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Management of Pulmonary Arterial Hypertension Associated with Congenital Systemic-to-Pulmonary Shunts and Eisenmenger's Syndrome

Nazzareno Galie,[1] *Alessandra Manes*,[1] *Massimiliano Palazzini*,[1] *Luca Negro*,[1] *Alessandro Marinelli*,[1] *Simona Gambetti*,[1] *Elisabetta Mariucci*,[2] *Andrea Donti*,[1] *Angelo Branzi*[1] and *Fernando M. Picchio*[2]

1 Institute of Cardiology, University of Bologna, Bologna, Italy
2 Pediatric Cardiology, University of Bologna, Bologna, Italy

Contents

Abstract

A large proportion of patients with congenital heart disease (CHD), in particular those with relevant systemic-to-pulmonary shunts, will develop pulmonary arterial hypertension (PAH) if left untreated. Persistent exposure of the pulmonary vasculature to increased blood flow, as well as increased pressure, may result in pulmonary obstructive arteriopathy, which leads to increased pulmonary vascular resistance that, if it approaches or exceeds systemic resistance, will result in shunt reversal. Eisenmenger's syndrome, the most advanced form of PAH associated with CHD, is defined as CHD with an initial large systemic-to-pulmonary shunt that induces severe pulmonary vascular disease and PAH, with resultant reversal of the shunt and central cyanosis.

The histopathological and pathobiological changes seen in patients with PAH associated with congenital systemic-to-pulmonary shunts, such as endothelial dysfunction of the pulmonary vasculature, are considered similar to those observed in idiopathic or other associated forms of PAH. A pathological and pathophysiological classification of CHD with systemic-to-pulmonary shunt leading to PAH has been developed that includes specific characteristics, such as the type, dimensions and direction of the shunt, extracardiac abnormalities and repair status. A clinically oriented classification has also been proposed.

The prevalence of PAH associated with congenital systemic-to-pulmonary shunts in Western countries has been estimated to range between 1.6 and 12.5 cases per million adults, with 25–50% of this population affected by Eisenmenger's syndrome.

Clinically, Eisenmenger's syndrome presents with multiple organ involvement, with progressive deterioration of function over time. The signs and symptoms of Eisenmenger's syndrome in the advanced stages include central cyanosis, dyspnoea, fatigue, haemoptysis, syncope and right-sided heart failure. Survival of patients with Eisenmenger's syndrome is clearly less than that of the general population, but appears to be better than that of patients with idiopathic PAH in a comparable functional class.

The treatment strategy for patients with PAH associated with congenital systemic-to-pulmonary shunts and, in particular, those with Eisenmenger's syndrome is based mainly on clinical experience rather than being evidence based. General measures include recommendations for physical activity, pregnancy, infections, air travel, exposure to high altitudes and elective surgery, and that psychological assistance be provided as necessary. Phlebotomies are required only when hyperviscosity of the blood is evident, usually when the haematocrit is

>65%. The use of supplemental oxygen therapy is controversial and it should be used only in patients in whom it produces a consistent increase in arterial oxygen saturation. Oral anticoagulant treatment with warfarin can be initiated in patients with pulmonary artery thrombosis and absent, or only mild, haemoptysis.

The following three classes of drugs targeting the correction of abnormalities in endothelial dysfunction have been approved recently for the treatment of PAH: (i) prostanoids; (ii) endothelin receptor antagonists; and (iii) phosphodiesterase-5 inhibitors. The efficacy and safety of these compounds have been confirmed in uncontrolled studies in patients with PAH associated with corrected and uncorrected congenital systemic-to-pulmonary shunts, as well as in patients with Eisenmenger's syndrome. One randomized controlled trial reported favourable short- and long-term outcomes of treatment with the orally active dual endothelin receptor antagonist bosentan in patients with Eisenmenger's syndrome. Lung transplantation with repair of the cardiac defect or combined heart-lung transplantation are options for Eisenmenger's syndrome patients with a poor prognosis. A treatment algorithm based on the one used in the treatment of PAH patients is proposed for patients with PAH associated with corrected and uncorrected congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome.

Congenital heart disease (CHD) is a common defect, with an incidence of approximately 1% in newborns. Pulmonary hypertension (PH) is a pathophysiological condition characterized by an increase in mean pulmonary pressure above the arbitrary limit of 25 mmHg.[1] PH may complicate CHD by two mechanisms, namely (i) left-sided heart lesions (post-capillary PH); or (ii) systemic-to-pulmonary shunts (pre-capillary PH), the latter being considered the more frequent. In fact, it is well known that, if left untreated, a large proportion of patients with CHD with relevant systemic-to-pulmonary shunts will develop pulmonary arterial hypertension (PAH). The most advanced form, comprising all systemic-to-pulmonary shunts leading to PAH that result in reversed (pulmonary-to-systemic) or bidirectional shunt, is known as Eisenmenger's syndrome, which was first described more than 100 years ago.[2] Advances in diagnostic procedures and cardiac surgery have resulted in the prevention of PAH in most children with CHD and congenital shunts in Western countries but, unfortunately, this is not yet the case in developing countries. Furthermore, a significant proportion of CHD patients who are treated successfully and survive into adulthood[3] may develop PAH.[4-6]

In the clinical classification of PH,[7] patients with congenital systemic-to-pulmonary shunts are included in group I, as part of the associated PAH (APAH) subgroup. In fact, apart from the presence of the congenital heart defect and its pathophysiological consequences, the histopathological changes associated with APAH are identical to those seen in other forms of PAH and all forms share similar causative pathobiological mechanisms. However, the monoclonal endothelial cell proliferation found in idiopathic PAH has not been confirmed in the other types of PAH,[8] suggesting possible differences in the altered cellular growth mechanisms.

1. Classifications of Congenital Systemic-to-Pulmonary Shunts Leading to Pulmonary Arterial Hypertension (PAH)

1.1 Pathological–Pathophysiological Classification

A pathological and pathophysiological classification of CHD with systemic-to-pulmonary shunts leading to PAH was proposed at the Third World Symposium on PAH in Venice in 2003. This classi-

Table I. Pathological–pathophysiological classification of congenital systemic-to-pulmonary shunts associated with pulmonary arterial hypertension (modified from the classification developed in Venice 2003)[7]

1. Type
Simple pre-tricuspid shunts
Atrial septal defect (ASD)
ostium stecundum
sinus venosus
Total or partial unobstructed anomalous pulmonary venous return
Simple post-tricuspid shunts
Ventricular septal defect (VSD)
Patent ductus arteriosus
Combined shunts
Describe combination and define predominant defect
Complex congenital heart disease
Atrioventricular septal defects
partial (Ostium primum ASD)
complete
Truncus arteriosus
Single ventricle physiology with unobstructed pulmonary blood flow
Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent ductus arteriosus
Other
2. Dimension (specify for each defect if more than one congenital heart defect)
Haemodynamic
Restrictive (pressure gradient across the defect)
Non-restrictive
Anatomical
Small to moderate (ASD ≤2 cm and VSD ≤1 cm)
Large (ASD >2 cm and VSD >1 cm)
3. Direction of shunt
Predominantly systemic-to-pulmonary
Predominantly pulmonary-to-systemic
Bidirectional
4. Associated extracardiac abnormalities
5. Repair status
Unoperated
Palliated (specify type of operation/s, age at surgery)
Repaired (specify type of operation/s, age at surgery)

fication system was relatively simple and highlighted the following four factors with diagnostic, prognostic and therapeutic implications: (i) type; (ii) dimensions; (iii) associated extracardiac anomalies; and (iv) correction status.[7] However, the heterogeneity of CHD and the complex haemodynamic and pathophysiological interactions require a more detailed description in order to appropriately define each condition. Table I provides an update to the Venice 2003 classification:[9,10] the original configuration is maintained, even when additional characteristics have been included. Recently, additional comments and refinements have also been proposed.[11,12]

1.1.1 Type

PAH and Eisenmenger's syndrome can be caused by both simple or complex (approximately 30% of patients) congenital heart defects.[13] Of the simple defects, ventricular septal defects (VSD) appear to be the most frequent, followed by atrial septal de-

fects (ASD) and patent ductus arteriosus (PDA).[13] It is estimated that 10% of patients with VSD of any size who are older than 2 years can develop Eisenmenger's syndrome, compared with 4–6% of patients with ASD.[14,15] Of patients with large defects, almost all of those with truncus arteriosus, 50% of those with VSD and 10% of those with ASD will develop PH.[16] Of patients with ASD, the incidence of PH is greater in those with sinus venosus defects (16%) compared with those with ostium secundum defects (4%).[17] The simple defects category has been divided further into in pre- and post-tricuspid shunts. The incidence of PAH pre-tricuspid shunts, which induce predominantly a volume overload on the right ventricle and on the pulmonary circulation (ASD and anomalies in pulmonary veins), is lower than that of post-tricuspid shunts, which produce a combined pressure and volume overload (mainly large VSD, PDA and atrioventricular septal defects).

1.1.2 Dimension

The development of PAH is also related to the size of the defect. In fact, only 3% of patients with small to moderately sized VSD develop PAH.[18,19] In contrast, 50% of patients with larger defects (>1.5 cm in diameter) will develop PAH. In the case of small defects, defined as VSD <1 cm and ASD <2 cm effective diameter, as assessed by echocardiography, the exact pathophysiological role of the heart defect in the development of PAH is not known. Note, this definition of a 'small' defect, adopted in the Venice 2003 classification, is based on both old epidemiological data and expert opinion, and may be considered somewhat arbitrary.[20] The dimension of the defect is described not only by its anatomical size, but also by its haemodynamic consequences. In fact, the presence of a pressure gradient defines a smaller restrictive defect compared with a larger non-restrictive defect that does not induce any pressure gradient. A combined description of the anatomical size of the defect and the presence and/or absence of a pressure gradient provides a more accurate definition of the extent of the shunt.

1.1.3 Direction of the Shunt

The direction of the shunt is included in the classification system because this information is relevant for the definition of the pathophysiology of Eisenmenger's syndrome (predominantly pulmonary-to-systemic or bidirectional shunt) compared with other defects with PAH in which there is a predominant systemic-to-pulmonary shunt.

1.1.4 Extracardiac Abnormalities

The description of associated extracardiac abnormalities, such as the presence of Down's syndrome, is important for obvious clinical and prognostic reasons.

1.1.5 Repair Status

In some patients, severe PAH can be detected after successful correction or palliation of the heart defect. In many of these patients, it is not clear whether irreversible pulmonary vascular lesions were already present before surgical intervention or whether the pulmonary vascular disease has progressed despite successful correction or palliation.

1.1.6 Additional Assessments

From the clinical viewpoint, this descriptive classification needs to be completed in individual patients with additional functional (WHO functional class and exercise capacity, as assessed by the 6-minute walk distance or cardiopulmonary exercise test), haematological (haematocrit, arterial oxygen saturation at rest and on exercise) and haemodynamic (pressures, flows and resistances) information.

In fact, functional class and functional capacity, as assessed by the 6-minute walk test and/or the cardiopulmonary exercise test, define the limitations of these patients. Oxygen saturation (both at rest and at peak exercise), haematocrit and haemodynamic parameters (pulmonary and systemic pressures, flows and resistance, right and left atrial and ventricular pressures) are additional important factors affecting prognosis and therapeutic decision making.

1.2 Clinical Classification

The pathological and pathophysiological classification allows a precise description of the anatomical

Table II. Clinical classification of congenital systemic-to-pulmonary shunts associated with pulmonary arterial hypertension

A. Eisenmenger's syndrome
Large defects and reversed (pulmonary-to-systemic) or bidirectional shunt, cyanosis, secondary erythrocytosis, etc.
B. Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts
Moderate to large septal defects, largely prevalent, systemic-to-pulmonary shunt, arterial oxygen saturation >90%
C. Pulmonary arterial hypertension with small septal defects
Clinical and pathophysiological pictures similar to those of idiopathic pulmonary arterial hypertension

and haemodynamic changes caused by systemic-to-pulmonary shunts that lead to PAH, but may be too complex for use in clinical practice. In addition, the percentage of patients with different types and sizes of systemic-to-pulmonary defects who go on to develop PAH has been derived on the basis of old studies with heterogeneous definitions of PH. Despite the clinical pictures of these patients representing a continuum of possibilities, three well defined phenotypes can be recognized (see table II).

1.2.1 Eisenmenger's Syndrome

The classical clinical picture of Eisenmenger's syndrome[2] comprises all systemic-to-pulmonary shunts caused by large defects, leading to a marked increase in pulmonary vascular resistance (PVR), which becomes similar to systemic vascular resistance, resulting in a reversed (pulmonary-to-systemic) or bidirectional shunt. Usually, after birth, a period of right-sided heart failure, which eventually reverses, is detected. Post-tricuspid shunts are the most frequent defects in these patients and there is multiple organ involvement (see section 4).

1.2.2 PAH Associated with Systemic-to-Pulmonary Shunts

In patients with PAH associated with systemic-to-pulmonary shunts caused by moderate to large septal defects, the increase in PVR is mild to moderate, the systemic-to-pulmonary shunt is still largely prevalent and no cyanosis is present at rest (arterial oxygen saturation >90%). Pre-tricuspid shunts are the most frequent defects and, in these patients, a late reversal of the shunt (pulmonary-to-systemic) may be initiated by an increase in right atrial pressure as a result of right ventricular failure.

1.2.3 PAH with Small Septal Defects

In patients with PAH caused by small septal defects (usually VSD <1 cm and ASD <2 cm effective diameter), the clinical picture is very similar to that of idiopathic PAH; cyanosis, if present, is mild and there is no multiple organ involvement. In this form, which can be considered an overlap between idiopathic PAH and PAH associated with systemic-to-pulmonary shunts, the relevance of the heart defect in the development of PAH is unclear.

Eisenmenger's syndrome and PAH associated with systemic-to-pulmonary shunts, when included in clinical trials, are usually defined as 'PAH associated with CHD', whereas PAH with small septal defects may be included as part of the idiopathic PAH group.

2. Epidemiology

In the Euro Heart Survey registry on adult patients with CHD, of 1897 patients with heart septal defects, 28% had PH and 7.1% had Eisenmenger's syndrome.[4,6] In a more recent survey,[5] the prevalence of PAH among 1824 adult CHD patients with septal defects was 6.1%, whereas 3.5% had Eisenmenger's syndrome.

The prevalence of PAH associated with CHD in the general population can be extrapolated from data of registries focusing on the entire spectrum of PAH. In the French registry,[21] the prevalence of PAH ranges from 5 to 25 cases per million adults (low average 15 cases per million), whereas in the Scottish registry[22] the prevalence of PAH ranges from 26 to 52 cases per million. In the French registry, 11.3% of patients with PAH had associated CHD, compared with 24% in the Scottish registry. Taking these figures together, the approximate prevalence of patients with PAH associated with CHD in Western countries may range between 1.6 and 12.5 cases per million adults, with 25–50% of this population affected by Eisenmenger's syndrome. The limita-

tions related to these data are due to the multiple assumptions adopted to generate the figures.

3. Pathobiology and Pathophysiology

The pathological obstructive changes in the microcirculation of patients with PAH associated with uncorrected or corrected CHD with systemic-to-pulmonary shunts are considered to be virtually identical to those observed in other forms of PAH.[23] Consequently, the pathobiological changes observed in other types of PAH may also play a role in PAH associated with CHD.[24] Initiating processes may include shear stress and circumferential stress exerted on the pulmonary endothelium by increased pulmonary flow and pressure typical of the early stages of CHD with systemic-to-pulmonary shunts (figure 1). These stimuli may induce endothelial dysfunction, which leads to chronically impaired production of vasodilators, such as nitric oxide and prostacyclin, along with overexpression of vasoconstrictors, such as thromboxane A_2 and endothelin.[25] Many of these abnormalities both elevate vascular tone and promote vascular remodelling. The process of pulmonary vascular remodelling involves all layers of the vessel wall and it is characterized by proliferative and obstructive changes that involve several cell types, including endothelial cells, smooth muscle cells and fibroblasts.[23,24] In addition, in the adventitia, there is increased production of extracellular matrix, including collagen, elastin, fibronectin and tenascin.[26] Moreover, angiopoietin-1, an angiogenic factor produced by smooth muscle cells and precursor pericytes that is essential for vascular lung development, seems to be upregulated in cases of PAH (including Eisenmenger's syndrome), correlating directly with the severity of the disease.[27]

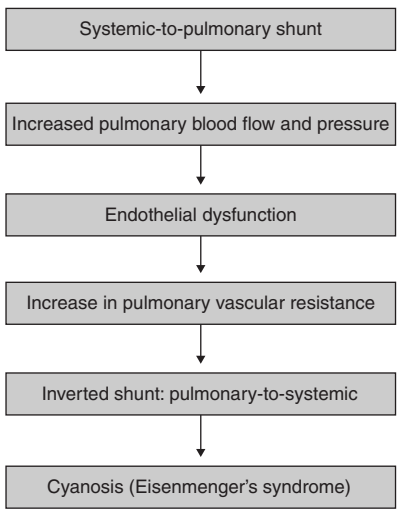

Fig. 1. Pathophysiological cascade in patients with pulmonary arterial hypertension associated with congenital heart defects and systemic-to-pulmonary shunts.

In pre-tricuspid shunts, the initial systemic-to-pulmonary shunting (figure 1) induces an increase in pulmonary blood flow and a mild elevation in pulmonary arterial pressure with normal or reduced PVR (hyperkinetic pulmonary circulation). Unrestricted post-tricuspid shunts may lead to large pulmonary left-to-right shunts and low PVR, without (at least initially) pulmonary vascular disease (hyperkinetic PH). Persistent exposure of the pulmonary vasculature to increased blood flow, as well as increased pressure, may result in pulmonary obstructive arteriopathy, which leads to increased PVR (PAH associated with CHD). The initial morphological changes (medial hypertrophy and intimal proliferation) are potentially reversible. However, as the disease progresses, the more advanced morphological changes (plexiform lesions and arteritis) appear to be irreversible. Obliteration of the pulmonary vascular bed leads to further increases in PVR and, if PVR approaches or exceeds systemic vascular resistance, the shunt is reversed. Eisenmenger's syndrome, which is considered the most advanced form of PAH associated with CHD, is defined as CHD that initially causes large systemic-to-pulmonary shunts resulting in severe pulmonary vascular disease and PAH, with subsequent reversal of the direction of the shunt and central cyanosis.[28]

4. Clinical Picture and Prognosis

Eisenmenger's syndrome affects multiple organs, the function of which deteriorates progressively over time. Cyanosis and secondary erythrocytosis are frequently observed in patients with PAH associated with systemic-to-pulmonary shunt and are

typical characteristics of patients with Eisenmenger's syndrome. Most patients with these conditions will have impaired exercise tolerance and dyspnoea on exertion,[29,30] but these symptoms may be well compensated for many years. Haemoptysis may occur as a result of rupture of dilated bronchial arteries. Because patients with reduced arterial oxygen saturation have abnormal haemostasis, including thrombocytopenia, they are at risk of both bleeding and thrombosis.[31] In particular, parietal thrombosis of enlarged proximal pulmonary arteries is found in up to one-fifth of adults with Eisenmenger's syndrome is associated with biventricular dysfunction and reduced pulmonary flow velocity, and may cause peripheral embolization and pulmonary infarctions.[32] Cerebrovascular accidents may occur as a result of paradoxical embolization, venous thrombosis of cerebral vessels or intracranial haemorrhage. In addition, patients with Eisenmenger's syndrome are at risk of brain abscesses, bacterial endocarditis and pneumonia.

Patients with Eisenmenger's syndrome may have syncope as a result of inadequate cardiac output (even if less frequently than those with other forms of PAH without shunts), or as a result of an arrhythmia and this is considered a negative prognostic factor.[33] Symptoms of heart failure, which are uncommon until the disease is far advanced, also portend a poor prognosis.[33] Renal dysfunction due to heart failure, glomerular abnormalities (as a consequence of hypoxaemia) and hyperuricaemia are frequent. Hepatic dysfunction includes cholelithiasis (calcium bilirubinate) and cholecystitis. The survival of patients with Eisenmenger's syndrome is clearly reduced compared with that of the general population,[33] but appears to be better than that of patients with idiopathic PAH in a comparable functional class.[34] In a series of 100 patients listed for transplantation, the survival of patients who did not receive transplants was reported to be 97% at 1 year, 89% at 2 years and 77% at 3 years for patients with Eisenmenger's syndrome, compared with 77%, 69% and 35%, respectively, for patients with idiopathic PAH.[34]

5. Treatment

The recommendations given for the treatment of patients with PAH associated with congenital systemic-to-pulmonary shunts, and in particular for patients with Eisenmenger's syndrome, are based mainly on clinical experience rather than being evidence based.[30,35,36] In fact, it is only recently that the first randomized controlled trial with a targeted treatment for Eisenmenger's syndrome has been performed.[37] However, the appropriate management of these patients, with their complex needs, requires the combined expertise of those in the fields of CHD and PAH.

5.1 General Measures

5.1.1 Physical Activity

Recent reports have shown favourable effects of rehabilitation programmes on the exercise capacity and quality of life (QOL) of PAH patients.[38] However, it is unclear whether physical activity itself has a positive impact on the outcome for these patients. In any event, the level of exercise in daily life should be adapted for each patient individually to avoid potentially hazardous symptoms, such as moderate to severe dyspnoea, syncope and chest pain. Exercise training programmes should be limited to a level at which patients are symptom free and yet allows adequate skeletal muscle conditioning. Physical activity after meals or in extreme temperatures should be avoided.

5.1.2 Pregnancy and Birth Control

Pregnancy and delivery in Eisenmenger's patients are associated with an increased rate of maternal deterioration, death (in up to 50%) and spontaneous abortion (in up to 40%).[39-42] Even though successful pregnancies have been reported for patients with Eisenmenger's syndrome, an appropriate method of birth control is highly recommended for women of child-bearing age who have Eisenmenger's syndrome. However, there is no agreement among experts as to the most appropriate method of birth control for these women. The safety of hormone-based contraception is questioned because of potential prothrombotic effects. However,

the current availability of low-dose estrogen products and concomitant oral anticoagulant therapy may limit the risk associated with the use of these contraceptives. Another alternative is to use barrier contraceptives and/or intrauterine devices. In clinically stable patients, laparoscopic tubal ligation can be performed with an acceptable surgical risk. Because of high maternal mortality and morbidity, it is suggested that unplanned pregnancies are terminated. In situations where patients refuse to terminate a pregnancy, an expert multidisciplinary team should monitor and assist the patient during the pregnancy, delivery and postpartum.[43]

5.1.3 Prevention of Infections

Patients with PAH associated with CHD are susceptible to pneumonia, which may result in deteriation and death. Pulmonary infections are poorly tolerated by these patients and need to be recognized and treated promptly. Vaccine strategies are recommended for the prevention of influenza and pneumococcal pneumonia. Any persistent fever in patients with Eisenmenger's syndrome should raise the suspicion of bacterial endocarditis and appropriate prophylaxis is recommended.

5.1.4 Air Travel/Exposure to High Altitudes

Hypoxia may aggravate vasoconstriction in PAH patients and hypobaric hypoxia starts at altitudes between 1500 and 2000 m above sea level (asl). Although commercial aeroplanes are pressurized to an altitude of 1600–2500 m asl, patients with Eisenmenger's syndrome seem to tolerate air travel reasonably well, without adverse events, even in the absence of oxygen supplementation.[44] If patients are clinically unstable and on extended flights, supplemental oxygen should be considered. Before patients embark on their travels, they should determine the location of the nearest PH clinics at their destination.

5.1.5 Elective Surgery

Even if appropriate studies are lacking, it is expected that elective surgery carries an increased risk in patients with PAH associated with CHD. In addition, the risk increases with the severity of the condition, as classified according to New York Heart Association (NYHA) criteria, and in thoracic and abdominal interventions. There is no clear indication as to which type of anaesthesia is better in patients with PAH associated with CHD, but it is likely that epidural anaesthesia is better tolerated than general anaesthesia. General anaesthesia should be performed by experienced anaesthetists with the support of PAH experts to decide on the most appropriate course of treatment in case of complications. Patients receiving targeted oral or inhalational treatments may have to endure temporary difficulties associated with drug administration, such as fasting, general anaesthesia and assisted ventilation. In case of prolonged withdrawal (more than 12–24 hours), a provisional shift to the use of intravenous prostanoid therapy may be required, with a subsequent return to the original therapy. In addition, prophylactic treatment for deep venous thrombosis should be considered.

5.1.6 Psychological Assistance

Patients with PAH associated with CHD will have had some time to come to terms with the limitations imposed upon them by their condition. However, the exercise limitations, decreased QOL and uncertainties related to their future may cause variable degrees of anxiety and/or depression, which can have further detrimental impact. The role of the PAH expert is important in supporting patients (e.g. when breaking bad news),[45] providing them with adequate information and providing referrals to psychologists or psychiatrists when needed. In addition, support groups for patients and their families (which may or may not be coordinated by psychologists or psychiatrists) are useful in improving an understanding and acceptance of the disease.[46]

5.2 Supportive Treatments

5.2.1 Hyperviscosity Syndrome and Phlebotomy

Phlebotomy with isovolumic replacement should be performed in patients with moderate or severe symptoms of hyperviscosity (e.g. headache, tinnitus, dizziness, visual disturbances, paresthesia, myalgia and poor concentration), which are usually present when the haematocrit is >65%. Optimizing fluid

balance and avoiding dehydration may prevent acute increases in the haematocrit and the possible subsequent induction of hyperviscosity syndrome. Phlebotomy should not be performed routinely or in asymptomatic or mildly symptomatic patients (regardless of haematocrit levels). The symptoms of hyperviscosity are usually relieved by removal of 250–500 mL blood, always with replacement by an equal volume of dextrose or saline.[36] Phlebotomies should be performed no more than two or three times a year to avoid depletion of iron stores and the production of iron-depleted red blood cells, which may increase blood viscosity, further limit exercise tolerance and increase the risk of stroke.[47] Under specific circumstances when excessive phlebotomies have been performed, iron supplementation should be provided. Iron supplementation may also be indicated without preceding phlebotomies, such as when patients are iron depleted, with low ferritin levels and a reduced mean red blood cell volume. In our experience, as also reported by others,[30] most patients with Eisenmenger's syndrome and chronic compensated secondary erythrocytosis do not exhibit symptoms of overt hyperviscosity and do not require phlebotomies.

5.2.2 Supplemental Oxygen

Supplemental oxygen therapy in the treatment of patients with Eisenmenger's syndrome is controversial[48] and it should be prescribed only in those in whom it produces a consistent increase in arterial oxygen saturation greater than 5–10% and improved clinical well-being. Under these circumstances, supplemental oxygen therapy corrects the desaturation caused by the restrictive lung component (cardiomegaly, chest abnormalities etc.) and it should be administered 24 hours a day.

5.2.3 Anticoagulation

The indication for the use of anticoagulants in Eisenmenger's patients is not clear and some authors suggest that their use be avoided because they can exacerbate haemorrhagic diathesis.[3] The use of antiplatelet agents is even more controversial. Empirically, oral anticoagulant treatment with warfarin can be initiated in patients with documented pulmonary arterial thrombosis and absent or only mild haemoptysis. In addition, oral anticoagulants may be required in patients with supraventricular arrhythmias, heart failure or the presence of permanent central venous catheters.

5.2.4 Diuretics

Diuretic treatment should be used in patients showing signs of right heart failure, increased jugular venous pressure and fluid retention. The appropriate dose of diuretics should be titrated carefully to maintain fluid balance, avoiding dehydration and increased haematocrit.

5.2.5 Arrhythmias

The treatment of arrhythmias in patients with Eisenmenger's syndrome does not differ substantially from that of other heart diseases. Sinus rhythm should be restored and maintained whenever possible. We tend not to use class I antiarrhythmic drugs and β-adrenoceptor antagonists (β-blockers) because of their negative inotropic effects.

5.2.6 Calcium Channel Antagonists

In patients with PAH, it is recommended that a vasoreactivity test to nitric oxide be performed to identify patients who can be treated successfully with calcium channel antagonists.[20,49] The classical definition of response based on a reduction in mean pulmonary arterial pressure is not appropriate in the presence of a congenital shunt. In addition, favourable results with the long-term use of calcium channel antagonists have been demonstrated mainly in patients with idiopathic PAH, whereas there are no consistent data available for adult patients with PAH associated with systemic-to-pulmonary shunts.[49] On the basis of results of a small study of 21 patients with PAH associated with CHD, it has been proposed that responsiveness to nitric oxide inhalation, defined as a fall of at least 20% in total pulmonary resistance, is predictive of a better outcome.[50] However, no calcium channel antagonist therapy was administered after the test and it is not clear how to use this information when making decisions regarding treatment for this patient population. Therefore, no clear data support the use of calcium channel antagonists in patients with PAH associated with systemic-to-pulmonary shunts. In particular, the

negative inotropic effects of calcium channel antagonists and systemic vasodilatation may predispose to serious adverse effects in Eisenmenger's patients.

5.3 Targeted Medical Treatments

In the past 15 years, multiple randomized controlled studies[37,51-66] have demonstrated the efficacy of three classes of drugs for the treatment of PAH patients, namely (i) prostanoids; (ii) endothelin receptor antagonists; and (iii) phosphodiesterase (PDE)-5 inhibitors. The rationale supporting the use of these drugs is based on correction of endothelial dysfunction, which is characterized by a reduction in the production of prostacyclin and nitric oxide, and increased secretion of endothelin.[67] Unfortunately, only a few randomized controlled studies have included patients with PAH associated with repaired or unrepaired CHD,[56-58,65,68,69] and the subgroup analysis appears unreliable for the small number of the patients. One reason for this is that untreated Eisenmenger's syndrome, despite having a natural history significantly worse than that of the general population, is considered, in most cases, a very slowly progressing disease, making the inclusion of such patients in randomized controlled studies problematic.

5.3.1 Prostanoids

The use of continuous intravenous epoprostenol in open-label studies has been shown to exert favourable effects on the haemodynamics and exercise capacity of patients with PAH associated with systemic-to-pulmonary shunts and Eisenmenger's syndrome.[68,70] The extent of these effects and the adverse events appear to be comparable with those observed in patients with idiopathic PAH,[71-73] even if the presence of a central intravenous catheter in patients with pulmonary-to-systemic shunts may increase the risk of paradoxical embolization.[70]

In a multicentre randomized study with subcutaneous treprostinil that included 109 patients with PAH associated with systemic-to-pulmonary shunts and Eisenmenger's syndrome, the favourable effects on exercise capacity (+16 m on the 6-minute walk distance) in this subgroup appeared to be no different from those observed in patients with idiopathic PAH.[56] In addition, increased exercise capacity was greater in patients with a lower baseline 6-minute walk distance.[56]

In another randomized trial, subgroup analysis on the effect of beraprost, an oral prostanoid, showed significant improvement in exercise capacity after 3 months in patients with idiopathic PAH, but not in other PAH subgroups, including systemic-to-pulmonary shunts and Eisenmenger's syndrome. Similar results have been reported for a second randomized study after 3 months treatment with beraprost, but the improvements were not evident after 12 months.[60] For these reasons, the effects of beraprost were not considered sufficient for regulatory approval to be granted for the use of beraprost in the treatment of any type of PAH in Western countries.

5.3.2 Endothelin Receptor Antagonists

The endothelin-1 system appears to be intimately involved in the pathobiology of PAH[24,74] and elevated plasma and tissue levels of endothelin-1 have been observed in patients with Eisenmenger's syndrome.[75,76] Accordingly, targeting the endothelin-1 system with endothelin receptor antagonists may prove to be an effective treatment strategy. Bosentan is an orally active dual endothelin ET_A and ET_B receptor antagonist that has been shown to be effective in the treatment of idiopathic PAH and PAH related to connective tissue disease in controlled clinical trials.[54,57] Several open-label uncontrolled studies have suggested that bosentan improves exercise capacity and haemodynamics in adult patients with Eisenmenger's syndrome.[77-80] In addition, favourable results have been confirmed for the long-term use of bosentan in these patients.[81,82]

BREATHE-5 (Bosentan Randomised Trial of Endothelin Antagonist THErapy)[37] was the first trial designed as a multicentre, double-blind, randomized (2 : 1), placebo-controlled study to assess the effects of bosentan on systemic oxygen saturation, pulmonary and systemic haemodynamics, and exercise capacity in patients with Eisenmenger's syndrome. In all, 54 patients were randomized 2 : 1 to bosentan (n = 37) or placebo (n = 17) for 16 weeks. The placebo-corrected effect on systemic

pulse oximetry was 1% (95% CI −0.7, 2.8), demonstrating that bosentan did not worsen oxygen saturation. Compared with placebo, bosentan reduced the PVR index (−472 dyn • s/cm^5; p = 0.0383). Mean pulmonary arterial pressure decreased (−5.5 mmHg; p = 0.0363) and exercise capacity increased (+53.1 m; p = 0.0079). Four patients withdrew from the study as a result of adverse events, two (5%) in the bosentan group and two (12%) in the placebo group. A total of 37 patients with Eisenmenger's syndrome who participated in BREATHE-5 were included in the open-label extended observation that confirmed the maintenance of the effects of bosentan for up to 24 weeks.[83]

Two interesting, ancillary observations can be derived from BREATHE-5: (i) despite the common concept that the haemodynamics of patients with Eisenmenger's syndrome are remarkably stable over time, a trend towards increased pulmonary and systemic vascular resistance, consistent with progressive deterioration, was observed in the placebo group in that study; and (ii) the observed improvements in both the 6-minute walk distance and the haemodynamics of the bosentan-treated patients were comparable with results reported for other controlled studies of other forms of PAH.[54,57] Although the time from diagnosis to the initiation of the investigational treatment was much longer in BREATHE-5 on patients with Eisenmenger's syndrome than other clinical trials with different types of PAH (>20 years vs 2–3 years, respectively),[54,57] bosentan therapy appears to be equally effective.

Recent observations suggest a possible decline in the effects of bosentan on exercise capacity in adults and children with PAH associated with systemic-to-pulmonary shunts.[84]

Two randomized controlled studies, STRIDE (Sitaxsentan To Relieve Impaired Exercise)-1 and STRIDE-2, assessed the efficacy and safety of the ET_A receptor-selective antagonist sitaxentan in 178 and 247 PAH patients, respectively. Subjects with PAH associated with repaired or unrepaired CHD were included in the studies (42 patients in STRIDE-1 and 26 in STRIDE-2), but no subgroup analysis was provided.[65,69]

5.3.3 Phosphodiesterase-5 Inhibitors

Sildenafil is an orally active PDE-5 inhibitor that augments the effects of nitric oxide by raising intracellular cyclic guanosine monophosphate levels[85] and has been associated with anti-proliferative effects on pulmonary vascular smooth muscle cells.[86] In addition, sildenafil has been shown to improve contractility in the hypertrophied human right ventricular myocardium in an *in vitro* model.[87] As in other forms of PAH,[88] endothelial nitric oxide production and release are impaired in patients with CHD and abnormal haemodynamics,[89] suggesting that sildenafil treatment may be beneficial in this setting. One large (SUPER-1 [Sildenafil Use in Pulmonary artERial hypertension])[64] and two smaller[63,90] randomized controlled trials have demonstrated the benefits of sildenafil on exercise capacity and haemodynamics of patients with PAH. In one of the small trials with sildenafil,[90] ten patients with Eisenmenger's syndrome were included. Furthermore, improvements in exercise capacity and haemodynamics have been documented in additional case series with sildenafil including 3,[91] 7[92] and 21[93] patients with PAH associated with unrepaired CHD. Comparable data have been reported for nine[94] paediatric patients with PAH associated with repaired or unrepaired CHD.

Similar favourable results have been reported for 16 patients with Eisenmenger's syndrome treated with the PDE-5 inhibitor tadalafil.[95]

In our experience of 22 patients with PAH associated with systemic-to-pulmonary shunts (18 with Eisenmenger's syndrome),[96] the increase in exercise capacity and the improvement in haemodynamics observed after a mean period of 4 months treatment with sildenafil is comparable with that observed in patients with idiopathic PAH or PAH associated with connective tissue diseases who were enrolled in the SUPER-1 study.[64]

All studies regarding the use of sildenafil and tadalafil to treat patients with PAH associated with CHD report excellent tolerability for both drugs.

5.3.4 Combination Therapy

Different uncontrolled[97-101] and controlled randomized[66,100,102,103] studies have reported the effi-

cacy of a combination therapy strategy in patients with PAH. Different combinations of the three classes of targeted compounds have been used and the magnitude of the effects observed is less than that reported for monotherapy trials. However, experience in patients with PAH associated with CHD and Eisenmenger's syndrome is limited. We have found that the efficacy of combination therapy seems to be reproducible in this specific patient population. However, because of the limited data available, the use of combination therapy should be on a case-by-case basis and only in expert centres.

5.3.5 Limitations of Targeted Medical Treatments

Limitations regarding the targeted medical treatment of patients with PAH associated with systemic-to-pulmonary shunts and Eisenmenger's syndrome are not only related to the small number of subjects included in the randomized controlled studies. In fact, it is not clear from the published data, except in the case of the BREATHE-5 study, just how many subjects had symptoms characteristic of Eisenmenger's syndrome. In addition, there is still uncertainty as to whether the favourable functional and haemodynamic effects of treatment persist over the longer term.[81,83,84] Moreover, there are no published data on the effects of targeted therapies on the morbidity and mortality of this patient population.

5.4 Corrective Interventions

Closure of the septal heart defect, either by percutaneous or surgical procedures, is generally contraindicated in adult patients with PAH associated with systemic-to-pulmonary shunts because of high mortality and poor outcome.[36] In addition, closure of the defect may take away the 'safety valve' in patients with further progression of pulmonary vascular disease and reversal of the pressure gradient between the systemic and pulmonary circulations. The indications for patients to be considered for correction are not uniformly defined and may include pulmonary artery vasoreactivity and/or the presence of a pulmonary-to-systemic flow ratio of at least 1.5 to 1.0.[104] Furthermore, correction of the defect in patients in whom a consistent reduction in PAH is achieved using targeted therapies (the so-called treat-and-repair strategy) remains controversial and only sporadic case reports have been published.[105-107] In fact, only large comparative studies and long-term follow-up can demonstrate the safety and efficacy of correction of septal heart defects in patients with PAH who are being treated successfully with targeted medical therapy.[108]

5.5 Lung Transplantation

Lung transplantation with repair of the cardiac defect or combined heart-lung transplantation are options for patients with Eisenmenger's syndrome who have indicators of a poor prognosis (syncope, refractory right-sided heart failure, NYHA functional class III or IV or severe hypoxaemia).[109] Because of the somewhat limited success of transplantation and the reasonably good survival of patients treated medically, careful selection of patients for transplantation is imperative. Conversely, because the current targeted medical treatments do not provide a cure for the disease, but rather only improve symptoms and haemodynamics, as well as delaying deterioration, it is conceivable that listing of patients for transplantation may be delayed and more patients with PAH, including those with Eisenmenger's syndrome, can remain stable while on the waiting list for a suitable organ donation. However, the current shortage of donor organs is a severe limitation to the widespread use of transplantation in PAH patients.

6. Treatment Algorithm

A treatment algorithm for patients with PAH associated with systemic-to-pulmonary shunts and Eisenmenger's syndrome is proposed in figure 2. The treatment algorithm we propose has been adapted from the algorithms used in the treatment of idiopathic PAH or PAH associated with different conditions.[20,83,110,111] However, because the algorithm is based mainly on expert opinion, there is no evidence provided and no recommendations made. It is intended that the algorithm provides a scheme that takes into consideration all available treatment options. Because of the complexity of the clinical condition and treatment options available, it is strongly recommended that patients with PAH

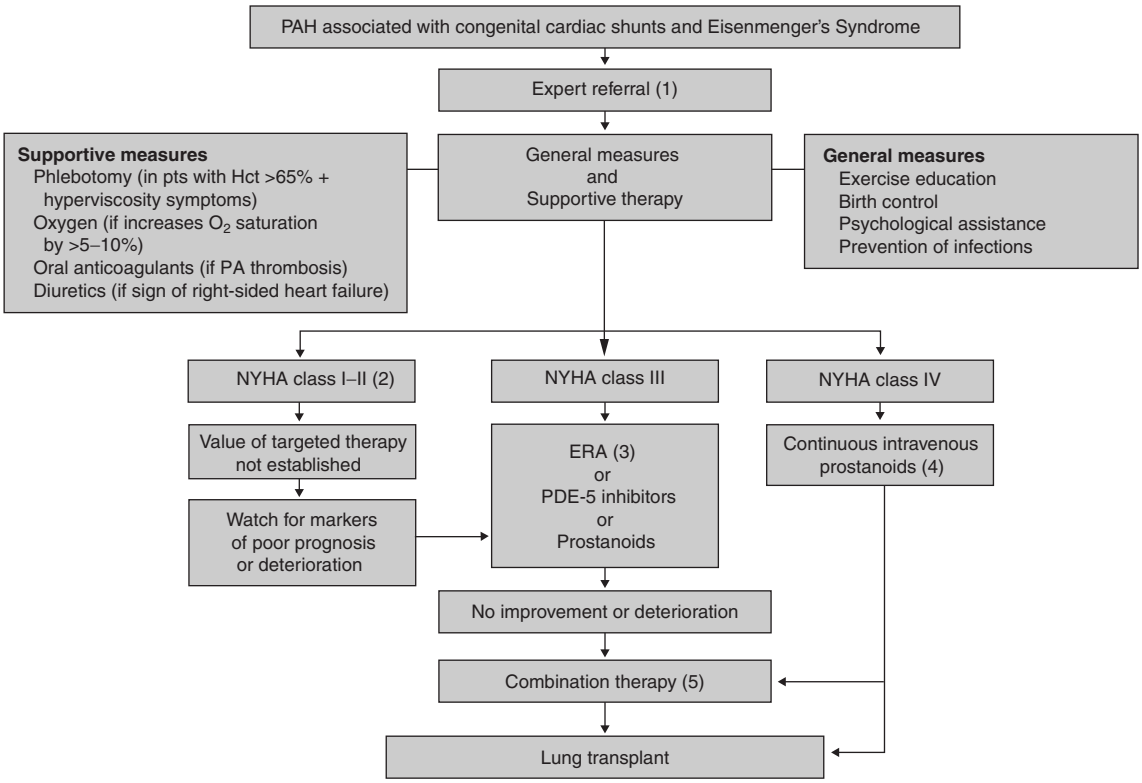

Fig. 2. Treatment algorithm for patients (pts) with pulmonary arterial hypertension (PAH) associated with congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome. (1) Owing to the complexity of the clinical condition and the treatment options available, it is strongly recommended that pts are referred to a specialized centre. (2) Pts may remain mildly symptomatic (New York Heart Association [NYHA] clinical class I and II) and clinically stable for prolonged periods of time and the efficacy-to-safety ratio of the use of targeted therapies in this patient population has not been established. (3) There is greater evidence for the efficacy of the dual endothelin receptor antagonist (ERA) bosentan because a specific randomized controlled trial has been performed with this compound.[37] (4) Most experts consider that unstable NYHA class IV PAH pts should be treated with intravenous prostanoids, even if the presence of a central intravenous catheter may increase the risk of paradoxical embolization. (5) In pts with no improvement or deterioration, combination therapy should be considered in expert centres, even if no studies are available in this specific pt population. **Hct** = haematocrit; **PA** = pulmonary arteries; **PDE-5** = phophodiesterase-5.

associated with systemic-to-pulmonary shunts and Eisenmenger's syndrome are referred to a specialized centre that has experience in both PAH and CHD.

General measures and supportive therapies should be implemented in all patients if required. General measures include recommendations for physical activity, pregnancy, infections, air travel, exposure to high altitudes and elective surgery, and that psychological assistance be provided as necessary. Phlebotomies are indicated only if relevant symptoms of hyperviscosity are present and usually when the haematocrit is >65%. The use of supplemental oxygen therapy is controversial and it should be prescribed only in patients in whom it produces a consistent increase in arterial oxygen saturation. Oral anticoagulant treatment with warfarin can be initiated in patients with pulmonary artery thrombosis and absent, or only mild, haemoptysis. Patients may remain mildly symptomatic (NYHA clinical class I an II) and in a stable clinical condition for an extended period of time. The efficacy-to-safety ratio of targeted therapies in this patient population has not been established and may be considered only when there is an indication that a given patient's

prognosis is poor (e.g. syncope, signs of heart failure or severe hypoxaemia).

The initiation of targeted treatment should be considered in NYHA class III patients and such treatment may include prostanoids, endothelin receptor antagonists and PDE-5 inhibitors. There is more evidence of the efficacy of the dual endothelin receptor antagonist bosentan because a specific randomized controlled trial has been performed using this drug. Most experts consider that unstable PAH patients in NYHA functional class IV should be treated with intravenous prostanoids. In case of no improvement or deterioration, combination therapy should be considered in expert centres, even if there are no studies supporting this treatment regimen in this specific patient population. Listing for lung transplantation with repair of the cardiac defect or combined heart-lung transplantation is required for patients with a poor prognosis (e.g. syncope, refractory right-sided heart failure, NYHA functional class III or IV or severe hypoxaemia).

7. Conclusions

Patients with PAH associated with congenital systemic-to-pulmonary shunts and those with fully developed Eisenmenger's syndrome present specific features, such as the presence of a heart septal defect and consequent central cyanosis, erythrocytosis, multiple organ involvement, prolonged clinical stability and extended survival. Despite these peculiar characteristics, the efficacy and safety of targeted treatments, such as prostanoids, endothelin receptor antagonists and PDE-5 inhibitors, in this patient population appear to be similar to those in other types of PAH, even if some doubts have been raised regarding the long-term persistence of the favourable treatment effects. Currently, there is more evidence supporting the efficacy of the dual endothelin-1 receptor antagonist bosentan in the treatment of patients with Eisenmenger's syndrome. We propose a treatment algorithm for patients with PAH associated with corrected and uncorrected CHD, as well as for patients with Eisenmenger's syndrome, that we have adapted from the algorithms used to treat PAH patients.

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Correspondence: Dr *Nazzareno Galie*, Institute of Cardiology, University of Bologna, Via Massarenti 9, 40138-Bologna, Italy.
E-mail: nazzareno.galie@unibo.it