

Pulmonary Arterial Hypertension in Adults With Congenital Heart Disease

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Pulmonary arterial hypertension is a chronic, persistent elevation in pulmonary artery pressure without evidence of left heart failure. Pulmonary hypertension is common in patients with adult congenital heart disease and is usually the result of an increase of pulmonary blood flow through a large left to right shunt. This condition is progressive and patients are symptomatic and usually die between the third and fifth decades of life. To date, there is no standardized treatment for this condition and a general policy of non-intervention to avoid destabilization of the balanced physiology is recommended. Intravenous prostanooids have been shown to have an effect but they are invasive and associated with major side effects. Lung and combined heart and lung transplantation might be a therapeutic option for selected patients. However, donor shortage is a major issue. Oral advanced therapies have been recently shown to improve haemodynamics and survival in idiopathic pulmonary hypertension or in pulmonary hypertension related to scleroderma and may have a role in patients with pulmonary hypertension secondary to congenital heart disease.

Key words: *Congenital heart disease. Pulmonary arterial hypertension. Eisenmenger syndrome.*

Hipertensión arterial pulmonar en adultos con cardiopatía congénita

La hipertensión arterial pulmonar es un cuadro de elevación persistente y crónica de la presión en la arteria pulmonar sin evidencia de insuficiencia cardíaca izquierda. La hipertensión pulmonar es frecuente en los pacientes adultos con cardiopatía congénita y suele ser el resultado del aumento del flujo sanguíneo pulmonar debido a la existencia de un cortocircuito izquierda-derecha de gran tamaño. Este trastorno es progresivo y los pacientes sintomáticos suelen fallecer entre el tercero y el quinto decenios de la vida. Hasta el momento, no se ha establecido un tratamiento estandarizado para este cuadro y se recomienda en términos generales un manejo conservador para evitar la desestabilización de una situación fisiológica equilibrada. Se ha demostrado que las prostaglandinas administradas por vía intravenosa pueden ser útiles, pero éste es un tratamiento limitado por su carácter invasivo y la asociación de efectos adversos importantes. El trasplante pulmonar y el trasplante combinado de corazón-pulmón podrían constituir una opción terapéutica en pacientes seleccionados, pero está limitado por la escasez de donantes. Recientemente, se ha demostrado que diversos tratamientos orales avanzados mejoran la hemodinámica y la supervivencia en pacientes con hipertensión pulmonar idiopática o con hipertensión pulmonar secundaria a esclerodermia, de manera que también podrían ser útiles en los pacientes con hipertensión pulmonar secundaria a una cardiopatía congénita.

Palabras clave: *Cardiopatía congénita. Hipertensión arterial pulmonar. Síndrome de Eisenmenger.*

Pulmonary arterial hypertension is a chronic, persistent elevation in pulmonary artery pressure without

evidence of left heart failure and is defined as any elevation of mean pulmonary artery pressure greater than 25 mm Hg at rest or 30 mm Hg with exercise. Pulmonary hypertension is common in patients with adult congenital heart disease (about 10%) and is usually the result of an excessive pulmonary blood flow early in life through a pre-existing large systemic-to-pulmonary circulation communication (left to right shunt). With time, when pulmonary arterial pressure reaches systemic levels, there is reversal of the direction of the shunt (bidirectional or right to left), resulting in hypoxemia and cyanosis. This situation, known

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TABLE 1. Poor Prognostic Markers in Adults With Eisenmenger Syndrome

Younger age at presentation
Complex congenital heart disease
Down syndrome
Right ventricular hypertrophy on surface electrocardiogram
Elevated mean atrial pressure
Reduced systemic blood flow
Poor functional capacity
Syncope
Supraventricular arrhythmia

as Eisenmenger syndrome, is at the extreme end of the spectrum of pulmonary hypertension and involves about 1%-2% of patients of congenital heart disease cohorts.

Congenital heart defects leading to pulmonary hypertension can be simple (atrial septal defect, ventricular septal defect, patent ductus arteriosus) or complex (atrioventricular septal defect, truncus arteriosus, "univentricular" heart). Establishment of pulmonary vascular obstructive disease depends on the size, location, and quantity of blood flow through the communication and the degree of pressure overload on the pulmonary vascular bed. Eisenmenger syndrome is established in almost every patient with truncus arteriosus, in 50% of those with a ventricular septal defect and only in 10% of patients with atrial septal defect, the latter are subjected mainly to volume rather than pressure and volume overload. Furthermore, some atrial septal defects with reversed shunting may represent idiopathic pulmonary hypertension coincidental with an intraatrial communication. Chronic exposure of the pulmonary vasculature to increased blood flow produces endothelial cell damage and release and activation of factors that ultimately lead to vasoconstriction and structural changes (intimal fibrosis, medial hypertrophy, and increased production of extracellular matrix in the adventitia). The structural changes are similar to those seen in other forms of pulmonary arterial hypertension and result in increased pulmonary vascular resistance and pulmonary arterial pressure. Proliferative changes are usually not reversible once developed.

Symptoms are related to a reduced cardiac output, congestive heart failure, arrhythmias, and hypoxemia. Patients usually have a good functional capacity up to the second decade of life but subsequently there is a progressive reduction of exercise tolerance and progressive cyanosis. The estimated survival for this cohort is 75% at 30 years and 55% at 50 years.¹ Survival of patients with Eisenmenger syndrome is better than those with idiopathic pulmonary hypertension. In a cohort of 100 patients with pulmonary

arterial hypertension, 37 of them with Eisenmenger syndrome, survival was 97% at 1 year, 89% at 2 years and 77% at 3 years in patients with Eisenmenger syndrome. In contrast, survival for patients with idiopathic pulmonary hypertension was 77%, 69%, and 35% respectively.² Sudden cardiac death accounts for two thirds of deaths in the Eisenmenger cohort. Other common causes of death are congestive heart failure and occasionally massive haemoptysis. General prognosis is related both to the severity of the pulmonary hypertension and to the underlying congenital heart disease. Predictors of bad prognosis are younger age at presentation, complex congenital heart disease, poor functional capacity, syncope, supraventricular arrhythmia, elevated mean atrial pressure, and Down syndrome^{1,3,4} (Table 1). Prognosis in patients with Eisenmenger syndrome is also related to the degree of hypoxemia. In cyanotic patients, compensatory mechanisms to increase the tissue oxygen delivery take place. Secondary erythrocytosis, consisted of an increase in the number of blood red cells, is a physiologic response to chronic hypoxemia. Erythrocytosis is different from polycythemia, a haematologic disorder with an increase not only of the red blood cells but also of the white blood cells and platelets. Chronic hypoxemia and erythrocytosis may result in complications related to different organs and systems such as haematologic, coagulation, renal, gastrointestinal, nervous system, etc (Table 2). Haemostatic abnormalities are of particular interest in this respect. Eisenmenger syndrome has been associated with both bleeding and thrombotic diathesis. Patients may experience superficial bleeding of skin or mucosae on one hand. On the other hand, up to two thirds of patients may present thrombus in the proximal pulmonary arteries. Pulmonary arterial thrombus can be the source for distal embolus or cause asphyxic death by increasing flow resistance—when marked—and thus, by augmenting right to left shunt leading to profound cyanosis.⁵

There is no standardized therapy for patients with Eisenmenger syndrome. The mainstay of management is to avoid any factor that may destabilize the balanced physiology.^{6,7} Dehydration, high altitude, and moderate to severe isometric exercise should be avoided. Pregnancy is strictly contraindicated for these patients, as it still carries a 30%-50% mortality risk. Relative anaemia secondary to iron deficiency should be treated with iron replacement. Routine phlebotomy compromises oxygen tissue delivery and should be abandoned (indicated only for symptomatic hyperviscosity syndrome with simultaneous isovolumic fluid replacement). Non-cardiac surgery of any kind is associated with a relatively high mortality and should be performed only when necessary.⁸ Air filters should be incorporated in all intravenous lines. The use of nocturnal oxygen has shown to be

TABLE 2. Multisystem/Organ Involvement in Eisenmenger Syndrome

Haematologic and haemostatic abnormalities
Secondary erythrocytosis
Iron deficiency
Hyperviscosity syndrome
Minor bleeding: dental bleeding, epistaxis, menorrhagia
Major bleeding: haemoptysis, gastrointestinal bleeding, cerebral haemorrhage
Pulmonary arterial thrombosis
Neurological disorders
Stroke
Transient ischaemic attack
Hypertrophic pulmonary osteoarthropathy
Hyperuricemia and gout
Renal dysfunction
Proteinuria
Renal failure
Gastrointestinal: cholelithiasis
Dermatological: acne
Infections
Bacterial infectious disease: brain abscess, endocarditis, pneumonia
Viral infections
Arrhythmias
Supraventricular tachycardia
Ventricular tachycardia
Right heart failure

of some benefit in children with congenital heart disease and pulmonary hypertension but it did not prove to be of benefit in adults with Eisenmenger physiology.⁹ Currently, oxygen therapy is not routinely recommended, although still employed on an ad hoc basis. Anticoagulation is also a challenge in terms of when to start therapy and how best to implement it (monitoring can be problematic due to presence of secondary erythrocytosis). The latter is further complicated by the known predisposition of patients with Eisenmenger syndrome to both a thrombotic and bleeding diathesis. In contrast to patients with idiopathic pulmonary hypertension, whereas anticoagulation has been shown to improve survival, the role of anticoagulation in patients with Eisenmenger syndrome remains unclear. Intrapulmonary thrombus, however, is common in Eisenmenger patients^{5,10} thus further studies in this field are clearly required.

New forms of advanced medical therapies are now being tried in patients with Eisenmenger physiology with the aim of reducing pulmonary vascular resistance, improving cardiac output, and functional class. Most of these drugs have been tested and shown to be beneficial in patients with idiopathic pulmonary hypertension or pulmonary hypertension secondary to other causes such as scleroderma. General application of these drugs in patients with congenital heart disease and pulmonary hypertension, extrapolating

information from studies in idiopathic pulmonary hypertension, is inappropriate at this stage, however. Ideally, advanced therapies for Eisenmenger patients should be employed within research protocols with the possible exemption of severely limited patients who experience further clinical deterioration. Nifedipine demonstrated a small but significant increase in exercise tolerance¹¹ and decrease in pulmonary vascular resistance in children in a small group of patients.¹² Nitric oxide is a highly selective pulmonary vasodilator with no haemodynamic effects on the systemic circulation^{13,14} but administration difficulties in the use of this gas has relegated it to responsiveness test for identification of patients who might benefit from other forms of vasodilator treatment. Sildenafil, a selective inhibitor of the cyclic guanosine monophosphate (c-GMP)-specific phosphodiesterase type 5, decreases the degradation of cGMP. This results in the local release of nitric oxide and vasodilatation. Intravenous sildenafil has shown to be as effective as inhaled nitric oxide as a pulmonary vasodilator in children with congenital heart disease.¹⁵ Experience in adults with congenital heart disease is very limited. As yet, no long-term survival benefits following sildenafil treatment have been demonstrated. Another group of drugs are the prostanoids. Prostacyclin or epoprostenol is a potent short-acting vasodilator that has been shown to improve haemodynamics, exercise performance, and survival in patients with idiopathic pulmonary hypertension.¹⁶ Epoprostenol is also shown to improve hemodynamic parameters (lower pulmonary vascular resistance and increase cardiac output) and quality of life in patients with pulmonary hypertension secondary to congenital heart disease.¹⁷ However, side effects (nausea, vomiting, dizziness, light headedness, and flushing) and the high rate of complications related to the need for continuous intravenous administration (risk of infection, catheter thrombosis, and rebound symptoms if the infusion is stopped) limit its use. To avoid the shortcomings of intravenous administration, newer forms of prostacyclin are being developed including inhaled, subcutaneous and oral forms. Iloprost, an aerosolized prostaglandin, has shown to improve the exercise capacity and right sided haemodynamics in patients with idiopathic pulmonary hypertension.¹⁸ Unfortunately, the short half life of the drug requiring frequent inhalations and the general side effects of the prostaglandins also limit its general use. Endothelin (ET-1) is a potent vasoconstrictor and mytogen. ET-1 levels are increased in patients with pulmonary hypertension.¹⁹ Bosentan is an oral, non selective dual endothelin receptor antagonist that causes vasodilatation in both the pulmonary and systemic circulation. Studies in patients with idiopathic pulmonary arterial hypertension or scleroderma have shown improvement in pulmonary

hemodynamics, exercise capacity and functional class.^{20,21} Preliminary data from a recent intention to treat pilot study involving 10 patients with Eisenmenger physiology suggest that bosentan is safe and well tolerated in adult patients. Oxygen saturations were maintained and the 6-minute-walk test and pulmonary haemodynamics seemed to improve after 3 months of Bosentan therapy.²² The BREATHE-5, an ongoing multicentre randomized placebo-control trial is expected to shed light on the potential role of bosentan for patients with pulmonary arterial hypertension secondary to congenital heart disease.

Lung transplantation with repair of a simple cardiac defect, or heart and lung transplantation if the cardiac anatomy is complex, or right ventricular dysfunction is advanced, should be considered for severely limited patients with an expected one year survival of less than 50%. Timing and patient selection for transplantation must, therefore, be evaluated very carefully as survival after lung or heart and lung transplantation may be worse than survival without transplantation. Quality of life, however, improves following transplantation. One-year survival for combined heart and lung transplantation is 70% and 55% for lung transplantation alone.²³

SUMMARY

Eisenmenger syndrome is a multisystem disorder that merits a multidisciplinary approach in tertiary centres by physicians understanding the complex pathophysiology of these challenging patients. The mainstay of therapy remains avoidance of mistakes—such as routine phlebotomy—and paying special attention to situations, which are usually well tolerated in the general congenital heart population but are of high risk in Eisenmenger patients (e.g. pregnancy or non cardiac surgery). Currently, there are promising new drugs that may delay or reverse the progression of pulmonary vascular disease and improve quality of life and survival in patients with pulmonary hypertension secondary to congenital heart disease. Additional studies addressing this specific patient group with pulmonary arterial hypertension secondary to congenital heart disease are clearly warranted and are currently under way.

Appendix

We wish to take the opportunity to invite our Spanish colleagues working in the field of adult congenital heart disease to join the International Society for Adult Congenital Cardiac Disease (ISACCD) <http://www.isaccd.org>.

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