A Classification System and Treatment Guidelines for PAH Associated with Congenital Heart Disease

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Congenital heart defects are among the most common congenital malformations at birth, with an incidence of approximately 8/1000 live births. These defects are characterized by a heterogeneous group of abnormal communications and connections between the cardiac chambers and great vessels with different hemodynamic consequences and hence, varying need for follow-up and interventions. The most common forms are congenital cardiac systemic to pulmonary shunts (ie, ventricular septal defects, atrial septal defects, patent ductus arteriosus) that account for almost 60 % of congenital cardiac malformations.

Classification

Pulmonary arterial hypertension remains a major complicating factor of many types of congenital heart disease characterized by a systemic to pulmonary shunt either by causing increased morbidity and mortality during or immediately after surgical repair or preventing complete repair for those with advanced pulmonary vascular disease.[1] Apart from the presence of a congenital cardiac defect, with potential mechanistic differences, the histopathological lesions encountered in pulmonary arterial hypertension associated with congenital heart defects (PAH-CHD) are grossly identical to those of idiopathic pulmonary arterial hypertension, and thus the pathobiological mechanisms are thought to be very similar. Based on this, PAH-CHD has been classified in group 1 of the classification made at the third World Symposium on Pulmonary Arterial Hypertension held in Venice (**Table 1**).[2] This classification groups different forms of pulmonary hypertension in order to standardize diagnosis and treatment, with special regard to the new therapies, and allows defining homogenous groups of patients to be enrolled in trials. Because of the great heterogeneity of patients with congenital cardiac shunts, an attempt to subclassify this group of patients was made during the last World Meeting on Pulmonary Hypertension in Venice in 2003 and was then adopted in the Guidelines on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology (**Table 2**).[3] Congenital cardiac shunts are classified according to the type of the defect, the dimension, the presence of associated extra cardiac abnormalities, and the correction status. Any of these factors are relevant for the development of pulmonary vascular disease and thus for prognosis. A further refined subclassification of PAH-CHD should be proposed in the very near future.

One must remember that as for the general pulmonary arterial hypertension classification, the PAH-CHD classification remains a descriptive clinical classification. It is not clear why an individual patient with a defined cardiac malformation will develop rapid and severe pulmonary vascular

Table 1. Diagnostic Classification of Pulmonary Hypertension

Pulmonary arterial hypertension
Idiopathic
Familial
Related to:
- Connective tissue diseases
- HIV infection
- Portal hypertension
- Anorexigens
- Congenital cardiac shunt
Persistent pulmonary hypertension of the newborn
Pulmonary veno-occlusive disease (venular/capillary invasion)
Pulmonary hypertension with left heart disease
Atrial or ventricular
Valvular
Pulmonary hypertension with lung diseases/hypoxemia
Chronic obstructive pulmonary disease
Interstitial lung diseases
Sleep-disordered breathing
Developmental abnormalities
Pulmonary hypertension due to chronic thrombotic and/or embolic disease
Thromboembolic obstruction of proximal pulmonary arteries
Thromboembolic obstruction of distal pulmonary arteries
Nonthrombotic pulmonary embolism
Miscellaneous

Source: Simonneau et al.[2]

Table 2. Guidelines for Classification of Congenital Systemic-to-Pulmonary Shunts

Type
Simple
-Atrial septal defect (ASD)
-Ventricular septal defect (VSD)
-Patent ductus arteriosus
-Total or partial unobstructed anomalous pulmonary venous return
Combined
Describe combination and define prevalent defect, if any
Complex
-Truncus arteriosus
-Single ventricle with unobstructed pulmonary blood flow
-Atrioventricular septal defects

Dimensions
Small (ASD <2.0 cm and VSD <1.0 cm)
Large (ASD >2.0 cm and VSD >1.0 cm)

Associated extracardiac abnormalities

Correction status
Uncorrected
Partially corrected (age)
Corrected spontaneously or surgically (age)

Source: Galie et al.[3]

disease compared to a subject with a similar malformation who will not develop it or develop it at a slower rate. Constitutional factors are suggested, but so far no clear background has been discovered.

Pathophysiology

Intense research activity has led to a better understanding of the pathophysiology of the development of pulmonary vascular disease in congenital cardiac shunt.

In congenital heart defects with significantly increased pulmonary blood flow, progressive anatomic and functional abnormalities of the pulmonary vascular bed occur (**Figure**). This state is characterized by progressive smooth muscle hypertrophy and hyperplasia, intimal proliferation, and pulmonary vasoconstriction. In addition, there are changes in extracellular matrix and adventitia with synthesis and deposition of collagen and elastin.[4] The role of hemodynamics in the development of pulmonary vascular disease has been clearly demonstrated. Endothelial dysfunction occurs before the onset of pulmonary hypertension or histological evidence of smooth muscle dysfunction.[5]

Complex interactions between vasoactive substances produced by the vascular endothelium may in part explain the changes in pulmonary vascular tone. Shear stress has been shown to alter the production of vasoactive substances. Endothelial shear stress is directly proportional to blood flow velocity and is inversely proportional to the radius of the vessel. A high blood flow rate alters the mean shear stress and may directly damage the endothelial cell.[6] This in turn may impair the balance of vasoconstrictor/vasodilator, as well as promitotic and antimitotic functions and lead to smooth

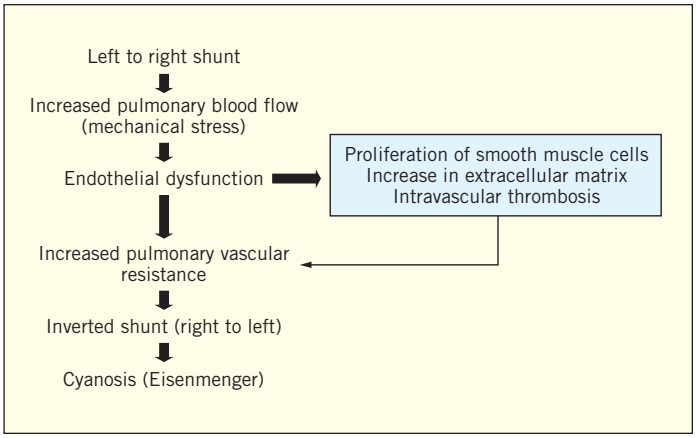

Figure. Pathophysiology leading to the Eisenmenger syndrome.

muscle cell hypertrophy and proliferation. This pathophysiology is very similar to the one postulated for idiopathic pulmonary arterial hypertension; however, the trigger differs, ie, shear stress. Vasoconstriction has correlated to a decreased production of prostacyclin and nitric oxide and an increased production of endothelin-1 and thromboxane A_2.[7-10]

Other additional factors have been suggested to be involved in the process, such as angiopoietin-1,[11] vascular endothelial growth factor,[12] serotonin,[13] TGF-B and its pathway, potassium channel abnormalities,[14] and as mentioned before, genetic or constitutional factors.[15]

The pulmonary vascular remodeling process is reversible in the early stages of the disease but may progress, with continuous stress, to smooth muscle cell proliferation in small arteries. As described before, it provokes changes in the extracellular matrix and adventitia with synthesis and deposition of collagen and elastin; this progression renders the vessels relatively unresponsive to vasodilators and may preclude corrective surgery. The age at which congenital heart lesions cause irreversible pulmonary vascular disease varies. The consequences of increased pulmonary blood flow are more severe in the immature than in the mature animal.[16,17] Endothelial cell morphology is modified as early as 2 months after birth in children with increased pulmonary blood flow. The development of irreversible lesions is also associated with the type of heart defect,[18-20] and it seems that a combination of high pressure and high flow causes more rapid and more severe remodeling. Thus, surgical correction should be performed early in life in children with massive increase in pulmonary blood flow; before 1 year of age for ventricular septal defects and even earlier (before 6 months) for atrioventricular septal defects, transposition of the great arteries with ventricular septal defect,[21] or truncus arteriosus.

Hemodynamics

It is of utmost importance to appraise the cause of pulmonary arterial hypertension in this particular setting. In congenital cardiac shunts, the increase in pulmonary arterial pressure may be due to an increase in pulmonary blood flow and/or an increase in pulmonary vascular resistance. In PAH-CHD echocardiography is essential to define the anatomy and allows measuring pulmonary arterial pressure in most patients. The

Table 3. Pulmonary Arterial Hypertension Associated with Congenital Cardiac Shunts

Group 1
Left to right shunt with high pulmonary blood flow and low pulmonary vascular resistance
-Therapy: surgical repair

Group 2
Bidirectional shunt with normal or slightly increased pulmonary blood flow and moderate increase in pulmonary vascular resistance
-Therapy: none or trial of new therapies

Group 3
Eisenmenger physiology: right to left shunt with decreased pulmonary blood flow and high pulmonary vascular resistance
-Therapy: empirical treatment and trial of new therapies

pulmonary systolic pressure can be measured, as for idiopathic pulmonary arterial hypertension, using the systolic regurgitant tricuspid jet and the Bernoulli equation ($4v^2$ + RAP, where v is the tricuspid jet velocity and RAP the right atrial pressure). RAP is either a standardized value or estimated from the characteristics of the inferior vena cava.[22] When left to right shunts are present such as in ventricular septal defects or patent ductus arteriosus the pulmonary arterial pressure can also be estimated through the measurement of the velocity of the flow crossing the defect, again using the Bernoulli equation. However, high systolic pulmonary arterial pressures are not always associated with high pulmonary vascular resistance, and it is not possible to measure pulmonary vascular resistance accurately with echocardiography. It is therefore understandable that the measurement of pulmonary arterial pressure alone does not give all the information.

In most of the experienced centers, young patients (under 2 years of age) presenting with large left to right shunts and signs of pulmonary overcirculation (dilatation of left cavities, cardiomegaly, etc) are operated on without the use of cardiac catheterization. In other patients this may be less clear and cardiac catheterization is mandatory in order to have pulmonary vascular resistance values before deciding on the therapeutic approach, as discussed later in this review.

Pulmonary vascular resistance cannot be directly measured by catheterization and is calculated as the ratio of the mean fall of pressure across the pulmonary vascular bed divided by the pulmonary blood flow. Pulmonary vascular resistance (R) is therefore derived from the formula PA – LA/Q, where PA is the mean pulmonary arterial pressure, LA the left atrial pressure, and Q the pulmonary blood flow. From this formula (R = P/R) it appears that an increase in pulmonary arterial pressure may be due to an increase in pulmonary blood flow (ie, a left-to-right shunt), an increase in pulmonary vascular resistance, or an increase in pulmonary venous pressure. In summary, there may be an increased pulmonary arterial pressure with normal or decreased pulmonary blood flow with variable degrees of increased pulmonary vascular resistance, or an increased pulmonary blood flow with variable degrees of pulmonary vascular resistance (normal, decreased, or increased). It is consequently understandable that an accurate etiological diagnosis must be done before embarking on treatment.

Management

The most important aspect of the management of PAH-CHD is to perform surgery early in life, before the development of irreversible pulmonary vascular lesions; this allows decreasing morbidity and mortality. On the basis of hemodynamic findings, three different groups of patients, in whom treatment strategies differ, may present with pulmonary arterial hypertension associated with congenital cardiac shunts: 1) patients with increased pulmonary blood flow and low pulmonary vascular resistance allowing for surgical repair, which, as already mentioned, is curative; 2) patients who present later in life with borderline pulmonary vascular resistance and pulmonary vascular disease at high risk for surgical repair, in whom pulmonary vascular lesions may not reverse despite surgical repair and thus potential short-term improvement in quality of life may ultimately lead to decreased survival; and 3) patients with Eisenmenger physiology and advanced pulmonary vascular disease considered inoperable, in whom, until now, treatment was largely empirical (**Table 3**).

Two other groups of patients may present but are not discussed in this review. These are the patients in whom a systemic to pulmonary connection is present but is not responsible for the pulmonary arterial hypertension (ie, restrictive ventricular septal defect or small atrial septal defects) where the pulmonary arterial hypertension should be considered idiopathic. Patients with closed cardiac shunts and persistent pulmonary arterial hypertension despite surgical repair[23] should be considered as having idiopathic pulmonary arterial hypertension as they present the same hemodynamic profile and potential for right ventricular failure, and they should be treated following the usual recommendations.[3]

Group 1: Patients with pulmonary arterial hypertension secondary to increased pulmonary blood flow and low pulmonary vascular resistance usually present with signs of congestive heart failure (tachypnea, dyspnea, failure to thrive, hepatomegaly, and recurrent respiratory tract infections). These patients are usually diagnosed during the first weeks or months of life and surgery (complete correction or palliation with a pulmonary arterial band) avoids the development of pulmonary vascular disease and is a cure when complete corrective surgery is performed. Some of these patients may develop pulmonary hypertensive crisis during the immediate postoperative phase. These episodes may be lethal events. They were particularly frequent but have decreased from 31% in the 1980-84 era to 6.8% in the 1990-94 era[24] and are even less frequent today, in relation to the improvement of surgical techniques and perioperative care. However, acute pulmonary arterial hypertension after surgery may still pose a problem.[25] Fortunately, modern therapies such as the use of inhaled nitric oxide,[26] prostacyclins,[27] or if necessary, extracorporeal membrane oxygenation (ECMO) usually allow treating these previously life-threatening postoperative events. This particular postoperative aspect is not the aim of the present review and will not be discussed further. Clinical and experimental evidence has shown that pulmonary vascular lesions are potentially reversible in these patients if

surgery is performed early in life. Thus, the age at which cardiac surgery is performed is crucial for prognosis. Surgery should be performed before one year and even before 3 to 6 months of age for some defects (truncus arteriosus, atrioventricular septal defects, or transposition of the great arteries with ventricular septal defect) to allow for regression of the lesions.

Group 2: This is a group of patients considered as "borderline" for surgery who may indeed present later in life. Frequently these patients present with reduced exercise capacity rather than with congestive heart failure. This is a difficult group as it may be complex to decide if hemodynamics permit proceeding with surgical repair without having the risk of persistent pulmonary arterial hypertension after surgery. This is a major problem as we may transform a patient with a life expectancy of several decades (Eisenmenger survival)[28] to a patient following the disappointing survival curve of an idiopathic pulmonary arterial hypertension if the pulmonary vascular resistance remains elevated postoperatively. The decision to perform or to prescribe surgery has been based originally on lung biopsy following the classification of Heath-Edwards,[29] according to which patients with grade I to III are considered operable (low resistance, high reserve) since there is the possibility of regression of the lesions, and patients with grade greater than III are considered to be at risk of further progression of the lesions despite surgery. However, one must remember that this study was performed with a particular group of patients aged more than 10 months and is therefore helpful for older patients. There are still controversies about the correlation of histology and hemodynamics. At present most centers rely on the hemodynamics to perform surgery. Catheterization with pulmonary vascular reactivity assessment is performed to evaluate the vasodilator capacity of the pulmonary vascular bed. The lowest pulmonary vascular resistance value obtained is considered for operability. This test is usually performed with inhaled nitric oxide and/or 100% oxygen, but prostacyclin may be used either inhaled or intravenously. There is no definitive cut-off but a pulmonary vascular resistance index of less than 6 $WU*m^2$ and/or a pulmonary over systemic vascular resistance index ratio of less than 0.35 would usually allow for safe complete intracardiac repair.[30] This is clearly not similar for complex congenital heart defects characterized by a single ventricle requiring partial or total cavopulmonary anastomosis, but this is beyond the scope of this review. With the advancement of new therapies (endothelin receptor blockers, phosphodiesterase inhibitors, and prostacyclins) used in other forms of pulmonary arterial hypertension and thought to allow for remodelling of the pulmonary vascular bed, a new concept may be raised and requires further studies. Would it be possible to remodel the pulmonary vascular bed and decrease pulmonary vascular resistance to a level where surgical repair may be performed with low morbidity and mortality, allowing for prolonged survival in borderline cases? Several noncontrolled studies have shown some promise with the dual endothelin receptor blocker bosentan, the phosphodiesterase inhibitor type V sildenafil, and prostacyclins.[31,32]

Group 3: A third group of patients present with the Eisenmenger physiology. The hemodynamics are characterized by decreased pulmonary blood flow and high pulmonary vascular resistance impeding surgery. The progression of the pulmonary vascular lesions has led to an increase in pulmonary vascular resistance sometimes at the level of the systemic vascular resistance, the shunt has reversed and is right to left and as a result the patient is cyanosed. It is well known that surgery (closure of the shunt) will lead to right ventricular failure and death; the shunt indeed acts as a decompressing valve for a right ventricle facing a very high afterload. These patients are cyanosed and most of the problems are related to the resulting polycythemia. As they show a clearly longer survival compared with patients with idiopathic pulmonary arterial hypertension, their therapy has been largely empirical: "Do not harm." Pregnancy and unnecessary surgery should be avoided. The empirical approach includes domiciliary oxygen (which has not shown a definite effect), anticoagulation (which is still controversial), venosection (which may be dangerous because of increased risk of thrombosis and emboli if the patient becomes iron deprived), and diuretics. None is clearly directed to the pulmonary vascular lesions. Most of the so-called vasodilators can cause systemic hypotension and aggravate cyanosis (ie, calcium channel blockers are not used). Recent data have shown that their exercise capacity and quality of life is not so good and finally there is a certain attrition, calling for more directed therapy.[33] Based on the results obtained with the new therapeutic approaches to pulmonary arterial hypertension and on the fact that congenital cardiac shunts are classified in the same group (Venice classification), several uncontrolled trials have shown that bosentan, sildenafil, and prostacyclin may improve exercise capacity in this group of patients.[34,35] However, because of the prolonged survival of these patients improvement in survival will be difficult to show. The first randomized placebo-controlled trial has been performed with bosentan. The drug seems to be safe and has shown beneficial effects in exercise capacity and hemodynamics (decrease in pulmonary vascular resistance) after 16 weeks of treatment.[36] Long-term data are still required to ensure that there is sustained effect. Finally, the only curative therapy is lung or heart/lung transplant or lung transplant with cardiac repair. However, the correct timing of this approach remains difficult to establish. Since results of transplantation remain unsatisfactory it should be decided only when survival is expected to be less than after transplant. It is hoped that the upcoming new therapies will further delay the need for transplantation in these patients.

In conclusion, in patients with pulmonary arterial hypertension associated with congenital cardiac shunts early surgical repair should be performed to avoid progression to pulmonary vascular disease and to allow for complete cure. For other patients with borderline hemodynamics or advanced pulmonary vascular disease the new therapeutic modalities applied for idiopathic pulmonary arterial hypertension are promising, but well-conducted trials should be performed to confirm the encouraging preliminary results. It is predictable that in the near future new approaches to pulmonary vascular disease secondary to congenital cardiac shunts will appear. ■

References

1. Beghetti M. Congenital heart disease and pulmonary hypertension. *Rev Port Cardiol*. 2004;23:273-281.
2. Simonneau G, Galie N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, Gibbs S, Lebrec D, Speich R, Beghetti M, Rich S,

Fishman A. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol.* 2004;43:5S-12S.
3. Galie N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, Olschewski H, Peacock A, Pietra G, Rubin LJ, Simonneau G, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, McGregor K, Morais J, Oto A, Smiseth OA, Barbera JA, Gibbs S, Hoeper M, Humbert M, Naeije R, Pepke-Zaba J. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J.* 2004;25:2243-2278.
4. Granton JT, Rabinovitch M. Pulmonary arterial hypertension in congenital heart disease. *Cardiol Clin.* 2002;20:441-457, vii.
5. Celermajer DS, Cullen S, Deanfield JE. Impairment of endothelium-dependent pulmonary artery relaxation in children with congenital heart disease and abnormal pulmonary hemodynamics. *Circulation.* 1993;87:440-446.
6. Rabinovitch M, Bothwell T, Hayakawa B, Williams W, Trusler G, Rowe R, Olley P, Cutz E. Pulmonary artery endothelial abnormalities in patients with congenital heart defects and pulmonary hypertension. *Lab Inv.* 1986;55:632-653.
7. Adatia I, Barrow SE, Stratton P, Miall-Allen VM, Ritter JM, Haworth SG. Thromboxane A2 and prostacyclin biosynthesis in children and adolescents with pulmonary vascular disease. *Circulation.* 1993;88:2117-2122.
8. Bando K, Vijayaraghavan P, Turrentine MW, Sharp TG, Ensing GJ, Sekine Y, Szekely L, Morelock RJ, Brown JW. Dynamic changes of endothelin-1, nitric oxide, and cyclic GMP in patients with congenital heart disease. *Circulation.* 1997;96:II-346-351.
9. Yoshibayashi M, Nishioka K, Nakao K, Saito Y, Matsumura M, Ueda T, Temma S, Shirakami G, Imura H, Mikawa H. Plasma endothelin concentrations in patients with pulmonary hypertension associated with congenital heart defects. Evidence for increased production of endothelin in pulmonary circulation. *Circulation.* 1991;84:2280-2285.
10. Dinh-Xuan AT, Higenbottam T, Welland C, Pepke-Zaba J, Cremona G, Wallwork J. Impairment of pulmonary endothelium-dependant relaxation in patients with Eisenmenger's syndrome. *Br J Pharmacol.* 1990;99:9-10.
11. Van Beneden R, Rondelet B, Kerbaul F, Ray L. Ang-1/BMPR2 signaling and the expression of MCP-1 and ICAM in overcirculation-induced experimental pulmonary hypertension. *Eur Respir J.* 2004;24:533S.
12. Rondelet B, Kerbaul F, Van Beneden R, Motte S, Fesler P, Hubloue I, Remmelink M, Brimioulle S, Salmon I, Ketelslegers JM, Naeije R. Signaling molecules in overcirculation-induced pulmonary hypertension in piglets: effects of sildenafil therapy. *Circulation.* 2004;110:2220-2225.
13. Rondelet B, Van Beneden R, Kerbaul F, Motte S, Fesler P, McEntee K, Brimioulle S, Ketelslegers JM, Naeije R. Expression of the serotonin 1b receptor in experimental pulmonary hypertension. *Eur Respir J.* 2003;22:408-412.
14. Black SM, Sanchez LS, Mata-Greenwood E, Bekker JM, Steinhorn RH, Fineman JR. sGC and PDE5 are elevated in lambs with increased pulmonary blood flow and pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol.* 2001;281:L1051-1057.
15. Roberts KE, McElroy JJ, Wong WP, Yen E, Widlitz A, Barst RJ, Knowles JA, Morse JH. BMPR2 mutations in pulmonary arterial hypertension with congenital heart disease. *Eur Respir J.* 2004;24:371-374.
16. Bush A, Busst CM, Haworth SG, Hislop AA, Knight WB, Corrin B, Shinebourne EA. Correlations of lung morphology, pulmonary vascular resistance, and outcome in children with congenital heart disease. *Br Heart J.* 1988;59:480-485.
17. Haworth SG. Pulmonary vascular disease in different types of congenital heart disease. *Br Heart J.* 1984;52:557-571.
18. Haworth SG. Pulmonary vascular disease in ventricular septal defect: structural and functional correlations in lung biopsies from 85 patients, with outcome of intracardiac repair. *J Pathol.* 1987;152:157-168.
19. Haworth S, Radley-Smith R, Yacoub M. Lung biopsy findings in transposition of the great arteries with ventricular septal defect:potentially reversible pulmonary vascular disease is not always synonymous with operability. *J Am Coll Cardiol.* 1987;9:327-333.
20. Haworth SG. Pulmonary vascular disease in secundum atrial septal defect in childhood. *Am J Cardiol.* 1982;51:265-272.
21. Newfeld EA, Paul MH, Muster AJ, Idriss FS. Pulmonary vascular disease in complete transposition of the great arteries: a study of 200 patients. *Am J Cardiol.* 1974;34:75-82.
22. Kircher BJ, Himelman RB, Schiller NB. Noninvasive estimation of right atrial pressure from the inspiratory collapse of the inferior vena cava. *Am J Cardiol.* 1990;66:493-496.
23. Sreeram N, Petros A, Peart I, Arnold R. Progressive pulmonary hypertension after the arterial switch procedure. *Am J Cardiol.* 1994;73:620-621.
24. Bando K, Turrentine MW, Sharp TG, Sekine Y, Aufiero TX, Sun K, Sekine E, Brown JW. Pulmonary hypertension after operations for congenital heart disease: analysis of risk factors and management. *J Thorac Cardiovasc Surg.* 1996;112:1600-1607; discussion 1607-1609.
25. Schulze-Neick I, Li J, Penny DJ, Redington AN. Pulmonary vascular resistance after cardiopulmonary bypass in infants: effect on postoperative recovery. *J Thorac Cardiovasc Surg.* 2001;121:1033-1039.
26. Beghetti M, Habre W, Friedli B, Berner M. Continuous low dose inhaled nitric oxide for treatment of severe pulmonary hypertension after cardiac surgery in paediatric patients. *Br Heart J.* 1995;73:65-68.
27. Rimensberger PC, Spahr-Schopfer I, Berner M, Jaeggi E, Kalangos A, Friedli B, Beghetti M. Inhaled nitric oxide versus aerosolized iloprost in secondary pulmonary hypertension in children with congenital heart disease: vasodilator capacity and cellular mechanisms. *Circulation.* 2001;103:544-548.
28. Daliento L, Somerville J, Presbitero P, Menti L, Brach-Prever S, Rizzoli G, Stone S. Eisenmenger syndrome. Factors relating to deterioration and death. *Eur Heart J* 1998;19:1845-1855.
29. Heath D, Edwards JE. The pathology of hypertensive pulmonary vascular disease; a description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. *Circulation.* 1958;18:533-547.
30. Balzer DT, Kort HW, Day RW, Corneli HM, Kovalchin JP, Cannon BC, Kaine SF, Ivy DD, Webber SA, Rothman A, Ross RD, Aggarwal S, Takahashi M, Waldman JD. Inhaled nitric oxide as a preoperative test (INOP Test I): the INOP Test Study Group. *Circulation.* 2002;106:I76-81.
31. Gilbert N, Luther YC, Miera O, Nagdyman N, Ewert P, Berger F, Lange PE, Schulze-Neick I. Initial experience with bosentan (Tracleer) as treatment for pulmonary arterial hypertension (PAH) due to congenital heart disease in infants and young children. *Z Kardiol.* 2005;94:570-574.
32. Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. *Circulation.* 1999;99:1858-1865.
33. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation.* 2005;112:828-835.
34. Gatzoulis MA, Rogers P, Li W, Harries C, Cramer D, Ward S, Mikhail GW, Gibbs JS. Safety and tolerability of bosentan in adults with Eisenmenger physiology. *Int J Cardiol.* 2005;98:147-151.
35 Fernandes SM, Newburger JW, Lang P, Pearson DD, Feinstein JA, Gauvreau K,
Landzberg MJ. Usefulness of epoprostenol therapy in the severely ill adolescent/adult with Eisenmenger physiology. *Am J Cardiol.* 2005;91:632-635.
36. Galiè N, Beghetti M, Gatzoulis M, Granton J, Berger R, Lauer A, Chiossi E, Landzberg M. Breathe-5: bosentan improves hemodynamics and exercise capacity in the first randomized placebo-controlled trial in eisenmenger physiology *Chest Meeting Abstracts.* 200**5**;128: 496S