Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Pulmonary arterial hypertension associated with congenital heart disease

Antonio Lopes, Khalid Alnajashi[1]

Heart Institute, University of São Paulo Medical School, São Paulo, Brazil, [1]Congenital Heart Disease, Prince Sultan Cardiac Center, Riyadh, Saudi Arabia

Address for correspondence:
Prof. Antonio A. Lopes, Professor of Medicine (Cardiology), Heart Institute (InCor), University of São Paulo Medical School, Department of Pediatric Cardiology and Adult Congenital Heart Disease, São Paulo, Brazil.
E-mail: aablopes@usp.br

Submission: 29-03-2014
Accepted: 05-04-2014

Access this article online

Quick Response Code:

Website: www.thoracicmedicine.org

DOI: 10.4103/1817-1737.134015

Abstract:

Congenital heart disease (CHD) with intracardiac/extracardiac shunts is an important etiology of pulmonary arterial hypertension (PAH). The majority of children with congenital cardiac shunts do not develop advanced pulmonary vasculopathy, as surgical repair of the anomalies is now performed early in life. However, if not repaired early, some defects will inevitably lead to pulmonary vascular disease (*truncus arteriosus, transposition of the great arteries* associated with a *ventricular septal defect* (VSD), *atrioventricular septal defects* remarkably in Down syndrome, large, nonrestrictive VSDs, *patent ductus arteriosus* and related anomalies). The majority of patients are now assigned to surgery based on noninvasive evaluation only. PAH becomes a concern (requiring advanced diagnostic procedures) in about 2-10% of them. In adults with CHD, the prevalence of advanced pulmonary vasculopathy (Eisenmenger syndrome) is around 4-12%.[1]

This article will discuss the diagnostic and management approach for PAH associated with CHD (PAH-CHD).

Key words:

Pulmonary arterial hypertension, congenital heart disease, saudi association for pulmonary hypertension guidelines

Congenital heart disease (CHD) with intra/extracardiac shunts is an important etiology of pulmonary arterial hypertension (PAH). The majority of children with congenital cardiac shunts do not develop advanced pulmonary vasculopathy, as surgical repair of the anomalies is now performed early in life. However, if not repaired early, some defects will inevitably lead to pulmonary vascular disease (truncus arteriosus, transposition of the great arteries associated with a ventricular septal defect (VSD), atrioventricular septal defects (AVSDs) remarkably in Down syndrome, large, nonrestrictive VSDs, patent ductus arteriosus and related anomalies). The majority of patients are now assigned to surgery based on noninvasive evaluation only. PAH becomes a concern (requiring advanced diagnostic procedures) in about 2-10% of them. In adults with CHD, the prevalence of advanced pulmonary vasculopathy (Eisenmenger syndrome) is around 4-12%.[1]

Diagnostic Approach to Pulmonary Arterial Hypertension-Adult Congenital Heart Disease

There has been growing interest on the assessment of pulmonary hemodynamics using noninvasive diagnostic methods (Doppler-echocardiography and magnetic resonance imaging in PAH-ACHD patients). A variety of echocardiographic indices derived from right ventricular/pulmonary arterial systolic flow velocity curve have been used for this purpose.[2] Estimates of pulmonary-to-systemic blood flow ratio and vascular resistance ratio (Q_p/Q_s and pulmonary vascular resistance [PVR]/systemic vascular resistance [SVR]) can be obtained as well. However, many of these indices are more physiologically related to the right ventricular function than they are to the PVR itself. Furthermore, a consistent association with outcomes has not been demonstrated yet.

Cardiac catheterization is crucial to define the anatomy in complex anomalies, identify multiple blood flow supplies to the lungs (aortopulmonary collateral vessels), and detect low flow states (for example, in failing Fontan circulation). In all these instances, accurate hemodynamic evaluation using noninvasive methodology is unrealistic. In simple defects, catheterization allows for direct assessment of PVR and PVR/SVR ratio, and the acute response to vasodilators.[3] The general opinion is that the ability to lower PVR significantly is associated with better outcomes. However, controversy remains about vasodilators (90-100% oxygen,

20-80 ppm inhaled nitric oxide, singly/combined), the duration of the test (~10 min), and the interpretation of the results. The exact magnitude of pulmonary vasodilatation to be used as a predictor of a favorable outcome in candidates to surgical treatment has not been defined.[4] Moreover, there are several possible sources of error in calculating the pulmonary blood flow and vascular resistance by the Fick method (thermodilution cannot be used to calculate a "cardiac output" in patients with shunts).[5-7]

Many new recommendations have been made since the last published Saudi Guidelines in 2008.[8] During the fifth world symposium on pulmonary hypertension (World Health Organization) that was held in Nice, France, February-March 2013, the taskforces came up with important recommendations in terms of CHD, two of which can be summarized as follows.

First, pulmonary hypertension (PH) associated with congenital left heart inflow or outflow obstructions will be classified from now on as "Group II" in the general classification of PH, that is, these patients will no longer be considered as PAH patients. The second point refers to the levels of PVR index (PVRi) to be considered as limits for discussion about operability.

The consensus was that a PVRi of <4 Wood units/m^2 should be considered as adequate, and PVRi of >8 Wood units/m^2 should be assumed as likely indicative of inoperability. Levels between 4 and 8 Wood units/m^2 would suggest that patients should be discussed carefully, case by case, on an individual basis [Table 1]. However, this was a general consensus, and there was no specification as to whether these levels should be considered differently in the adult and pediatric populations with CHD.

Recommendations

1. In PAH-ACHD, complete diagnosis is crucial for decision-making (surgery, drug therapy, or both). This includes a report of age, associated syndromes, the presence/absence of congestive heart failure and failure to thrive, systemic oxygen saturation at rest and during exercise (upper and lower extremities), detailed anatomy, and the direction of flow across the defects (class of recommendation I; level of evidence C).
2. Noninvasive measurements/parameters can be of help for repeated evaluations over the course of treatments, but cannot be used alone for decision-making (class of recommendation IIa; level of evidence B).
3. Catheterization and the acute pulmonary vasodilator test are essential not strictly for decision about operability, but for an appropriate establishment of the whole therapeutic strategy, which includes surgery (if so), drug administration or the combination of both (class of recommendation IIa; level of evidence B).
4. Cardiac catheterization should be considered in all patients without clinical evidence of left-to-right shunting causing congestive heart failure (pulmonary congestion) (class of recommendation IIa; level of evidence C).
5. Preoperative testing with vasodilators is reasonable, but parameters/values that correlate with outcomes remain unclear (class of recommendation IIa; level of evidence B).
6. A ≥ 20% decrease in PVRi and PVR/SVR ratio from baseline, during inhalation of 20-40 ppm nitric oxide, with lowest levels of <4 Wood units/m^2 and <0.3 respectively is likely associated with a lower risk of serious postoperative complications (biventricular repair), but should not be considered alone (class of recommendation I; level of evidence B).

Table 1: Criteria for closing cardiac shunts in PAH patients associated with CHD

PVRI wood units/m^2	PVR wood units	Operability
<4	<2.3	Yes
>8	>4.6	No
4-8	2.3-4.6	Individual patient evaluation

PAH = Pulmonary arterial hypertension, CHD = Congenital heart disease, PVRi = Pulmonary vascular resistance index

Operability and management of postoperative pulmonary hypertension

When deciding about operability in patients with PAH-ACHD, one must consider that it is not synonymous of reversibility of pulmonary vasculopathy. Some patients are at risk of marked elevations of pulmonary artery pressure after weaning from cardiopulmonary bypass or subsequently will have persistent PAH late after repair. Those subjected to percutaneous repair are free from pump-related disturbances, but not from residual elevation of pulmonary artery pressure. Thus, considering a given patient as operable means that surgery can be performed with an acceptable risk, and he or she is likely to improve substantially on a long-term basis, even in the presence of residual PH.

There is no single preoperative index that can predict outcomes accurately. Although, there is general agreement that data collected during cardiac catheterization can help, no precise correlation has been found between preoperative hemodynamics and prognosis in PAH-ACHD.[4] There has been a consensus of opinion that a PVRi of <4 Wood units/m^2 during the RHC should be adopted to assign patients to operation.[9] According to more stringent criteria, patients (especially the pediatric population) with a baseline PVRi of >6 Wood units/m^2 should be considered for surgery only in the presence of a ≥20% decrease in PVR and PVR/SVR ratio during nitric oxide inhalation (20-40 ppm), with respective lowest levels of <6 Wood units/m^2 (preferably <4 Wood units/m$^{2)}$ and <0.3.[3,10,11] However, patients with elevated PVRi (e.g. a PVR of >8 units/m^2 or a PVR/SVR ratio of >0.5) should not be directly assigned to surgery, even in the presence of a positive vasodilator response.

Adults with atrial septal defects are expected to have improvement of the functional status if preoperative pulmonary artery systolic pressure, PVRi, and the pulmonary-to-systemic blood flow ratio are <70 mm Hg, <7 Wood units/m^2, and >2, respectively.[11,12]

Operability cannot be defined purely on the basis of catheterization data. An ideal candidate to surgical treatment should be young at presentation, with congestive heart failure and failure to thrive in the clinical history, absence of comorbidities or associated syndromes, predominant left-to-right shunting across the communication, and absence of systemic oxygen desaturation. Besides, with growing interest

on the use of the new therapies for PAH in subjects with PAH-ACHD, the response to a mid-term trial will likely provide useful information for decision-making.

Once decision to operate is made, immediate postoperative care becomes critical, as severe hemodynamic disturbances (life-threatening pulmonary hypertensive crises in around 1% of cases) cannot be precisely predicted.[13] Patients particularly at risk of having crises are those older at repair, with a high degree of pulmonary vasoreactivity, with an extra-cardiac syndrome, and an elevated pulmonary venous or left atrial pressure.[14] Specific postoperative measures include the use of a pulmonary arterial catheter in selected cases, the use of narcotics and muscle relaxation, avoidance of low cardiac output (epinephrine if necessary), hypoxia and acidosis, and the use of hyperoxic alkalosis (pH ≥7.4 or 7.5), inhaled nitric oxide and sildenafil.[14-16]

Recommendations

1. Early cardiac surgical repair has been considered as the only way to effectively reduce the risk of postoperative PH in patients with congenital cardiac shunts. Early repair is particularly recommended for subjects with truncus arteriosus, transposition of the great arteries with a VSD, complete AVSD, and large, nonrestrictive VSD (class of recommendation I; level of evidence B).
2. Preoperative cardiac catheterization should be considered for all patients without clinical evidence of left-to-right shunting causing pulmonary congestion (class of recommendation IIa; level of evidence C).
3. A positive response to pulmonary vasodilators suggests that pulmonary vasculopathy is not advanced, although it is not necessarily predictive of a favorable outcome (class of recommendation IIa; level of evidence B).
4. Because the precise values of these parameters that best correlate with early and late outcomes remain unclear, decision to operate must be made on an individual basis, taking into consideration all diagnostic data obtained from noninvasive and invasive evaluation (class of recommendation I; level of evidence C).
5. Direct measurement of pulmonary artery pressure using a pulmonary arterial catheter is recommended if the mean pulmonary pressure is 50-60% of the systemic mean pressure after weaning from cardiopulmonary bypass, or specific vasodilator therapy is used in the operating room. However, there has been no evidence that measurements improve outcomes (class of recommendation I; level of evidence C).
6. Avoiding low cardiac output, hypoxia and acidosis, and the use of narcotics and muscle relaxation are important postoperative adjunctive measures to avoid pulmonary hypertensive crises (class of recommendation I; level of evidence B).
7. In patients with postoperative PAH, inhaled nitric oxide (2-20 ppm) decreases pulmonary artery pressure and vascular resistance, and may prevent pulmonary hypertensive crises and shorten time to reach extubation criteria. Sildenafil prevents rebound PH after weaning from inhaled nitric oxide, and reduces the time of mechanical ventilation and intensive care unit stay (class of recommendation I; level of evidence B).

Possibilities of combining medical and surgical therapeutic strategies

The vast majority of CHD with intracardiac or extracardiac communications are now amenable to correction in the 1st days, weeks or months of life, with low incidence of residual PH. In about 2-10% of cases; however, PH (sometimes severe and life-threatening) constitutes a real problem in the early or late postoperative course. Before the era of the so-called advanced therapies for PAH, the risk of serious postoperative events (including right cardiac failure and death) in patients with elevated PVRi (for example, higher than 10 Wood units/m^2, PVR/SVR >0.5) was close to 20% or even higher depending on the report.[10,17,18] On the other hand, some adolescents and adults with moderate to severe PAH-ACHD (not yet characterized as Eisenmenger syndrome) may develop a hyperkinetic state with increased pulmonary blood flow while on treatment with the "new drugs" for PAH, requiring consideration about surgery. Although the combination of medical (drug) and surgical therapies seems attractive and logical in these instances, there is a long way ahead and many problems to be solved before high-level recommendations can be developed. In young patients, the current suggestion is that a trial with a PAH drug (or drugs) could be the third step in the characterization of operability, after complete noninvasive evaluation (first step, including careful clinical history, physical examination and detailed echocardiographic analysis) and cardiac catheterization (second step, including the acute pulmonary vasodilator test). However, the usefulness of this approach needs to be confirmed.

There has been scarce literature on the possibility of combining drug and surgical therapies in PAH-ACHD, essentially case reports, mostly involving atrial septal defect repair in adults (generally percutaneous repair).[19,20] On the other hand, regardless of the publication type, results obtained in adults cannot be directly transposed to the pediatric population, and the risk of percutaneous repair is not equivalent to the risk of on-pump cardiac surgery.

The goals to be achieved must be clearly specified. "To render potentially operable patients better surgical candidates" (with either normalization or just improvement of pulmonary hemodynamics) is not the same as "to make inoperable cases become operable". While there has been opinion that patients with a PVRi in the range of 4-8 Wood units/m^2 may improve and some will eventually normalize, those in the range of 9-12 Wood units/m^2 are far less likely to normalize.[21] Currently, there are no data to support the concept that patients with PVRi close to the systemic level (for example, a young patient with PVRi > 15 units/m^2 and PVR/SVR > 0.75) will benefit from surgical treatment on a long-term basis.[11] Of course, these are just numbers, and should be looked on with caution. Other variables are likely to influence outcomes: Age at surgery, the severity of pulmonary vasculopathy (as determined by lung biopsy in selected cases), the presence or absence of associated syndromes and the complexity of the underlying cardiac anomaly.

Recommendations

1. Until evidence is available, decision to combine drug and surgical therapies in PAH-ACHD must be individualized and based on complete diagnostic evaluation, including cardiac catheterization. Using full diagnostic data, one

Table 2: Major steps in the management of the eisenmenger syndrome

Counseling, therapeutic measures and parameter control	Rationale	Class of recommendation/level of evidence
Lifestyle: Appropriate occupations and avoidance of dehydration (particularly in long flights)	Prevention of hyperviscosity-related complications	I/C
Contraception and avoidance of pregnancy	Reduction of maternal and fetal mortality	I/B
Infections: Vigilance, prophylaxis and immunization	Prevention of influenza and pneumococcal infections, endocarditis and brain abscess	I/B
Control of hematocrit, blood viscosity and iron stores (replenishment). Mild isovolemic hemodylution in symptomatic patients	Prevention and treatment of hyperviscosity-related symptoms and thrombosis	I/B
Chronic anticoagulation with warfarin	Management of intrapulmonary thrombosis	IIa/B
Oxygen therapy	Improvement of symptoms and oxygen saturation	IIa/B
Advanced therapies for patients with class III/IV symptoms	Improvement of the physical capacity, quality of life, hemodynamics and survival	I/B
Transplantation in highly symptomatic patients	Improvement of symptoms and quality of life	IIa/B
Antiarrhythmic drugs and implantable defibrillators	Prevention of hemodynamic disturbances/ deterioration and sudden death	IIa/B

should try to differentiate between patients who are likely to have complete hemodynamic normalization after surgery, those who may improve albeit without normalization, and those for whom the risks clearly outweigh the potential benefits (class of recommendation I; level of evidence C).

2. Currently, there is no evidence to support the recommendation of a "treat-and-repair" approach for patients with PAH-ACHD. Decision must be made on a strictly individual basis (class of recommendation I; level of evidence C).
3. Long-term follow-up is needed, since late postoperative PH may occur even in patients who have normalization of pulmonary hemodynamics, for example, 1 year after repair (class of recommendation I; level of evidence B).

Advanced pulmonary arterial hypertension-adult congenital heart disease

The Eisenmenger syndrome is the most advanced form of PAH-ACHD. Patients have pulmonary artery pressure and PVR close to or above the systemic level, systemic oxygen desaturation (right-to-left shunting), decreased exercise capacity, and a number of conditions and complications associated to erythrocytosis and increased blood viscosity (including pulmonary and systemic thrombosis, cerebrovascular events and bleeding episodes). Other complications are: Hyperuricemia, gout, cholelithiasis, pulmonary and systemic infection (including cerebral abscess) and arrhythmias.[8,22,23] The contemporary prevalence among adults with CHD is around 4%,[22] but frequencies of around 12% have been reported.[1] Survival rates from diagnosis are 50-80% at 10 years, and 40-50% at 20-25 years,[24,25] but probably severely ill pediatric patients are missing. In terms of diagnosis, the armamentarium must cover all of the associated conditions and potential complications mentioned above.[19-23]

The general therapeutic measures [Table 2] remain central.[18,20-25] With growing interest on the use of the so-called specific target therapies for PAH, prostanoids, endothelin receptor antagonists and phosphodiesterase inhibitors have been attempted.[20] In the only multicenter, randomized, placebo-controlled study available in the literature, a beneficial effect of bosentan was demonstrated on the physical capacity and hemodynamics, without deterioration in oxygen saturation.[26] Advanced therapies for PAH (including the three classes of drugs mentioned above) have proved beneficial in improving survival in the Eisenmenger syndrome.[27] Lung transplantation with repair of the underlying cardiac defect or heart and lung transplantation may improve symptoms and the quality of life in highly symptomatic patients with a short life expectancy.[20]

References

1. Engelfriet PM, Duffels MG, Möller T, Boersma E, Tijssen JG, Thaulow E, *et al*. Pulmonary arterial hypertension in adults born with a heart septal defect: The Euro Heart Survey on adult congenital heart disease. Heart 2007;93:682-7.
2. Nakahata Y, Hiraishi S, Oowada N, Ando H, Kimura S, Furukawa S, *et al*. Quantitative assessment of pulmonary vascular resistance and reactivity in children with pulmonary hypertension due to congenital heart disease using a noninvasive method: New Doppler-derived indexes. Pediatr Cardiol 2009;30:232-9.
3. Lopes AA, O'Leary PW. Measurement, interpretation and use of haemodynamic parameters in pulmonary hypertension associated with congenital cardiac disease. Cardiol Young 2009;19:431-5.
4. 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:S57-69.
5. Berger RM. Possibilities and impossibilities in the evaluation of pulmonary vascular disease in congenital heart defects. Eur Heart J 2000;21:17-27.
6. Wilkinson JL. Haemodynamic calculations in the catheter laboratory. Heart 2001;85:113-20.
7. Lopes AA, Dos Anjos Miranda R, Gonçalves RC, Thomaz AM. A computer-based matrix for rapid calculation of pulmonary hemodynamic parameters in congenital heart disease. Ann Thorac Med 2009;4:124-7.
8. Idrees MM, Al-Hajjaj M, Khan J, Al-Hazmi M, Alanezi M, Saleemi S, *et al*. Saudi guidelines on diagnosis and treatment of pulmonary arterial hypertension. Ann Thorac Med 2008;3:1-57.
9. Gatzoulis MA, Alonso-Gonzalez R, Beghetti M. Pulmonary arterial hypertension in paediatric and adult patients with congenital heart disease. Eur Respir Rev 2009;18:154-61.
10. Balzer DT, Kort HW, Day RW, Corneli HM, Kovalchin JP, Cannon BC, *et al*. Inhaled nitric oxide as a preoperative test (INOP Test I): The INOP Test Study Group. Circulation 2002;106:I76-81.

11. Feinstein JA. Evaluation, risk stratifi cation, and management of pulmonary hypertension in patients with congenital heart disease. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2009;12:106-11.
12. Attie F, Rosas M, Granados N, Zabal C, Buendía A, Calderón J. Surgical treatment for secundum atrial septal defects in patients >40 years old. A randomized clinical trial. J Am Coll Cardiol 2001;38:2035-42.
13. Lindberg L, Olsson AK, Jögi P, Jonmarker C. How common is severe pulmonary hypertension after pediatric cardiac surgery? J Thorac Cardiovasc Surg 2002;123:1155-63.
14. Adatia I, Beghetti M. Immediate postoperative care in pulmonary hypertension associated with congenital heart disease. Cardiol Young 2009;19 E-Suppl 1:23-7.
15. Miller OI, Tang SF, Keech A, Pigott NB, Beller E, Celermajer DS. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: A randomised double-blind study. Lancet 2000;356:1464-9.
16. Namachivayam P, Theilen U, Butt WW, Cooper SM, Penny DJ, Shekerdemian LS. Sildenafil prevents rebound pulmonary hypertension after withdrawal of nitric oxide in children. Am J Respir Crit Care Med 2006;174:1042-7.
17. Bush A, Busst CM, Haworth SG, Hislop AA, Knight WB, Corrin B, *et al*. Correlations of lung morphology, pulmonary vascular resistance, and outcome in children with congenital heart disease. Br Heart J 1988;59:480-5.
18. Kannan BR, Sivasankaran S, Tharakan JA, Titus T, Ajith Kumar VK, Francis B, *et al*. Long-term outcome of patients operated for large ventricular septal defects with increased pulmonary vascular resistance. Indian Heart J 2003;55:161-6.
19. Dimopoulos K, Giannakoulas G, Wort SJ, Gatzoulis MA. 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;23:545-54.
20. Dimopoulos K, Peset A, Gatzoulis MA. Evaluating operability in adults with congenital heart disease and the role of pretreatment with targeted pulmonary arterial hypertension therapy. Int J Cardiol 2008;129:163-71.
21. Lopes AA. Pre-operative pulmonary hypertension in congenital heart disease, and aspects of the Eisenmenger syndrome. In: Beghetti M, Barst R, Humpl T, Berger R, Ivy D, Schulze-Neick I, editors. Pediatric Pulmonary Hypertension. Munich: Elsevier Urban & Fischer; 2011. In press.
22. Diller GP, Gatzoulis MA. Pulmonary vascular disease in adults with congenital heart disease. Circulation 2007;115:1039-50.
23. Vongpatanasin W, Brickner ME, Hillis LD, Lange RA. The Eisenmenger syndrome in adults. Ann Intern Med 1998; 128:745-55.
24. Kidd L, Driscoll DJ, Gersony WM, Hayes CJ, Keane JF, O'Fallon WM, *et al*. Second natural history study of congenital heart defects. Results of treatment of patients with ventricular septal defects. Circulation 1993;87:I38-51.
25. Oya H, Nagaya N, Uematsu M, Satoh T, Sakamaki F, Kyotani S, *et al*. Poor prognosis and related factors in adults with Eisenmenger syndrome. Am Heart J 2002;143:739-44.
26. Galiè N, Beghetti M, Gatzoulis MA, Granton J, Berger RM, Lauer A, *et al*. Bosentan therapy in patients with Eisenmenger syndrome: A multicenter, double-blind, randomized, placebo-controlled study. Circulation 2006;114:48-54.
27. Dimopoulos K, Inuzuka R, Goletto S, Giannakoulas G, Swan L, Wort SJ, *et al*. Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. Circulation 2010;121:20-5.

How to cite this article: Lopes A, Alnajashi K. Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Pulmonary arterial hypertension associated with congenital heart disease. Ann Thorac Med 2014;9:S21-5.

Source of Support: Nil, **Conflict of Interest:** None declared.