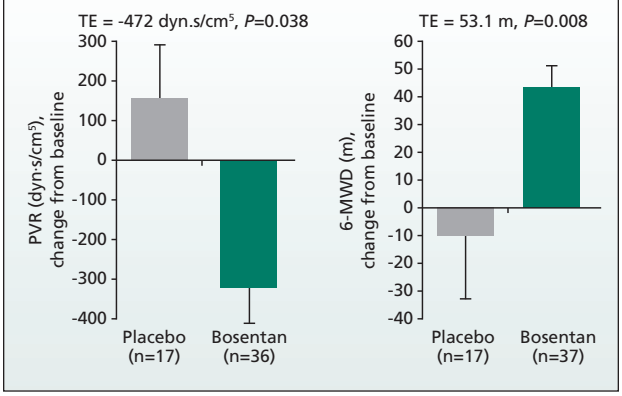


5 inhibitors, namely sildenafil and tadalafil, have been demonstrated in patients with EP in open-label studies that have involved a relatively small number of patients.[10-12] Of these agents, the dual endothelin-receptor antagonist bosentan has been most extensively studied and has the strongest supportive dataset.[5] Indeed, it is the only PAH therapy that has been studied in a randomized, double-blind, placebo-controlled study of EP patients (the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 [BREATHE-5]).[13] In addition, several prospective, open-label studies of bosentan in PAH-CHD patients have demonstrated significant improvements in exercise capacity, World Health Organization (WHO) functional class and hemodynamics.[14-16] Based on these results, the ESC/ERS guidelines recommend bosentan as first-line treatment in WHO functional class III patients with EP. With the advent of disease-targeting PAH treatments, new therapeutic opportunities are emerging for patients with PAH-CHD.

In BREATHE-5, 54 patients aged >12 years with WHO functional class III Eisenmenger syndrome were randomized to bosentan (n=37) or placebo (n=17) for 16 weeks. Compared with placebo, bosentan significantly reduced the PVR index (primary efficacy endpoint) by 472.0 dyne-sec/cm^5 (P=0.0383) and improved exercise capacity (6-minute walking distance) by 53.1 m (P=0.008; Figure 2), without worsening systemic oxygenation (primary safety endpoint); ie, it did not cause shunt aggravation.

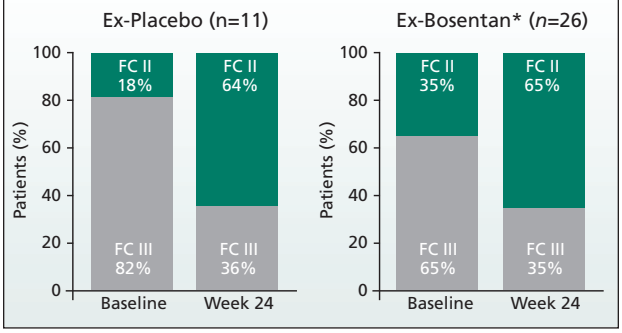
The BREATHE-5 investigators conducted an open-label extension,[17] in which 37 patients received bosentan over an additional 24 weeks. Subjects were analyzed according to the group into which they were randomized in the original study: ex-bosentan and ex-placebo. The researchers noted continued improvements in 6-minute walk distance in the bosentan-treated patients (6.7 m; total improvement in 2 studies: 61.3 m; 95% confidence interval [CI] 44.7-78.0) and

Figure 2: BREATHE-5[13] – Effect of Bosentan on PVR Index and Exercise Capacity



PVR = pulmonary vascular resistance; 6-MWD = 6-minute walk distance; TE = treatment effect

Figure 3: BREATHE-5 Open-label Extension[17] – Improvements in World Health Organization Functional Class (FC)

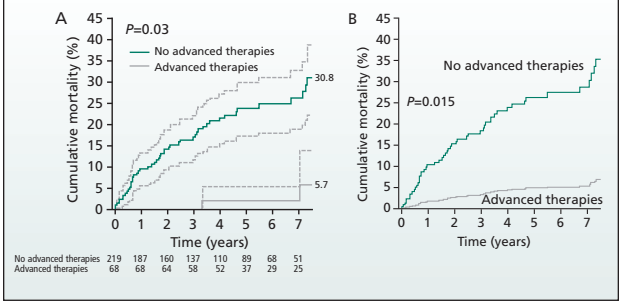


* Median exposure (BREATHE-5 plus open-label extension) was 41.1 weeks

notable improvements in the ex-placebo patients commenced on bosentan (33.2 m). Both groups experienced improvements in their WHO functional class (Figure 3). These results from BREATHE-5 and its extension illustrate that the clinical course of EP is far from stable and that patients with EP can benefit from bosentan. Based on these results, bosentan is currently the only approved treatment in Europe for PAH associated with congenital systemic-to-pulmonary shunts with EP in and WHO functional class III symptoms.

Recently, a retrospective study of patients with EP was conducted by Dimopoulos et al[18] to evaluate the potential effect of advanced therapy on survival in this population. The researchers collected data on all patients with Eisenmenger syndrome attending their centre over the past 10 years (N=229). Survival rates were compared between patients who received advanced therapy (AT) – ie, prostanoids, endothelin-receptor antagonists, and phosphodiesterase-5 inhibitors – compared with those who were never started on these agents. Baseline differences were adjusted for the use of propensity scores. Most subjects had complex anatomy, and 53.7% were in New York Heart Association class III-IV at baseline assessment. Among the 68 patients who received AT, 73.5% were started on bosentan, 25% on sildenafil, and 1.5% (1 patient) on epoprostenol. Patients starting AT were generally older (P=0.001) and more functionally impaired (P<0.0001) than those never on AT. After an average follow-up of 4.0 years, 52 patients died: 2 (2.9%) in the AT group and 50 (31.1%) in the non-AT group. Patients on AT were at a significantly lower risk of death during this study period, both unadjusted and after adjustment for baseline clinical differences by propensity score regression adjustment (C statistic=0.80; hazard ratio 0.16; 95% CI 0.04-0.71; P=0.015) and propensity score matching (hazard ratio 0.10; 95% CI 0.01-0.78; P=0.028) (Figure 4). These data therefore highlight the important role of advanced therapy in improving outcomes for PAH-CHD patients.

Figure 4: Dimopoulos et al[18] – Survival Rate Curves by Treatment with Advanced Therapy



Transplantation

Despite improvements in PAH therapy, transplantation is the only potentially curative option for patients with PAH-CHD. The optimal timing is difficult to determine, due to the reasonably good prognosis of PAH-CHD patients and the risks associated with transplantation.

Conclusion

With improvements in surgical and medical management, the outlook for patients with PAH-CHD continues to improve. In conjunction with the recent guidelines from the ESC/ERS, earlier and greater uptake of PAH therapy among EP patients will likely further improve patient outcomes.

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