Targeted Pulmonary Arterial Hypertension Therapies and a Combined Medical-Surgical Approach for Congenital Heart Disease Patients

Warren A. Zuckerman, MD
Pulmonary Hypertension Center
Columbia University College of Physicians and Surgeons
New York, NY

Erika B. Rosenzweig, MD
Pulmonary Hypertension Center
Columbia University College of Physicians and Surgeons
New York, NY

Pulmonary arterial hypertension (PAH) with increased pulmonary vascular resistance (PVR) is a frequent complication of congenital heart disease (CHD), most commonly occurring with systemic-to-pulmonary shunt lesions. The natural disease progression involves pulmonary endothelial damage due to exposure to increased pulmonary blood flow and pressure, and in its most severe form results in Eisenmenger syndrome (ES), in which there is shunt reversal and cyanosis. Due to anatomic and histopathologic similarities of PAH in patients with CHD, as well as those with idiopathic and other forms of Group 1 PAH, there is an evolving interest and role for the use of the newer targeted PAH therapies in CHD patients. While early closure of shunt lesions is the best preventive measure, the use of targeted medical therapies when a patient is too high risk for surgery, following surgical repair, and even in those with reversal of shunting due to advanced disease, has emerged over the past decade.

Pulmonary arterial hypertension with increased PVR is a frequent complication of CHD, known as associated pulmonary arterial hypertension (APAH)-CHD.[1,2] This results from pulmonary vascular remodeling due to nonrestrictive, shunt-related increases in pulmonary blood flow (PBF) and/or exposure to increased pulmonary artery pressure (PAP) and sheer stress.[3] While the currently accepted definition of PAH no longer includes elevated PVR, it is very important to determine PVR when evaluating a patient with APAH-CHD, as an isolated elevation in PAP with normal PVR may occur with increased PBF and can be amenable to surgery as opposed to representing true pulmonary vasculopathy. Therefore, these authors continue to use the classic definition of PAH when evaluating APAH-CHD, which includes a mean PAP $\geq$25 mm Hg with normal left-sided filling pressures (left ventricular end-diastolic pressure or pulmonary capillary wedge pressure $\leq$15 mm Hg) and an elevated PVR (PVR indexed to body surface area [PVRI] $>$3 Wood units [WUxm^2]).[4-6] In cases of APAH-CHD, it is also important to differentiate PAH from pulmonary venous hypertension, in which there is increased PAP in the setting of elevated left-sided filling pressures and normal PVR, or a mixed picture with elevation of PAP, left-sided filling pressures, and also PVR. It is critical to distinguish between patients with PAH, pulmonary venous hypertension, and mixed disease (PAH/PVH), as the treatments for these various forms of disease not only vary, but targeted medical therapies may be unsafe in patients with associated postcapillary pulmonary hypertension.

As more patients with CHD are surviving into adulthood, APAH-CHD has become an important medical management issue. The development of PAH in the setting of CHD is partly dependent on the type and size of the cardiac defect, as well as other predisposing environmental and genetic factors. Post-tricuspid valve lesions such as ventricular septal defect (VSD) and patent ductus arteriosus (PDA) are more prone to the development of PAH than pre-tricuspid valve lesions such as atrial septal defect (ASD).[7] With progression of disease in these patients, cyanosis eventually develops as a result of reversal of left to right shunting, and this is known as Eisenmenger syndrome.[7] It is generally believed that in order to avoid the development of pulmonary vascular disease (PVD), nonrestrictive post-tricuspid defects such as large VSDs and PDAs should be repaired prior to 1 or 2 years of age, while ASDs may be repaired later in childhood. In addition, there are more complex cardiac defects that are associated with the early development of PAH. These include truncus arteriosus, transposition of the great vessels (especially in the presence of a VSD), and complete atrioventricular septal defect (especially in the setting of trisomy 21). If these defects are not repaired within the first few weeks of life, severe PVD will almost invariably develop.[8]

The clinical presentation of APAH-CHD can be divided into 4 physiologic subtypes (Table). This clinical classification becomes very important in the management of these patients, as treatment strategies are not necessarily the same for each subtype. The latter 2 categories, PAH in the setting of small defects and PAH after corrective cardiac surgery, are physiologically analogous to idiopathic PAH (IPAH), with respect to the lack of an adequate "pop-off" for the failing right ventricle (RV). These patients are likely at increased risk for more rapidly progressive RV failure and worse outcomes than those patients with adequate RV "pop-off." The medical approach in these patients does not differ from that of other forms of WHO Group 1 PAH, although there are less controlled data on the use of targeted PAH therapies available for such patients.

During the last 2 decades there have been significant improvements in the treatment and outcomes of patients with WHO Group 1 PAH. Nine medications have become available in the United States to target 3 main pathways involved in the pathophysiology of PAH: the prostacyclin, endothelin, and nitric oxide path-

Key Words—associated PAH, Eisenmenger syndrome, endothelin receptor agonist, phosphodiesterase-5 inhibitors, prostanoids
Correspondence: wz2116@columbia.edu

Table: Clinical classification of congenital systemic-to-pulmonary shunts associated with PAH. From Simonneau, et al. 2009[55]

Eisenmenger syndrome	Patients with unrepaired systemic-to-pulmonary shunts resulting from large nonrestrictive defects leading to a severe, progressive increase in PVR, bidirectional shunting, and ultimately reversed shunting with central cyanosis
PAH with moderate to large defects	PVR is mildly to moderately increased, systemic-to-pulmonary shunt is still present, and no cyanosis is present at rest
PAH with small defects	Smaller defects generally include VSD ≤1 cm and ASD ≤2 cm, and clinical picture is similar to IPAH
PAH following corrective cardiac surgery	CHD has been corrected, but PAH is present either immediately after surgery or recurs several months or years after surgery in the absence of significant residual shunts

ways, and treatment options now span the oral, inhaled, subcutaneous, and intravenous routes. Much of the initial testing occurred in small observational trials of APAH-CHD or in patients with Group 1 PAH; however, only a small number of the Group 1 patients included in many of the early landmark trials were APAH-CHD patients. In 1999, Rosenzweig et al reported on the benefits in functional capacity and hemodynamics of long-term intravenous epoprostenol in patients with APAH-CHD,[9] and Simonneau et al reported similar benefits of subcutaneous treprostinil following a 12-week randomized, double-blind, placebo-controlled trial in which 109 of 470 enrolled patients either had repaired or unrepaired congenital shunt lesions.[10] The early, randomized, double-blind, placebo-controlled trials involving the phophodiesterase-5 inhibitors sildenafil (SUPER-1 trial) and tadalafil (PHIRST trial) included 7% and 12% APAH-CHD patients (either ASD or repaired shunt lesions).[11,12] Although the earlier trials involving the endothelin receptor antagonists bosentan and ambrisentan did not include APAH-CHD patients, the first randomized, double-blind, placebo-controlled drug trial solely on ES patients was the BREATHE-5 trial involving bosentan, published in 2006.[13] Due to the similarities in histopathology and pathophysiology within WHO Group 1 PAH patients, including those with IPAH and APAH-CHD, the targeted PAH therapies are often used in the treatment of APAH-CHD patients, as well. However, the absence or small percentage of APAH-CHD patients included in these drug trials underscores the need for future studies designed specifically to study this heterogeneous patient population. Medical management of APAH-CHD patients within the first 2 subtypes of APAH-CHD (Table), those with ES and those with PAH in the setting of unrepaired moderate to large defects, requires additional attention to the impact of residual shunting on medical management. The clinical picture within these groups of patients spans a wide range, and at either end of the spectrum, medical decision making is relatively straightforward. At one end, an infant with a large nonrestrictive VSD will have elevated PAP and normal PVRI (≤3 WUxm^2), and can be treated with surgical closure of the shunt with little fear that PAP will remain elevated postoperatively. On the opposite end of the spectrum are patients with severe pulmonary vasculopathy, or ES, demonstrated by shunt reversal, low PBF, and cyanosis in the setting of elevated PAP and high PVR. In these patients with significantly elevated PVR and reversal of shunting, surgical closure would not be advisable; however, these patients may benefit from some of the newer targeted PAH medical therapies.[13-16] With advances made in targeted PAH therapies, the concept of a combined medical-surgical approach has also become more feasible for subgroup 2 patients (PAH with moderate to large defects in whom PVR is at least mildly increased, systemic-to-pulmonary shunt is still prevalent, and no cyanosis is present at rest), with optimization first medically prior to consideration of surgery. In addition, the idea of a partial repair has emerged in which a fenestration, most commonly an interatrial communication, is left by the surgeon to serve as a "pop-off valve" for the RV.[8] This determination of operability is one of the more challenging and more important aspects of the management of patients with APAH-CHD.

PAH ASSOCIATED WITH CONGENITAL SYSTEMIC TO PULMONARY SHUNTS: PRE-EISENMENGER SYNDROME

For patients with APAH-CHD in the second physiologic subgroup (Table) with mildly to moderately elevated PVR and moderate to large increases in PBF, the determination of operability is based on whether PAH will improve or progress following surgery. While there is no accepted protocol or algorithm to make this determination, a vital tool at the disposal of the cardiologist in such cases is the cardiac catheterization. Although no validated criteria exist for predicting postoperative morbidity and mortality, a complete set of hemodynamics should be obtained, along with acute vasodilator testing and possible balloon occlusion of the defect. In IPAH patients, the most prognostic catheterization data are indices of right heart function, such as cardiac index and right atrial pressure,[17] and PAP is generally less useful for assessing disease severity and prognosis, as it may in fact decrease with worsening right heart failure, due to the RV's inability to generate higher pressure. In shunt lesions, it is important to realize that by having a nonrestrictive VSD or PDA, PAP will be at systemic levels regardless of the PVR. In order to evaluate the degree of PVD, it is important to examine PVR, the ratio of PVR to systemic vascular resistance (SVR), and the ratio of pulmonary to systemic blood flow. In pediatrics, by convention, PVR is indexed to body surface area (PVRI) to allow for a more direct

comparison of hemodynamics between disparately sized patients.[18]

During evaluation of a systemic-to-pulmonary shunt, if there is no evidence of pulmonary venous hypertension once baseline data are collected and PVRI is >3 WUxm^2, acute vasodilator testing should be performed with inhaled nitric oxide or intravenous epoprostenol, during which another full hemodynamic assessment should be performed. Separate assessment with 100% oxygen may be performed, as well. An extensive review of hemodynamic parameters in determining operability in APAH-CHD was recently published by Giglia and Humpl.[19] The authors acknowledged limitations to many of the studies reviewed, and were clear that any parameters be used as a guide within the context of the complete clinical picture. PVRI values in the range of 6 to 8 WUxm^2 or lower are generally considered operable.[19] The ability to lower PVRI to 6 WUxm^2 or lower with vasodilator testing with inhaled nitric oxide +/− oxygen has been associated with better outcomes, as well.[20-22] Additionally, a >10% decrease in PVR and PVR/SVR ratio in response to acute vasodilator testing, with a final PVR/SVR ratio of <0.3 are predictive of better postoperative outcomes.[23,24]

Due largely in part to advances in targeted PAH therapies and studies demonstrating improved hemodynamics in APAH-CHD patients with such therapies, there is an evolving role for a combined medical-surgical approach to those patients that are either borderline operable, or in some cases initially inoperable.[25-28] It is reasonable to treat with targeted therapies for a period of months and reevaluate by catheterization, sometimes requiring serial reevaluations. If medical treatment of a patient with a shunt and moderate PVD is effective, PVR will lower and result in increased PBF. As a result, surgical measures may actually be necessary to protect the pulmonary vasculature from the development of further damage.

Cardiac catheterization alone, however, cannot determine operability, since catheterization data are often obtained under "ideal" resting conditions. While a patient at rest may seem to be operable, with a minor respiratory illness and hypoxic vasoconstriction, it may become evident that a shunt should not be closed, or at least not completely. A thorough medical history and physical examination, and exercise testing when possible, play important roles in the determination of operability. Important elements of the history include age, type of CHD, and time of and circumstances surrounding diagnosis. The importance of the type of CHD has been previously discussed; and in general, the earlier a shunt lesion is diagnosed, the more likely the patient is operable. In addition, a history of cyanosis and/or dyspnea with exertion is important. Signs of cyanosis such as blue lips or nail beds with exercise, clubbing, and erythrocytosis also help provide a complete picture to determine operability.

EISENMENGER SYNDROME

In 1897, Viktor Eisenmenger first described a 32-year-old patient who died of massive hemoptysis and had a VSD on postmortem examination. The term "Eisenmenger syndrome" was coined by Paul Hamilton Wood in 1958 to define the condition of increased PAP and PVR in relation to a VSD with resultant shunt reversal and cyanosis. Subsequently, ES has been used to describe any CHD or shunt between the great arteries with resultant increase in PVR and shunt reversal.[29] Advances in CHD diagnosis and cardiac surgery, especially during infancy and early childhood, have helped to increase the number of CHD patients surviving into adulthood, and decrease the number of patients with ES in the Western world. Only around 5% of adults with CHD will develop PAH.[30] However, in developing countries where patients seek medical care later in life, ES still remains a significant problem. The worldwide prevalence of PAH in adults with CHD has recently been estimated at between 1.6 and 12.5 million, with 25% to 50% presenting with ES.[31] In Latin America, the prevalence of advanced APAH-CHD relative to IPAH at cardiovascular centers is between 2:1 and 3:1.[32]

Although life expectancy is reduced in ES, it is significantly better than IPAH, with many patients surviving into their third and fourth decades,[33] and even some into their seventh decade.[33,34] More than 40% of subjects are expected to be alive 25 years after diagnosis.[7,35] There is some bias in these data as many patients were from the era prior to targeted PAH therapies. As a result, many who died early of severe hypoxemia and RV failure due to advanced ES may not have been included. However, with advances in targeted therapies, the hope is for future improvements to these numbers, supported by a recent study predicting 5-year survival of 95.3% in children with ES.[36]

Conventional Therapies for Eisenmenger Syndrome

Historically, treatment options for ES patients had been limited to palliative therapies and heart-lung transplantation or lung transplantation with surgical correction of a simple shunt. Currently, conventional management is used in combination with targeted PAH therapies. Commonly used conventional therapies may include digoxin, diuretics, and anticoagulation, as well as antiarrhythmics when warranted, although none of these agents have been shown to improve survival in ES. Although supporting evidence is not particularly strong, digoxin is generally used for right heart failure.[37] Diuretics are often employed in this situation, as well; however, they should be used cautiously, as they may reduce plasma volume in patients with erythrocytosis, and also lead to dehydration. Anticoagulation in ES patients is a debatable subject due to increased risks of pulmonary artery thrombosis as well as hemoptysis, stroke, and hemorrhage.[37] Although the benefit of anticoagulation in IPAH patients has been demonstrated,[38,39] no such data exist in ES patients. Given the potential complications, the decision to anticoagulate should be made carefully on an individual, case-by-case basis. Long-term use of oxygen is often employed in ES patients; and while it may be associated with improvement in subjective status, no survival benefit has been reported.[37,40]

ES patients that are chronically cyanotic may develop secondary erythrocytosis. With hemoglobin above 20 g/dL, hyperviscosity symptoms may develop,

including headache, fatigue, and difficulty concentrating. Phlebotomy, combined with isovolumic fluid replacement, is reserved only for patients with symptomatic hyperviscosity and no iron deficiency or dehydration.[41,42] Iron deficiency, often missed in this patient population due to the requirement of a relatively high resting hemoglobin in the setting of chronic cyanosis, is associated with lower event-free survival and higher mortality in ES patients, and should be treated when recognized.[41,43]

Targeted Therapies for Eisenmenger Syndrome

There are emerging data on the use of all 3 main classes of targeted PAH therapies (prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors) for the treatment of ES patients. As opposed to APAH-CHD with moderate PVD, ES patients are unlikely to experience a significant decrease in PVR that would be enough to reverse shunting and allow for surgical correction of CHD. The aim of targeted therapies in these cases is to improve exercise tolerance, hypoxemia, physical capacity, and ultimately survival.

Intravenous epoprostenol has been used in pediatric PAH,[44] and specifically in APAH-CHD,[9,45] leading to improvements in functional capacity, hemodynamics, and survival. In 1999, Rosenzweig et al reported the first benefit of PAH-targeted therapy of any form in this patient population, with improvements in cardiac index, PVR, and quality of life in 20 patients with APAH-CHD.[9] Similarly, in 2003, Fernandes et al demonstrated improvements in functional capacity, oxygen saturation, and hemodynamics in 8 ES patients using epoprostenol.[45] Treatment with epoprostenol requires use of a permanent central venous catheter, which can be problematic in the setting of right to left shunt due to the potential for thromboembolic events. In addition, systemic and local complications may include infections, sepsis, and line breakage with drug interruption. Treprostinil, a similar and longer-acting prostanoid, can be delivered either intravenously, subcutaneously, or by inhalation, and offers potential advantages over epoprostenol in terms of a longer half-life and mode of delivery. Although efficacy and safety has not been fully established in this patient population, open-label multicenter trials involving the intravenous and subcutaneous formulations have included patients with APAH-CHD,[10,46] and the inhaled formulation has recently been FDA-approved for use in patients in WHO Group 1.

The first randomized, double-blind, placebo-controlled study in ES patients was the BREATHE-5 trial, which investigated the efficacy and safety of the dual endothelin receptor antagonist bosentan in adult ES patients.[13] It remains the only trial of its kind dedicated solely to the ES population. During the 16-week study, bosentan significantly reduced PVR and improved PAP and exercise capacity compared to placebo.[13] Longer-term data from the follow-up portion of the study demonstrated continued improvements in exercise capacity and functional class over an additional 24 weeks.[15] Safety findings were of particular importance, given the potential for worsening of right to left shunting in the face of decreased SVR with vasodilator therapies. There was no significant difference in oxygen saturation change between the bosentan and placebo groups during the study period. In addition, there was a worsening of PVR in the placebo group, underscoring the progressive nature of untreated ES. Smaller-scale, open-label studies demonstrate sustained effects over longer periods of time using bosentan in the ES population.[47-49] The selective endothelin receptor antagonist ambrisentan offers potential advantages over bosentan given its selectivity for the endothelin-A receptor, which demonstrates vasoconstrictor effects. Although less studied, ambrisentan has also been noted to be safe and efficacious in APAH-CHD and ES.[28]

Oral sildenafil is the most widely used of the phosphodiesterase-5 inhibitors in the treatment of PAH, and has been used in pediatrics and APAH-CHD, with benefits on exercise capacity and hemodynamics demonstrated.[26,50,51] Singh et al performed a randomized, placebo-controlled, double-blind, crossover study in 10 IPAH and 10 ES patients in 2006, and found that sildenafil significantly improved functional status, exercise capacity, and PAP compared to placebo.[50] Similarly, a recent prospective, open-label, multicenter study out of China on 84 ES patients demonstrated safety and improved functional status, exercise capacity, oxygen saturation, PAP, and PVR after 12 months of sildenafil therapy.[14] Sildenafil also comes in an intravenous form, and there may be a role for its use perioperatively in the intensive care setting. The longer-acting, once-daily dosed tadalafil is less well studied than sildenafil; however, a recent randomized, placebo-controlled, double-blind, crossover study in ES patients also demonstrated safety and short-term improvements in exercise capacity, functional class, oxygen saturation, and hemodynamics after 6 weeks of therapy.[52]

Due to the progressive nature of PAH and the efficacy limitations of each of the drug classes, one of the mainstays of the treatment of PAH has become combination therapy. In this manner, drugs with different mechanisms of action may provide an additive effect, or even the same effect at lower doses. Although data are limited in ES patients, in 2010, Iversen et al performed a randomized, placebo-controlled, double-blind, crossover study evaluating the effect of combination therapy with bosentan and sildenafil in 21 ES patients.[53] In this study, patients were treated with bosentan for 9 months and were then treated for 3 months with sildenafil or placebo, followed by a 3-month crossover. They found improvements in exercise capacity and hemodynamics after treatment with bosentan, but no further benefit after addition of sildenafil, although there was an increase in oxygen saturation and the combination was well tolerated. The future of PAH therapy in ES patients certainly involves evaluation of such combination therapies, as well as studies evaluating cutting-edge, targeted PAH therapies such as oral prostacyclin (selexipag), tissue-targeting endothelin receptor antagonist (macitentan), receptor tyrosine kinase antagonist (imatinib), and soluble guanylate cyclase inhibitor (riociguat).[54] Over the last decade, the outlook for the ES patient has gone

from a "hands-off" strategy to a hopeful one, in the form of targeted PAH agents that may lead to improvements in functional status, exercise capacity, and survival. Further study in clinical trials will be essential for optimization of medical therapies for APAH-CHD over the next decade.

CONCLUSIONS

While PAH associated with CHD is classified with many other subgroups as Group 1 pulmonary hypertension, this group is very heterogeneous in terms of anatomic, physiologic, and clinical features. Improvements in diagnosis and surgery for CHD have dramatically improved the short- and long-term outlook for patients with APAH-CHD. Although advancements in noninvasive imaging such as echocardiography have helped in the evaluation of this patient population, the importance of cardiac catheterization cannot be overstated in helping with management. In addition, the newer targeted PAH therapies appear to have short-term benefits in these patients, but require further investigation, and their use in patients with borderline hemodynamics has paved the way for a combined medical-surgical approach to management in select patients.

References

1. Rose ML, Strange G, King I, et al. Congenital heart disease-associated pulmonary arterial hypertension: preliminary results from a novel registry. *Intern Med J.* 2012;42(8):874-879.
2. Gatzoulis MA, Alonso-Gonzalez R, Beghetti M. Pulmonary arterial hypertension in paediatric and adult patients with congenital heart disease. *Eur Respir Rev.* 2009;18(113):154-161.
3. Fratz S, Geiger R, Kresse H, et al. Pulmonary blood pressure, not flow, is associated with net endothelin-1 production in the lungs of patients with congenital heart disease and normal pulmonary vascular resistance. *J Thorac Cardiovasc Surg.* 2003; 126(6):1724-1729.
4. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol.* 2009; 53(17):1573-1619.
5. 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(20):2493-2537.
6. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest.* 2010; 137(2):376-387.
7. Kidd L, Driscoll DJ, Gersony WM, et al. Second natural history study of congenital heart defects. Results of treatment of patients with ventricular septal defects. *Circulation.* 1993;87(2 Suppl):I38-I51.
8. Rosenzweig EB, Barst RJ. Congenital heart disease and pulmonary hypertension: pharmacology and feasibility of late surgery. *Prog Cardiovasc Dis.* 2012;55(2):128-133.
9. Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. *Circulation.* 1999;99(14):1858-1865.
10. Simonneau G, Barst RJ, Galiè N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med.* 2002;165(6):800-804.
11. Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med.* 2005;353(20):2148-2157.
12. Galiè N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation.* 2009;119(22):2894-2903.
13. 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(1): 48-54.
14. Zhang ZN, Jiang X, Zhang R, et al. Oral sildenafil treatment for Eisenmenger syndrome: a prospective, open-label, multicentre study. *Heart.* 2011; 97(22):1876-1881.
15. 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(1):27-32.
16. 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(1):20-25.
17. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med.* 1991;115(5):343-349.
18. Ofori-Amanfo G, Hsu D, Lamour JM, et al. Heart transplantation in children with markedly elevated pulmonary vascular resistance: impact of right ventricular failure on outcome. *J Heart Lung Transplant.* 2011;30(6):659-666.
19. Giglia TM, Humpl T. Preoperative pulmonary hemodynamics and assessment of operability: is there a pulmonary vascular resistance that precludes cardiac operation? *Pediatr Crit Care Med.* 2010; 11(2 Suppl):S57-S69.
20. Atz AM, Adatia I, Lock JE, Wessel DL. Combined effects of nitric oxide and oxygen during acute pulmonary vasodilator testing. *J Am Coll Cardiol.* 1999;33(3):813-819.
21. Bush A, Busst CM, Haworth SG, et al. Correlations of lung morphology, pulmonary vascular resistance, and outcome in children with congenital heart disease. *Br Heart J.* 1988;59(4):480-485.
22. Neutze JM, Ishikawa T, Clarkson PM, Calder AL, Barratt-Boyes BG, Kerr AR. Assessment and follow-up of patients with ventricular septal defect and elevated pulmonary vascular resistance. *Am J Cardiol.* 1989;63(5):327-331.
23. Berner M, Beghetti M, Spahr-Schopfer I, Oberhansli I, Friedli B. Inhaled nitric oxide to test the vasodilator capacity of the pulmonary vascular bed in children with long-standing pulmonary hypertension and congenital heart disease. *Am J Cardiol.* 1996;77(7):532-535.
24. Balzer DT, Kort HW, Day RW, et al. Inhaled Nitric Oxide as a Preoperative Test (INOP Test I): the INOP Test Study Group. *Circulation.* 2002; 106(12 Suppl 1):I76-I81.
25. Rosenzweig EB, Ivy DD, Widlitz A, et al. Effects of long-term bosentan in children with pulmonary arterial hypertension. *J Am Coll Cardiol.* 2005;46(4):697-704.
26. Humpl T, Reyes JT, Holtby H, Stephens D, Adatia I. Beneficial effect of oral sildenafil therapy on childhood pulmonary arterial hypertension: twelve-month clinical trial of a single-drug, open-label, pilot study. *Circulation.* 2005;111(24):3274-3280.
27. Barst RJ, Ivy D, Dingemanse J, et al. Pharmacokinetics, safety, and efficacy of bosentan in pediatric patients with pulmonary arterial hypertension. *Clin Pharmacol Ther.* 2003;73(4):372-382.
28. Zuckerman WA, Leaderer D, Rowan CA, Mituniewicz JD, Rosenzweig EB. Ambrisentan for pulmonary arterial hypertension due to congenital heart disease. *Am J Cardiol.* 2011;107(9):1381-1385.
29. Vongpatanasin W, Brickner ME, Hillis LD, Lange RA. The Eisenmenger syndrome in adults. *Ann Intern Med.* 1998;128(9):745-755.
30. 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(2):198-204.
31. 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(8): 1049-1066.
32. Lopes AA, Bandeira AP, Flores PC, Santana MV. Pulmonary hypertension in Latin America: pulmonary vascular disease: the global perspective. *Chest.* 2010;137(6 Suppl):78S-84S.
33. Diller GP, Dimopoulos K, Broberg CS, et al. Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: a combined retrospective and case-control study. *Eur Heart J.* 2006; 27(14):1737-1742.

34. Daliento L, Somerville J, Presbitero P, et al. Eisenmenger syndrome. Factors relating to deterioration and death. *Eur Heart J.* 1998;19(12):1845-1855.
35. Saha A, Balakrishnan KG, Jaiswal PK, et al. Prognosis for patients with Eisenmenger syndrome of various aetiology. *Int J Cardiol.* 1994;45(3):199-207.
36. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001-2006. *Heart.* 2009;95(4):312-317.
37. Deanfield J, Thaulow E, Warnes C, et al. Management of grown up congenital heart disease. *Eur Heart J.* 2003;24(11):1035-1084.
38. Frank H, Mlczoch J, Huber K, Schuster E, Gurtner HP, Kneussl M. The effect of anticoagulant therapy in primary and anorectic drug-induced pulmonary hypertension. *Chest.* 1997;112(3):714-721.
39. Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation.* 1984;70(4):580-587.
40. Diller GP, Gatzoulis MA. Pulmonary vascular disease in adults with congenital heart disease. *Circulation.* 2007;115(8):1039-1050.
41. Oechslin E. Hematological management of the cyanotic adult with congenital heart disease. *Int J Cardiol.* 2004;97 Suppl 1:109-115.
42. Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). *Circulation.* 2008;118(23):e714-e833.
43. 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(22):2790-2799.
44. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. *Circulation.* 1999;99(9):1197-1208.
45. Fernandes SM, Newburger JW, Lang P, et al. Usefulness of epoprostenol therapy in the severely ill adolescent/adult with Eisenmenger physiology. *Am J Cardiol.* 2003;91(5):632-635.
46. Tapson VF, Gomberg-Maitland M, McLaughlin VV, et al. Safety and efficacy of IV treprostinil for pulmonary arterial hypertension: a prospective, multicenter, open-label, 12-week trial. *Chest.* 2006; 129(3):683-688.
47. Baptista R, Castro G, da Silva AM, Monteiro P, Providencia LA. Long-term effect of bosentan in pulmonary hypertension associated with complex congenital heart disease. *Rev Port Cardiol.* 2013; Epub ahead of print.
48. 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(5):379-384.
49. Williams R, Houser L, Miner P, Aboulhosn J. Efficacy and safety of bosentan in adults with simple and complex Eisenmenger's syndrome. *Congenit Heart Dis.* 2012;7(1):12-15.
50. Singh TP, Rohit M, Grover A, Malhotra S, Vijayvergiya R. A randomized, placebo-controlled, double-blind, crossover study to evaluate the efficacy of oral sildenafil therapy in severe pulmonary artery hypertension. *Am Heart J.* 2006;151(4): 851.e1-5.
51. Raposo-Sonnenfeld I, Otero-Gonzalez I, Blanco-Aparicio M, Ferrer-Barba A, Medrano-Lopez C. [Treatment with sildenafil, bosentan, or both in children and young people with idiopathic pulmonary arterial hypertension and Eisenmenger's syndrome]. *Rev Esp Cardiol.* 2007;60(4):366-372.
52. Mukhopadhyay S, Nathani S, Yusuf J, Shrimal D, Tyagi S. Clinical efficacy of phosphodiesterase-5 inhibitor tadalafil in Eisenmenger syndrome–a randomized, placebo-controlled, double-blind crossover study. *Congenit Heart Dis.* 2011;6(5):424-431.
53. Iversen K, Jensen AS, Jensen TV, Vejlstrup NG, Sondergaard L. Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial. *Eur Heart J.* 2010;31(9):1124-1131.
54. Yao A. Recent advances and future perspectives in therapeutic strategies for pulmonary arterial hypertension. *J Cardiol.* 2012;60(5):344-349.
55. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol.* 2009;54(1 Suppl):S43-S54.