Pulmonary Arterial Hypertension in Adults With Congenital Heart Disease

Beatriz Bouzas, a,b and Michael A. Gatzoulis b

a Servicio de Cardiología, Complejo Hospitalario Universitario Juan Canalejo, A Coruña, Spain.
b Adult Congenital Heart Programme, Royal Brompton Hospital and National Heart & Lung Institute, Imperial College, London, United Kingdom.

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 prostanoids 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.

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...
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. 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. 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.

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. 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. Air filters should be incorporated in all intravenous lines. The use of nocturnal oxygen has shown to be
however, is common in Eisenmenger patients. Anticoagulation in patients with Eisenmenger syndrome 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 and may require treatment with anticoagulants.

New forms of advanced medical therapies are now being tried in patients with Eisenmenger syndrome. These therapies include vasodilators, oxygen therapy, and epoprostenol. Vasodilators are used to decrease pulmonary vascular resistance and improve exercise capacity. Oxygen therapy is used to decrease right-sided cardiac work and improve exercise capacity. Epoprostenol is a prostacyclin analogue that is approved for use in Eisenmenger syndrome. It is a potent pulmonary vasodilator that can improve exercise capacity and survival in patients with Eisenmenger syndrome.

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. 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 and further studies in this field are clearly required.

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hemodynamics, exercise capacity and functional class. 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. 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.

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.

REFERENCES


