An Approach to Pulmonary Arterial Hypertension in the Adult Patient With Congenital Heart Disease

Jun 13, 2013 | Wayne J. Franklin, M.D., FACC; Mehul Dilip Patel, MD

Expert Analysis

Abstract

Pulmonary arterial hypertension in adult patients with congenital heart disease is a heterogeneous condition caused by pulmonary vascular disease, pulmonary vasoconstriction or by overcirculation. These pathophysiologies may occur in isolation or in combination. The most common form is seen in patients with unrepaired large shunts. The initial, innocent, high flow hyperkinetic PAH gradually progress to malignant, irreversible PAH due to permanent structural alterations of the pulmonary vascular bed. The shunt may then become bidirectional or reverse with the development of Eisenmenger's syndrome. The incidence and prevalence of PAH in ACHD patients has shown a gradual decline due to early diagnosis and complete correction of lesions at a younger age along with the advent of newer medications. This review article focuses on clinical presentation and approach to the management of PAH in ACHD patients.

Introduction

Pulmonary arterial hypertension (PAH) may evolve during the natural history in adult patients with congenital heart disease (ACHD) with repaired or unrepaired structural defects. The systemic-to-pulmonary shunt induced initial increased pulmonary flow is accommodated by increased capacitance of the pulmonary vascular bed. However persistently high pulmonary blood flow with elevated PA pressure over time leads to structural alterations, vascular remodeling and endothelial dysfunction. The resultant increase in pulmonary vascular resistance (PVR) with reversal of the shunt leads to the development of Eisenmenger's syndrome, representing the most advanced form of PAH in ACHD patients.

The development of PAH in patients with ACHD portrays poor prognosis with increased mortality and morbidity.[1, 2] Depending on their age at closure, PAH may develop even in patients who have had a full repair making it a complex phenomenon to unfold. With an estimated prevalence of CHD of approximately 6-10 per 1,000 live births [5, 6] about 4–15% of such patients end up developing PAH.[5] It is interesting to note that data from the European registry studies show an overall prevalence of PAH in adult patients with CHD as 4–28% and of Eisenmenger's syndrome as 1–6%.[5-7] The major predictors of future PAH include the location, size and complexity of the native lesion.[8] The risk of developing Eisenmenger's syndrome is 10–17% in patients with an ASD (pre-tricuspid shunt), 50% with a VSD (post-tricuspid shunt), 90% of those with unrepaired AVSD and almost all patients with truncus arteriosus.[5,6, 9-12] The dynamically growing numbers and spectrum of adult patients with congenital heart disease and PAH presents a range of challenges in the management of complex cardiac and non-cardiac comorbidities. With early closure and recent advances in the PAH-specific therapies, there have been noteworthy improvements in treatment outcomes of such patient.[3,4]

Clinical groups

The clinical classification of PAH has undergone a series of changes since the first version in 1973 at the first international conference on primary pulmonary hypertension endorsed by the World Health Organization. The current European Society of Cardiology guidelines provide a clinical classification of congenital left-to-right shunts associated with PAH with stratification in four main clinical groups (Table 1). [8].

For those with *Eisenmenger's syndrome (Group A)*, the diagnosis is quite straightforward. *Group B patients with left-to-right shunts represent a spectrum from unrepaired lesions, the most common been ASDs,[13] to partially palliated patients with unrestricted shunts or unrepaired conditions such as pulmonary atresia with major aortopulmonary collateral arteries.* Group B patients are usually symptomatic and there is no clear consensus for management of these patients. Patients with small defects who develop PAH form *Group C who have a clinical picture similar to that seen in idiopathic PAH*. These patients have the distinct advantage of a shunt that may act as a ''pop off'' for the right heart, effectively decompressing the right side with high pressures.[13] Finally, there is a small group of patients *(Group D) who have progress to develop PAH despite corrective surgery*, in the absence of a residual

shunt. These patients have poor prognosis as the repair occurs at the time of significantly elevated pulmonary vascular resistance.[14] Mortality rates in PAH-CHD are frequently reported as being more favorable than for other PAH etiologies. However it is important to understand that PAH-CHD differ pathobiologically from other PAH etiologies and have a better prognosis then IPAH.

Eisenmenger's syndrome

The development of endothelial dysfunction with remodeling of the pulmonary arterial bed arising from persistently increased pulmonary pressure is a dynamic and multifactorial process indicating a''point of no return'' after which changes in the pulmonary vasculature may not be possible despite correction of the associated defect.[15-19] First described by Victor Eisenmenger in 1897,[20] Eisenmenger's syndrome was later defined in 1958 as ''pulmonary hypertension at systemic level due to high PVR with reversed or bidirectional blood flow through a septal defect.''[21] Right to left shunt with cyanosis leads to poor exercise intolerance, secondary polycythemia and hyperviscosity with abnormalities of hemostasis, thrombosis, stroke, gout, hypertrophic

Table 1: Clinical classification of congenital, systemic-to-pulmonary shunts associated with pulmonary arterial hypertension

osteoarthropathy, cerebral abscesses and endocarditis.[22, 23] Long-term cardiac complications include severe reduction in effort tolerance, heart failure, syncope, cardiac arrhythmia and sudden death. Contrary to idiopathic PAH, the development of the right-to-left shunt with Eisenmenger's syndrome means preservation of right ventricular function and relatively better prognosis.[7] Daliento L et al in a retrospective analysis of 188 patients over 31 yrs demonstrated that the most frequent causes of death in patients with Eisenmenger's syndrome were sudden unexpected death (30%), heart failure (23%) and massive haemoptysis (11%), usually as a result of pulmonary artery rupture [24]. The multiple systemic effects of this disease impart a particularly poor quality of life (QoL).

A. Eisenmenger's syndrome	Eisenmenger's syndrome includes all systemic-to-pulmonary shunts due to large defects leading to a severe increase in PVR and resulting in a reversed (pulmonary-to-systemic) or bidirectional shunt. Cyanosis, erythrocytosis, and multiple organ involvement are present.

Segmental PAH

Pulmonary arterial hypertension (PAH) in adult patients with congenital heart disease (CHD) though a heterogeneous condition

usually has a homogeneous pressure distribution. More rarely, complex CHD patients with large collaterals may have segmental PAH. This is often with large aorto-pulmonary collaterals resulting in regional differences in pulmonary artery pressure and pathophysiologic severity.

Comorbidities with PAH

ACHD patients with PAH suffer from a wide range of comorbidities associated with their underlying cardiac disorder, most commonly arrhythmias, heart failure along with renal failure, hepatic dysfunction and diabetes mellitus.[25] Arrhythmias, ranging from bradyarrhythmias to ventricular tachycardia and atrial fibrillation, are common late complications of CHD and signify hemodynamic alterations that deserve immediate attention. The early diagnosis and recognition of atrial arrhythmia is very important in these patients as it signifies increased risk of mortality due to heart failure-related death, sudden cardiac death

B. Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts	In these patients with moderate to large defects, the increase in PVR is mild to moderate, systemic-to-pulmonary shunt is still largely present, and no cyanosis is present at rest.

and perioperative death in ACHD patients with PAH.[26]

Clinical presentation

The symptoms of PAH are quite non-specific and may include shortness of breath, fatigue, weakness, angina, syncope, and abdominal distension. Symptoms at rest are reported only in very advanced cases. The physical signs of PAH include left parasternal lift, an accentuated pulmonary component of second heart sound, a holosystolic murmur of tricuspid regurgitation, a diastolic murmur of pulmonary insufficiency, and an RV third sound. Jugular vein distension, hepatomegaly, peripheral edema, ascites, and cool extremities characterize patients in a more advanced state. The examination may also provide clues as to other causes of PH. Telangiectasia, digital ulceration, and sclerodactyly are seen in scleroderma, while inspiratory crackles may point towards interstitial lung disease. The stigmata of liver disease such as spider naevi, testicular atrophy, and palmar erythema should be

C. Pulmonary arterial hypertension with small defects	In cases with small defects (usually ventricular septal defects, 1 cm and atrial septal defects, 2 cm of effective diameter assessed by echocardiography) the clinical picture is very similar to idiopathic PAH.

considered. If digital clubbing is encountered in 'IPAH', an alternative diagnosis such as CHD or PVOD should be sought. These patients may also present in crisis to the emergency room with spontaneous PA thrombosis, PA dissection, rupture and life threatening hemoptysis.

Treatment

A full and detailed chronological history with the functional class and 6-minute walk time and distance is important when considering therapy in ACHD patients with PAH. Eisenmenger's syndrome patients due to early adaptation often underestimate the degree to which their symptoms affect their activities.[27] This underestimation can affect their functional classification and thus treatment. It is, therefore, important to have an extensive questionnaire for Eisenmenger's syndrome patients to assess their functional capabilities.[28] Current guidelines recommend that ACHD patients requiring PAH-specific therapy be managed in specialized centers. Guidelines for management

D. Pulmonary arterial hypertension after corrective cardiac surgery	In these cases, congenital heart disease 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 sequelae to previous surgery.

of these patients are generally based on the clinical experience of experts rather than formal evidence from clinical trials, although some data on the use of PAH-specific therapies especially for Eisenmenger's syndrome patients is available.

a The size applies to adult patients.
PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance. From the ESC guidelines on PAH, 2008

General strategies

Behavioral modification, education of potential risk factors and a comprehensive team approach are critical to the management of ACHD patients with PAH. General measures include avoidance of strenuous physical exertion, although mild activity is beneficial, and prevention of dehydration. Patients with Eisenmenger's syndrome are at particular risk during perioperative period, and special care is required to avoid fluid shifts, arrhythmia and infections. Pregnancy is an absolute contraindication in patients with Eisenmenger's syndrome as there is a high risk of maternal and fetal mortality; and thus an effective contraception is mandatory and should be an important part of the discussion during clinic visit. Long-term supplemental oxygen therapy at home may improve symptoms and is recommended only in cases in which it produces a consistent increase in arterial oxygen saturation and reduces symptoms.[8] However, this has not been shown to modify survival, at least when given only at night.[23]

Patients with Eisenmenger's syndrome are at an increased risk of coagulation disorders. The high incidence of spontaneous pulmonary artery thrombosis (up to 20%) is associated with biventricular dysfunction, increasing age and dilatation of the pulmonary arteries.[29] However, the use of anticoagulants in this population is controversial as there is also an increased risk of hemoptysis and hemorrhage.[30] Given the lack of data, guidelines do not recommend the use of anticoagulants in PAH in ACHD patients, but suggest they may be considered in patients with pulmonary artery thrombosis, signs of heart failure and absent or mild hemoptysis.[8] Routine phlebotomy should not be performed as secondary erythrocytosis is beneficial for oxygen transport and delivery.[8] If moderate-to-severe symptoms of hyperviscosity are present, and iron deficiency and

dehydration have been excluded, phlebotomy with isovolumic replacement should be performed carefully when the hematocrit is 65%.[31] Iron deficiency has been shown to be associated with a higher risk of adverse outcomes (all cause mortality, transplantation and hospitalization due to cardiopulmonary causes) in Eisenmenger's syndrome patients[32] and iron replacement therapy improves exercise tolerance and QoL.[33] However, care should be taken in patients with low oxygen saturations to avoid hemoglobin levels becoming too high.[32] There are no data to support the use of calcium channel blockers in ACHD patients with PAH and their use must be avoided.[8] In particular, their use is contraindicated in Eisenmenger's syndrome patients as this treatment class can result in an acute decrease in systemic arterial pressure and increase of the right-to-left shunt, which may lead to syncope and sudden death [18]. Patients who present with significant hemoptysis should be considered for embolization of relevant collateral vessels if appropriate.[34]

Specific therapies

Reflecting available data, current European Society of Cardiology guidelines focus on patients with Eisenmenger's syndrome and recommend that treatment with the endothelin receptor antagonist Bosentan is initiated in Eisenmenger's syndrome patients in functional class III (class I, level of evidence B), with consideration being given to the use of other endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, prostanoids or combination therapy (class IIa, level of evidence C).[31] This difference in recommendation level between Bosentan and the other PAH-specific therapies occurs because only one randomised controlled trial of PAH-specific therapies has been conducted and this involved bosentan. The BREATHE-5 (Bosentan Randomised Trial of Endothelin Antagonist-5) trial and its long-term open-label extension study demonstrated the benefit of Bosentan in patients with Eisenmenger's syndrome in terms of significant improvements in exercise capacity, hemodynamics and functional class compared with placebo, independently of the location of the septal defect.[35-37] Data from a number of studies have since confirmed these benefits in the longer term in ACHD patients with PAH and specifically in patients with Eisenmenger's syndrome.[38-43] Importantly, treatment with Bosentan has been shown not to reduce systemic arterial blood oxygen saturation over short and long-term treatment,[35, 40] demonstrating that it had no negative effect on the overall shunt. Treatment with Bosentan has also been shown to have a positive long-term effect on QoL, a particularly important consideration for Eisenmenger's syndrome

patients.[42] Despite the lack of randomised controlled trials for other PAH-specific therapies, data are available from small, open-label studies; the earliest showing treatment benefit with epoprostenol.[44] Treatment with Sildenafil has been shown to improve exercise capacity, Borg dyspnea score, functional class, QoL and hemodynamics in patients with PAH-ACHD/Eisenmenger's syndrome and appears to be well tolerated,[45-50] while a single study of ambrisentan suggests that this endothelin receptor antagonist may also be beneficial in this patient population.[51] There is clearly an interest in using PAH- specific treatments in patients with PAH-ACHD, but without further randomized controlled studies being initiated, evidence will continue to be based on single center studies. A retrospective case series suggested significant improvement of functional class and exercise capacity after bosentan treatment in patients with segmental PAH. These findings however warrant a prospective study of the potential benefit of selective pulmonary vasodilator therapy in these complex patients.

Combination therapies

Although potentially attractive, there are mixed results from studies investigating the benefits of combination therapy using different classes of PAH-specific therapies. While some studies suggest that the addition of sildenafil to bosentan therapy may improve hemodynamics and exercise capacity [25], others have shown no benefit.[52] However, overall, data suggest that treatment of PAH-ACHD patients with PAH-specific therapy improves outcome. In a retrospective, single-center analysis including 229 patients with Eisenmenger's syndrome, the use of PAH-specific therapies (advanced therapy: Bosentan 73.5%; Sildenafil 25%; Epoprostenol 1.5%) was associated with a significantly lower rate of cumulative mortality over seven years vs. no therapy.[53] To adjust for differences in clinical and demographic characteristics on advanced therapy and those not receiving this form of treatment, propensity scores were calculated with the use of logistic regression with advanced therapy as the dependent variable, and the baseline demographic and clinical variables as independent variable. Each patient on advanced therapy was matched with three patients not on advanced therapy and 10 matched populations were generated. Long-term PAH-specific therapy in patients with Eisenmenger's syndrome has been shown to improve both objective exercise capacity and subjective symptoms, although escalation of therapy over time may be required if symptoms deteriorate during treatment.[54] There are also data to show that PAH-specific therapies increase QoL scores in patients with PAH-ACHD.[42] Heart and lung transplantation is a potential treatment option for

patients with PAH-ACHD, but this is limited by the scarcity of donor organs in developed countries and the lack of organ specificity in developing countries. Although not studied extensively, as a result of the limitations mentioned above, it is possible that the comorbidities experienced by patients with PAH-ACHD may affect the success of transplantation in this patient population.

Unique situations: "Treat to close" consideration

Correction of an underlying congenital heart defect in infancy can prevent the development of PAH in adult life; however, a proportion of patients with left-to-right shunts may get diagnosed only later in their life, when they already have changes to the pulmonary vasculature and increased PVR. In those patients with increased PAP and Qp, but with a PVR within normal limits or only slightly raised, pulmonary vascular changes are likely to be minimal and the patient may benefit from surgery.[55] Conversely, those patients with high PAP and high PVR are likely to have extensive changes to the pulmonary vasculature and corrective surgery is contraindicated. There remains, therefore, a population of patients with medium-to- large defects and moderate increases in PVR in whom the extent of pulmonary vascular changes and their potential to be reversed are unknown and so, in whom, the benefits or otherwise of corrective surgery are unclear. Currently there are no established markers of reversibility, although a number of candidates have been proposed. To date, the most promising marker is the number of circulating endothelial cells. This is a noninvasive marker of vascular damage and remodeling, which has been shown to be significantly raised in ACHD patients with irreversible PAH post-surgery.[56] Further studies are required to confirm whether this is an appropriate marker. There are no evidence-based algorithms to guide assessment for operability in these patients, and decisions need to be made based on careful evaluation of the individual patient.

Prognosis

Biomarker such as high sensitive Troponins have shown to have a bad prognosis in ACHD patients with PAH. Potentially, the detection of elevated hsTnT levels could help clinicians to determine optimal timing to start advanced combination therapy.[57] The measurements of biomarker levels in a single blood sample for functional and prognostic evaluation of PAH patients complies with the guideline-recommended monitoring during visits in a specialized outpatient clinic. The difficulties of using standard measures of prognosis such as functional class and 6MWD, has compelled researches to establish new prognostic indicators of

congestive heart failure in ACHD patients and tailored QoL questionnaires for better assessment with minimal subjective bias.

Conclusions

Medical advances with improvements in the diagnosis and management of CHD have led to a significant increase in the number of patients surviving into adulthood. Early diagnosis and ''timely'' repair still remain the best form of prevention of PAH. Once developed and especially with Eisenmenger's syndrome, these patients show significantly increased morbidity and mortality. Recent pharmacotherapy advancement for PAH-specific therapy has shown to improve exercise capacity and quality of life. Nevertheless, mortality still remains relatively high, and the need for newer therapeutic options and approaches continue. The treat-to-close strategy has added a new dimension in the management of patients with complex defects and borderline elevation of pulmonary vascular resistance. However due to lack of randomized clinical studies, therapy may need to be individualized. Although we are beginning to see progress in the management and treatment of ACHD patients with PAH, future randomized controlled trials may help guide newer therapies that may have a significant impact on the survival of these patients.

References

1. Rodriguez FH 3rd, Moodie DS, Parekh DR, et al. Outcomes of hospitalization in adults in the United States with atrial septal defect, ventricular septal defect, and atrioventricular septal defect. *Am J Cardiol* 2011; 108: 290–293.
2. Lowe BS, Therrien J, Ionescu-Ittu R, et al. Diagnosis of pulmonary hypertension in the congenital heart disease adult population impact on outcomes. *J Am Coll Cardiol* 2011; 58: 538–546.
3. Report of the British Cardiac Society Working Party. Grown-up congenital heart (GUCH) disease: current needs and provision of service for adolescents and adults with congenital heart disease in the UK. *Heart* 2002; 88: Suppl. 1, i1–i14.
4. Diller GP, Gatzoulis MA. Pulmonary vascular disease in adults with congenital heart disease. *Circulation* 2007; 115: 1039–1050.
5. Duffels MG, Engelfriet PM, Berger RM, et al. Pulmonary arterial hypertension in congenital heart disease: an epidemiologic perspective from a Dutch registry. *Int J Cardiol* 2007; 120: 198–204.
6. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006; 173:

1023–1030.

7. Engelfriet PM, Duffels MG, Mo¨ller T, et al. Pulmonary arterial hypertension in adults born with a heart septal defect: the Euro Heart Survey on adult congenital heart disease. *Heart* 2007; 93: 682–687.
8. Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009; 30:2493–2537.
9. Beghetti M, Galiè N. Eisenmenger syndrome a clinical perspective in a new therapeutic era of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 53: 733–740.
10. Collins-Nakai RL, Rabinovitch M. Pulmonary vascular obstructive disease. *Cardiol Clin* 1993; 11: 675–687.
11. Vongpatanasin W, Brickner ME, Hillis LD, et al. The Eisenmenger syndrome in adults. *Ann Intern Med* 1998; 128: 745–755.
12. Diller GP, Dimopoulos K, Broberg CS, et al. Presentation, survival prospects and predictors of death in Eisenmenger's syndrome: a combined retrospective and case-control study. *Eur Heart J* 2006; 27: 1737–1742.
13. Galiè N, Manes A, Palazzini M, et al. Management of pulmonary arterial hypertension associated with congenital systemic-to- pulmonary shunts and Eisenmenger's syndrome. *Drugs* 2008; 68: 1049–1066.
14. Van Loon RL, Roofthooft MT, Hillege HL, et al. Pediatric pulmonary hypertension in the Netherlands: epidemiology and characterization during the period 1991 to 2005. *Circulation* 2011; 124: 1755–1764.
15. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med* 2004; 351: 1425–1436.
16. Haworth SG. Pulmonary hypertension in the young. *Heart* 2002; 88: 658–664.
17. Balint OH, Samman A, Haberer K, et al. Outcomes in patients with pulmonary hypertension undergoing percutaneous atrial septal defect closure. *Heart* 2008; 94: 1189–1193.
18. Hopkins WE. The remarkable right ventricle of patients with Eisenmenger syndrome. *Coron Artery Dis* 2005; 16: 19–25.
19. Hopkins WE, Waggoner AD. Severe pulmonary hypertension without right ventricular failure: the unique hearts of patients with Eisenmenger syndrome. *Am J Cardiol* 2002; 89: 34–38.

20. Eisenmenger V. Die angeborenen Defecte der Kammerscheide-wand des Herzens. *Z Klin Med* 1897; 32: 1–28.
21. Wood P. The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. I. *Br Med J* 1958; 2: 701–709.
22. DeFilippis AP, Law K, Curtin S, et al. Blood is thicker than water: the management of hyperviscosity in adults with cyanotic heart disease. *Cardiol Rev* 2007; 15: 31–34.
23. Somerville J. How to manage the Eisenmenger syndrome. *Int J Cardiol* 1998; 63: 1–8.
24. Daliento L, Somerville J, Presbitero P, et al. Eisenmenger syndrome. Factors relating to deterioration and death. *Eur Heart J* 1998; 19: 1845–1855.
25. D'Alto M, Romeo E, Argiento P, et al. Bosentan-sildenafil association in patients with congenital heart disease-related pulmonary arterial hypertension and Eisenmenger physiology. *Int J Cardiol* 2012; 155: 378–382.
26. Yap SC, Harris L, Chauhan VS, et al. Identifying high risk in adults with congenital heart disease and atrial arrhythmias. *Am J Cardiol* 2011; 108: 723–728.
27. Dimopoulos K, Giannakoulas G, Wort SJ, et al. Pulmonary arterial hypertension in adults with congenital heart disease: distinct differences from other causes of pulmonary arterial hypertension and management implications. *Curr Opin Cardiol* 2008; 23: 545–554.
28. Raphael C, Briscoe C, Davies J, et al. Limitations of the New York Heart Association functional classification system and self- reported walking distances in chronic heart failure. *Heart* 2007; 93: 476–482.
29. Sandoval J, Aguirre JS, Pulido T, et al. Nocturnal oxygen therapy in patients with the Eisenmenger syndrome. *Am J Respir Crit Care Med* 2001; 164: 1682–1687.
30. Broberg CS, Ujita M, Prasad S, et al. Pulmonary arterial thrombosis in Eisenmenger syndrome is associated with biventricular dysfunction and decreased pulmonary flow velocity. *J Am Coll Cardiol* 2007; 50: 634–642.
31. Baumgartner H, Bonhoeffer P, De Groot N, et al. ESC guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010; 31: 2915–2957.
32. Van De Bruaene A, Delcroix M, Pasquet A, et al. Iron deficiency is associated with adverse outcome in Eisenmenger patients. *Eur Heart J* 2011; 32: 2790–2799.
33. Tay EL, Peset A, Papaphylactou M, et al. Replacement therapy for iron deficiency improves exercise capacity and quality of life in patients with

cyanotic congenital heart disease and/or the Eisenmenger syndrome. *Int J Cardiol* 2011; 151: 307–312.

34. Mamas MA, Clarke B, Mahadevan VS. Embolisation of systemic- to-pulmonary collaterals in patients with the Eisenmenger reaction presenting with haemoptysis. *Cardiol Young* 2008; 18: 528–531.
35. Galiè N, Beghetti M, Gatzoulis MA, et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation* 2006; 114: 48–54.
36. Gatzoulis MA, Beghetti M, Galiè N, et al. Longer-term bosentan therapy improves functional capacity in Eisenmenger syndrome: results of the BREATHE-5 open-label extension study. *Int J Cardiol* 2008; 127: 27–32.
37. Berger RM, Beghetti M, Galiè N, et al. Atrial septal defects versus ventricular septal defects in BREATHE-5, a placebo-controlled study of pulmonary arterial hypertension related to Eisenmenger's syndrome: a subgroup analysis. *Int J Cardiol* 2010; 144: 373–378.
38. Diller GP, Dimopoulos K, Kaya MG, et al. Long-term safety, tolerability and efficacy of bosentan in adults with pulmonary arterial hypertension associated with congenital heart disease. *Heart* 2007; 93: 974–976.
39. Diaz-Caraballo E, Gonzalez-Garcia AE, Renones M, et al. Long- term bosentan treatment of complex congenital heart disease and Eisenmenger's syndrome. *Rev Esp Cardiol* 2009; 62: 1046–1049.
40. Monfredi O, Griffiths L, Clarke B, et al. Efficacy and safety of bosentan for pulmonary arterial hypertension in adults with congenital heart disease. *Am J Cardiol* 2011; 108: 1483–1488.
41. D'Alto M, Romeo E, Argiento P, et al. Therapy for pulmonary arterial hypertension due to congenital heart disease and Down's syndrome. *Int J Cardiol* 2011; [Epub ahead of print DOI: 10.1016/ j.ijcard.2011.07.009].
42. Vis JC, Duffels MG, Mulder P, et al. Prolonged beneficial effect of bosentan treatment and 4-year survival rates in adult patients with pulmonary arterial hypertension associated with congenital heart disease. *Int J Cardiol* 2011; [Epub ahead of print DOI: 10.1016/ j.ijcard.2011.06.064].
43. Kaya MG, Lam YY, Erer B, et al. Long-term effect of bosentan therapy on cardiac function and symptomatic benefits in adult patients with Eisenmenger syndrome. *J Card Fail* 2012; 18: 379–384.
44. Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. *Circulation* 1999; 99: 1858–1865.

45. Lu XL, Xiong CM, Shan GL, et al. Impact of sildenafil therapy on pulmonary arterial hypertension in adults with congenital heart disease. *Cardiovasc Ther* 2010; 28: 350–355.
46. Tay EL, Papaphylactou M, Diller GP, et al. Quality of life and functional capacity can be improved in patients with Eisenmenger syndrome with oral sildenafil therapy. *Int J Cardiol* 2011; 149: 372–376.
47. Zhang ZN, Jiang X, Zhang R, et al. Oral sildenafil treatment for Eisenmenger syndrome: a prospective, open-label, multicentre study. *Heart* 2011; 97: 1876–1881.
48. Chau EM, Fan KY, Chow WH. Effects of chronic sildenafil in patients with Eisenmenger syndrome versus idiopathic pulmonary arterial hypertension. *Int J Cardiol* 2007; 120: 301–305.
49. Zeng WJ, Lu XL, Xiong CM, et al. The efficacy and safety of sildenafil in patients with pulmonary arterial hypertension associated with the different types of congenital heart disease. *Clin Cardiol* 2011; 34: 513–518.
50. Mukhopadhyay S, Sharma M, Ramakrishnan S, et al. Phosphodiesterase-5 inhibitor in Eisenmenger syndrome: a preliminary observational study. *Circulation* 2006; 114: 1807–1810.
51. Zuckerman WA, Leaderer D, Rowan CA, et al. Ambrisentan for pulmonary arterial hypertension due to congenital heart disease. *Am J Cardiol* 2011; 107: 1381–1385.
52. Iversen K, Jensen AS, Jensen TV, et al. Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial. *Eur Heart J* 2010; 31: 1124–1131.
53. Dimopoulos K, Inuzuka R, Goletto S, et al. Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. *Circulation* 2010; 121: 20–25.
54. Diller GP, Alonso-Gonzalez R, Dimopoulos K, et al. Disease targeting therapies in patients with Eisenmenger syndrome: response to treatment and long-term efficiency. *Int J Cardiol* 2012; [Epub ahead of print DOI: 10.1016/j.jicard.2012.02.007].
55. Beghetti M, Galiè N, Bonnet D. Can ''inoperable'' congenital heart defects become operable in patients with pulmonary arterial hypertension? Dream or reality? *Congenit Heart Dis* 2012; 7: 3–11.
56. Smadja DM, Gaussem P, Mauge L, et al. Circulating endothelial cells: a new candidate biomarker of irreversible pulmonary hypertension secondary to congenital heart disease. *Circulation* 2009; 119: 374–381.

57. Schuuring MJ, van Riel AC, Vis JC, Duffels MG, van Straalen JP, Boekholdt SM, Tijssen JG, Mulder BJ, Bouma BJ. High-sensitivity Troponin T Is Associated with Poor Outcome in Adults with Pulmonary Arterial Hypertension due to Congenital Heart Disease. *Congenit Heart Dis.* 2012 Dec 14. doi: 10.1111/chd.12022. [Epub ahead of print].

Clinical Topics: **Congenital Heart Disease and Pediatric Cardiology, Diabetes and Cardiometabolic Disease, Prevention, Vascular Medicine, Congenital Heart Disease, CHD & Pediatrics and Prevention, Hypertension**

Keywords: *Early Diagnosis, Eisenmenger Complex, Heart Defects, Congenital, Hypertension, Masked Hypertension, Pulmonary Circulation, Vascular Diseases*