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## Pulmonary Vascular Disease in Adults With Congenital Heart Disease

Gerhard-Paul Diller, MD; Michael A. Gatzoulis, MD, PhD

**Abstract**—Pulmonary arterial hypertension of variable degree is commonly associated with adult congenital heart disease. Depending on size and location of the underlying cardiac defect as well as on repair status, pulmonary arterial hypertension may present with or without reversed shunting and associated cyanosis (ie, Eisenmenger syndrome). We review available data on etiology, clinical presentation, prognosis, and management strategies of pulmonary arterial hypertension in adult patients with congenital heart disease. In addition, we discuss the numerous complications associated with Eisenmenger syndrome, representing a multisystem disorder. Finally, we present general management strategies and emerging disease-targeting therapies.

**Key Words:** heart defects, congenital ■ hypertension, pulmonary ■ pulmonary vascular disease

Adults with congenital heart disease represent an expanding patient population requiring life-long tertiary medical care.<sup>1</sup> Approximately 5% to 10% of them develop pulmonary arterial hypertension (PAH) of variable severity that affects quality of life, morbidity, and mortality.<sup>2–4</sup>

The extreme manifestation of PAH in this setting, known as Eisenmenger syndrome, has become the epitome of PAH associated with congenital heart disease.<sup>5,6</sup> Our understanding of its clinical phenotype as PAH with reversed central shunt has continued to develop during the past 5 decades.<sup>7</sup> In the same era, advances in pediatric cardiology and cardiac surgery helped to prevent PAH in most pediatric patients in the Western world. Sadly, when patients present with established severe PAH, treatment options are generally limited to palliative measures or lung/heart-lung transplantation for highly selected cases. Recently, however, an improved pathophysiological understanding and the advent of disease-targeting therapies for PAH<sup>8–12</sup> have led to a renewed interest in this condition and stand to benefit a large number of patients with congenital heart disease.

### Definition and Clinical Classification

PAH is defined as an elevated mean pulmonary arterial pressure of >25 mm Hg at rest or 30 mm Hg on exercise.<sup>13</sup> It has been traditionally classified according to the presence or absence of an identifiable underlying cause into primary or secondary PAH. Improved pathophysiological insight as well as a more accurate detection of underlying causes have led to the introduction of a new clinical classification at the Third World Symposium on Pulmonary Arterial Hypertension in Venice in 2003 (Table 1), which has replaced the previous

Evian classification.<sup>14</sup> It is now recommended that PAH is classified as idiopathic, familial, or PAH related to risk factors and associated conditions. Congenital heart disease represents such a condition commonly associated with PAH. The classification of PAH in the setting of congenital heart disease (Table 2) is challenging because of the dynamic nature of the disease as well as the fact that patients with similar underlying cardiac lesions may develop PAH of variable severity.<sup>7,15</sup> Much emphasis has been placed in the past on the extreme end of the spectrum of PAH in the setting of congenital heart disease, namely, the Eisenmenger syndrome. In 1897 Victor Eisenmenger, an Austrian physician, described vividly the clinical features and some of the pathological features of what has become known as Eisenmenger syndrome in a patient with a large ventricular septal defect.<sup>5</sup> It was, however, not possible for Eisenmenger to recognize pulmonary hypertension and shunt reversal at that time. Our current understanding of the condition is largely influenced by Paul Wood and others who, in the 1950s, recognized the underlying pathophysiology as “pulmonary hypertension with reversed central shunt” and described the clinical phenotype of Eisenmenger physiology. On the basis of Dr Wood’s observations that a remarkably similar pathophysiological condition may develop irrespective of the location of the shunt, the term *Eisenmenger syndrome* has since been used in very different cardiac malformations associated with severe PAH. However, there are differences in certain pathophysiological and clinical aspects among Eisenmenger patients. In patients with a large, nonrestrictive ventricular or arterial communication, shunt volume and direction are determined mainly by the pressure difference

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**TABLE 1. Clinical Classification of Pulmonary Hypertension (Venice, 2003)\***

PAH
• Idiopathic PAH
• Familial PAH
• Associated with risk factors and associated conditions
• Connective tissue disease
• Congenital systemic-to-pulmonary shunts
• Portal hypertension
• Associated with HIV
• Associated with drugs and toxins
• Miscellaneous
• Associated with significant venous or capillary involvement
• Persistent pulmonary hypertension of the newborn
Pulmonary hypertension associated with left-heart disease
Pulmonary hypertension associated with lung disease and/or hypoxemia
Pulmonary hypertension due to chronic thrombotic or embolic disease
Miscellaneous

\*Modified according to References 14 and 99.

between systemic and pulmonary circulation. In contrast, patients with a large atrial communication may have a right-to-left shunt not necessarily due to systemic or supra-systemic pulmonary arterial pressures. In this latter group, right-to-left shunting may rather reflect lower right ventricular compliance (a consequence of right ventricular hypertro-

**TABLE 2. Classification of PAH Associated With Congenital Heart Disease**

Type of lesion
Simple
ASD
Sinus venosus defects
VSD
Aortopulmonary window
PDA
Total or partial unobstructed anomalous pulmonary venous return
Combinations of the above lesions
Complex congenital heart disease
Atrioventricular septal defects
Truncus arteriosus
Single-ventricle physiology with unobstructed pulmonary blood flow
Transposition of the great arteries with ventricular or arterial shunt
Lesion dimensions
Small to moderate (ASD $\leq$ 2.0 cm, VSD and PDA $\leq$ 1.0 cm)
Large (ASD $>$ 2.0 cm, VSD and PDA $>$ 1.0 cm)
Associated extracardiac abnormalities
Repair status
Unoperated
Palliated
Repaired

ASD indicates atrial septal defects; VSD, ventricular septal defects; and PDA, patent ductus arteriosus.

phy). Furthermore, the natural course of patients with atrial communications is different in general. Although penetrance of PAH is high and onset of Eisenmenger physiology is relatively early and is the rule in patients with large shunts at the ventricular or arterial level, the majority of patients with even large atrial septal defects do not develop Eisenmenger physiology, and those who develop PAH often do so much later in life.<sup>3,7,14,16–23</sup>

Therefore, when one refers to Eisenmenger syndrome, additional information needs to be provided. The underlying defect should be stratified into simple and complex lesions because this has prognostic implications.<sup>24</sup> Furthermore, the location, direction, and magnitude of the shunt need to be described. In addition, associated extracardiac abnormalities should be registered. Last but not least, knowledge of repair status is essential because pathophysiology in patients with repaired congenital heart disease and PAH often parallels that encountered in patients with idiopathic PAH and does not usually represent Eisenmenger physiology.

### Epidemiology

It has been reported that 5% to 10% of patients with congenital heart disease develop PAH of variable severity.<sup>2,3</sup> These numbers are approximate because pulmonary arterial pressures are available only in a subset of patients with congenital heart disease, whereas many patients have been lost to follow-up after repair of simple or even complex defects. The prevalence of Eisenmenger syndrome, representing a clinical diagnosis at the extreme end of the spectrum, is easier to quantify. The frequency of Eisenmenger syndrome has declined from  $\approx$ 8% in the 1950s<sup>7</sup> to  $\approx$ 4% among contemporary adult congenital heart patients under follow-up at tertiary centers in London, Toronto, and Zurich.<sup>25</sup> It is anticipated that, with increasing awareness and improved infrastructure for managing congenital heart disease, the numbers of patients with PAH and simple cardiac lesions such as ventricular septal defect and patent arterial duct will continue to decrease. In contrast, there will be more patients with complex congenital heart disease such as patients with single-ventricle physiology who will go on to develop PAH after having undergone palliative procedures in early childhood.

### Pathophysiology and Genetic Factors

PAH is a dynamic and multifactorial process related to vasoconstriction and remodeling of the pulmonary vascular bed that may be aggravated by thrombosis. Several histopathological abnormalities associated with congenital heart disease and PAH, such as extension of smooth muscle cells into peripheral pulmonary arteries,<sup>26</sup> medial hypertrophy, formation of plexiform lesions,<sup>27</sup> and rarification of the pulmonary arterial tree, have been observed.<sup>28</sup> Reflecting these histological changes, classifications of pulmonary vascular changes have been developed, including those introduced by Heath and Edwards in 1958<sup>27</sup> and Rabinovitch in 1978.<sup>28</sup> It has been suggested that these histological changes may correlate with clinical severity of PAH.<sup>29</sup> In addition to histological studies in patients with PAH, several animal models of congenital heart disease have been established<sup>30–32</sup>

and have provided additional insights into the pathophysiology of the disease.

It has been proposed that high flow and pressure may induce pulmonary vascular endothelial damage, leading to a loss of endothelial barrier function. This may be associated with degradation of extracellular matrix (activation of endogenous vascular elastase and matrix metalloproteinases) as well as release of growth factors (fibroblast growth factor and transforming growth factor- $\beta$ ). In turn, these factors induce smooth muscle cell hypertrophy and proliferation, resulting in extension of smooth muscle cells into peripheral pulmonary vasculature and smooth muscle cell migration with neointima formation.<sup>33</sup> Furthermore, endothelial damage may result in adherence and activation of platelets and leukocytes favoring immune inflammation and thrombosis as well as activation of coagulation pathways.

Endothelial dysfunction also affects the production of vasoconstrictors (such as endothelin-1 and thromboxane) and vasodilators (such as nitric oxide, vasoactive intestinal peptide, and prostaglandin I<sub>2</sub>), shifting the balance in favor of factors inducing vasoconstriction and ultimately pulmonary vascular remodeling.<sup>34</sup>

Different mediators influencing pulmonary vascular tone have been identified, some of which are currently amenable to pharmacological therapy. Extensive activation of the endothelin system is one of the hallmarks of PAH and is likely to contribute to pulmonary vasoconstriction and vascular remodeling.<sup>35,36</sup> In addition, circulating endothelin levels have been found to correlate with disease severity and outcome in PAH patients.<sup>37</sup> Decreased production of prostacyclin is an additional feature of PAH. Prostacyclin, a metabolite of arachidonic acid, is a potent pulmonary and systemic vasodilator.<sup>38</sup> In patients with PAH, prostacyclin production is impaired,<sup>39</sup> and levels of prostacyclin metabolites are reduced.<sup>40</sup> Furthermore, nitric oxide, a potent endothelium-derived factor inducing vasodilation and antiproliferation, is involved in the pathophysiology of PAH.<sup>15</sup> Nitric oxide activates cyclic guanylate cyclase in vascular smooth muscle cells, leading to increased intracellular levels of cGMP; cGMP in turn is degraded by phosphodiesterases. Pharmacological inhibition of phosphodiesterases provides a way to induce cGMP-dependent vasodilation. Sildenafil, a phosphodiesterase-5 inhibitor, has been tried in PAH of different etiologies with favorable results.<sup>9,41</sup> Recently, Rondelet et al<sup>42</sup> demonstrated in an animal model that sildenafil can partially prevent overcirculation-induced PAH and is associated with favorable changes in signaling pathways involved in the pathogenesis of PAH. Additional abnormalities have been described in PAH associated with congenital heart disease that might provide new insights into pathophysiology and also may have future therapeutic implications. These include increased turnover of serotonin, a pulmonary vasoconstrictor, compared with healthy individuals<sup>43</sup> and emerging evidence of altered intrapulmonary expression of transforming growth factor- $\beta$ , and its receptors in an animal model of shunt-induced pulmonary vascular disease.<sup>44</sup> Furthermore, altered expression of pulmonary potassium channels associated with an accentuated response to hypoxia has been shown in an ovine model.<sup>45</sup>

Mutations in receptors of the transforming growth factor- $\beta$  family (bone morphogenetic protein receptor type 2 and activin-like kinase type 1) have been identified as causes of familial PAH.<sup>15,46</sup> In a recent study, 6% of patients with PAH associated with congenital heart disease were found to have bone morphogenetic protein receptor type 2 missense mutations, a frequency that was comparable to that reported in patients with anorexigen-associated PAH (8%) but was considerably lower than that observed in patients with idiopathic or familial PAH (26% and  $\approx$ 50%, respectively).<sup>47</sup> This is likely to reflect the complex interplay between genetic susceptibility and environmental factors such as pulmonary blood flow or pressure in the etiology of PAH associated with congenital heart disease.

### Clinical Presentation

Clinical signs and symptoms of PAH are variable and depend on underlying heart defect, patient age, repair status, and degree and direction of shunting. General symptoms suggestive of PAH are nonspecific and may include breathlessness, chest pain, and syncope. In patients with Eisenmenger physiology, central cyanosis and clubbing are the most visible clinical consequences. However, it should be emphasized that not all Eisenmenger patients are cyanotic at rest, and some may exhibit differential cyanosis.

Patients with longstanding large systemic-to-pulmonary shunts who develop Eisenmenger syndrome have a multisystem disorder (Table 3). This is dominated by cyanosis, bleeding, thrombotic diathesis (Figure 1), ischemic complications, ongoing risk of bacterial endocarditis or cerebral abscess (Figure 2), hepatic and renal involvement, congestive heart failure, and sudden cardiac death.

### Exercise Intolerance

Most adult patients with Eisenmenger physiology are highly symptomatic. In our practice, >90% of patients are in New York Heart Association class II or higher, and  $\approx$ 50% report severe limitations (New York Heart Association class III or higher), in agreement with previous reports.<sup>48</sup>

### Chronic Cyanosis

Cyanosis is common in patients with congenital heart disease and PAH. Right-to-left shunting reduces arterial oxygen content and is associated with secondary hypoxic damage to other organ systems, thus leading to multiorgan disease.<sup>49,50</sup> Cyanosis and PAH are strong correlates of poor exercise capacity, and the combination of both, as in patients with Eisenmenger physiology, severely limits exercise tolerance. Indeed, patients with Eisenmenger physiology are the most limited adult congenital heart subgroup with the lowest mean peak oxygen uptake (mean of 11.5 mL/kg per minute; Figure 3).<sup>4</sup>

### Secondary Erythrocytosis

Chronic cyanosis results in elevated renal production of erythropoietin,<sup>51</sup> thus promoting erythropoiesis and secondary erythrocytosis. The term *secondary erythrocytosis* refers to an isolated increase in red blood cells (as opposed to polycythemia, in which all cell lines proliferate). Elevated hemoglobin levels represent a physiological adaptation to

**TABLE 3. Multiorgan Involvement in Patients With Chronic Cyanotic Congenital Heart Disease and PAH**

Ischemic and embolic complications
Cerebrovascular accidents (stroke or transient ischemic attack)
Bleeding and thrombotic diathesis
Hemoptysis
Intrapulmonary thrombosis
Pulmonary hemorrhage
Cerebral bleeding
Menorrhagia
Epistaxis
Hematologic involvement
Secondary erythrocytosis
Thrombocytopenia
Infections
Bacterial endocarditis
Cerebral abscess
Pneumonia
Progressive right ventricular failure
Cardiac arrhythmias and sudden cardiac death
Renal dysfunction
Glomerular abnormalities
Hyperuricemia and gout
Hepatic dysfunction
Cholelithiasis (calcium bilirubinate) and cholecystitis
Acne
Skeletal disease
Scoliosis
Hypertrophic osteoarthropathy

chronic cyanosis and are essential in maintaining adequate tissue oxygenation and preventing hypoxic end-organ damage.<sup>52</sup> Raised hematocrit levels have been linked with hyperviscosity symptoms such as headaches, dizziness, visual disturbances, paresthesia, and myalgia,<sup>53</sup> although data on the association between hematocrit and viscosity are inconclusive and are confounded by iron deficiency.<sup>54–56</sup>

### Bleeding and Thrombotic Diathesis

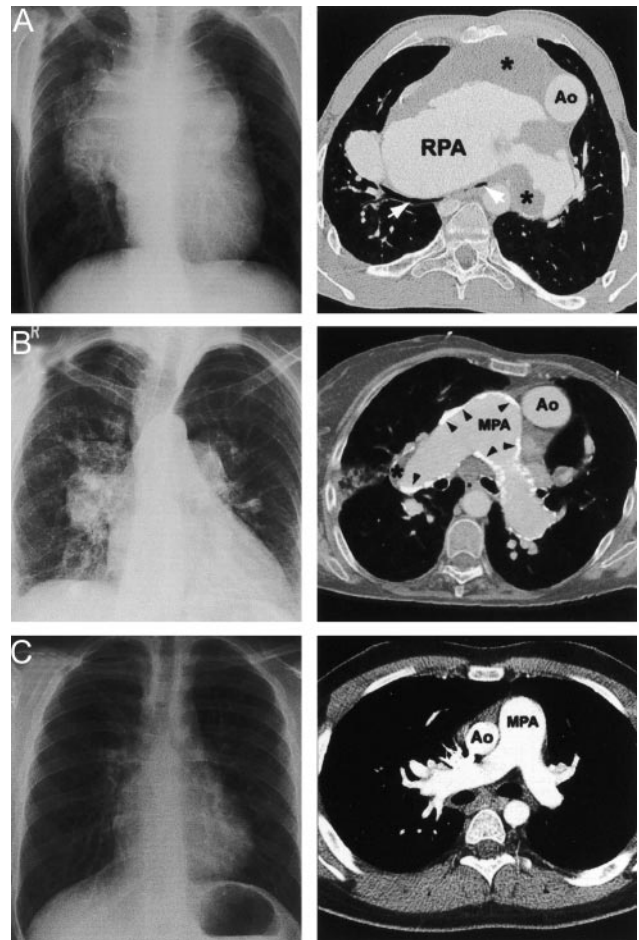
Abnormal hemostasis is common in Eisenmenger patients. PAH and chronic cyanosis are associated with thrombocytopenia, platelet dysfunction, and abnormalities in the clotting cascade.<sup>50,57</sup>

### Intrapulmonary Thrombosis

Intrapulmonary thrombosis occurs in up to a third of adult patients with Eisenmenger physiology, particularly in Eisenmenger patients with large atrial septal defects.<sup>58–60</sup> Intrapulmonary thrombosis in this setting has been associated with hemoptysis and pulmonary infarction.<sup>7,61</sup>

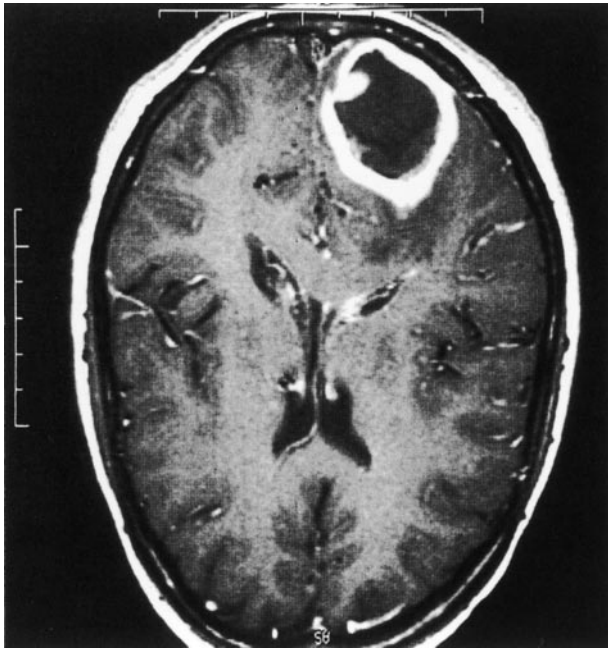
### Hemoptysis

Hemoptysis is common in patients with Eisenmenger physiology with a reported incidence between 11% and 100%, increasing with age.<sup>7,24,48</sup> Although it is an alarming symptom



**Figure 1.** Chest radiographs and computed tomography pulmonary angiography in patients with Eisenmenger syndrome (courtesy of Dr M. Rubens, Royal Brompton Hospital, London, UK). A, A 24-year-old patient with transposition of the great arteries and non-restrictive ventricular septal defect. The patient underwent palliative Mustard operation at the age of 7 years without closure of the ventricular septal defect. Chest radiography shows situs solitus, levo-cardia, left aortic arch, no cardiomegaly, and dilatation of central pulmonary arteries. Computed tomography pulmonary angiography reveals extensive thrombus (marked with an asterisk) within the severely dilated proximal pulmonary arteries. In addition, the dilated pulmonary arteries are causing considerable compression of both main stem bronchi (arrows). RPA indicates right pulmonary artery; Ao, aorta. B, A 69-year-old female patient with single-ventricle physiology (double-inlet left ventricle, rudimentary right ventricle, and a nonrestrictive inlet ventricular septal defect) and unprotected pulmonary circulation. On chest radiograph there is marked bilateral enlargement of the proximal pulmonary artery. Computed tomography pulmonary angiography reveals bilaterally enlarged pulmonary arteries with mural thrombus (asterisk) and calcifications (arrows). MPA indicates main pulmonary artery. C, An 18-year-old male patient with complete atrioventricular septal defect and Down syndrome. Chest radiography reveals a heart size at the upper limit of normal with a normal vascular pattern. Computed tomography pulmonary angiography shows dilatation of the proximal pulmonary artery (with the main pulmonary artery clearly larger than the aorta) but no other significant abnormalities. This case illustrates that chest radiography can be essentially normal in patients with Eisenmenger syndrome.

for the patient, hemoptysis is an uncommon mode of death.<sup>7,48</sup> Furthermore, hemoptysis does not seem to be predictive of mortality.



**Figure 2.** Cerebral abscess in a 33-year-old patient with Eisenmenger syndrome. Magnetic resonance imaging demonstrates a typical cerebral abscess in the right occipital lobe with contrast enhancement of the abscess wall and surrounding edema. From Oechslin,<sup>77</sup> with permission of the author.

**Infections**

Patients with repaired or unrepaired congenital heart disease have a considerable risk of developing bacterial endocarditis. The lifetime risk of developing endocarditis in a patient with unrepaired ventricular septal defect may be as high as 13%.<sup>62</sup> Of 188 Eisenmenger patients reported by Daliento et al,<sup>24</sup> 4% developed bacterial endocarditis. One of them died of subsequent embolic cerebral abscess. Endocarditis prophylaxis<sup>63,64</sup> is therefore paramount for patients with Eisenmenger physiology. Intracerebral abscess (Figure 2) in itself is not uncommon in these patients. In a series reported by Cantor et al,<sup>48</sup> 7 of 109 patients (6.5%) developed this complication during a

median follow-up of 6.3 years. Diagnostic vigilance and a low threshold for appropriate investigations are clearly required if neurological signs and symptoms of cerebral abscess are not to be interpreted incorrectly as manifestations of the hyperviscosity syndrome.

**Arrhythmias and Sudden Cardiac Death**

Arrhythmias are frequent late sequelae in patients with Eisenmenger physiology and may pave the way for clinical deterioration, heart failure, or sudden cardiac death. In the series reported by Daliento et al,<sup>24</sup> 42% of Eisenmenger patients were found to have supraventricular arrhythmias on routine ECG or 24-hour Holter monitoring during long-term follow-up.

Additional common complications such as calcium bilirubinate gallstones, gout arthritis, and renal involvement are summarized in Table 3.

**Patient Evaluation**

**Physical Examination**

Physical signs of PAH in the setting of congenital heart disease include central cyanosis, clubbing, peripheral edema, abdominal tenderness, right ventricular heave, a loud pulmonary ejection click, and an accentuated pulmonary component of the second heart sound. In addition, murmurs associated with valvar regurgitation (tricuspid or pulmonary) may also be present. Murmurs due to previous left-to-right shunts at the ventricular (systolic) or arterial (continuous murmur) level usually disappear as soon as Eisenmenger physiology develops.

**Investigations**

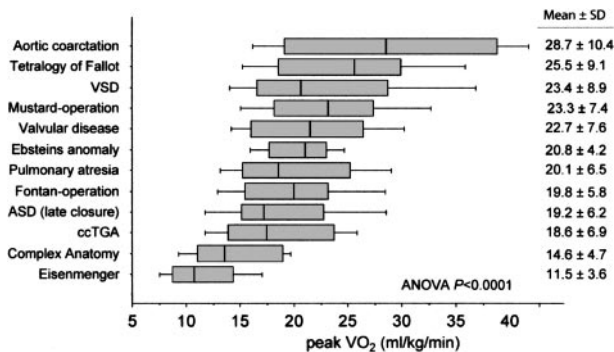
The comprehensive evaluation of patients with PAH associated with congenital heart disease should include a chest radiograph, ECG, measurement of arterial oxygen saturations, laboratory investigations, objective assessment of exercise tolerance, and echocardiography. In addition, high-resolution chest computerized tomography and magnetic resonance imaging provide additional information on the pulmonary vascular bed and the right ventricle.

**Chest Radiography**

Typical abnormal radiological findings in patients with PAH associated with congenital heart disease include dilatation, aneurysm, or calcification of the central pulmonary arteries (Figure 1). In contrast to idiopathic PAH, attenuation of peripheral vascular markings (pruning) is not a common feature in these patients. Signs of right atrial and right ventricular enlargement may also be present (cardiothoracic ratio should be recorded). Furthermore, chest radiography may show consolidations suggestive of pulmonary infiltrates or pulmonary hemorrhage. Radiographic findings, however, are variable, and the chest radiograph may be remarkably normal in some patients (Figure 1C).<sup>7</sup>

**Electrocardiography**

The ECG (in addition to showing abnormalities related to the underlying cardiac defect) is useful in assessing underlying heart rhythm and may indicate atrial dilatation or right ventricular strain. It has been suggested that voltage criteria



**Figure 3.** Distribution of peak oxygen consumption on cardio-pulmonary (treadmill) exercise testing in different diagnostic subgroups of adult congenital heart disease (n=335). Patients with Eisenmenger syndrome have by far the worst exercise capacity in this cohort. VSD indicates ventricular septal defect; ASD, atrial septal defect; and ccTGA, congenitally corrected transposition of the great arteries. From Diller et al,<sup>4</sup> with permission. Copyright © 2005, American Heart Association.

for right ventricular hypertrophy, derived as the sum of the R-wave amplitude in  $V_1$  and the maximum amplitude of the S wave in  $V_5$  or  $V_6$ , may provide prognostic information in patients with Eisenmenger physiology.<sup>48</sup>

#### **Formal Exercise Testing**

Exercise capacity in patients with PAH may reflect disease severity and assist prognostic evaluation. For patients with Eisenmenger physiology, exercise testing also provides information on change in arterial oxygen saturations during exercise. Exercise capacity is assessed by either measurement of 6-minute walk test distance or cardiopulmonary exercise testing with measurement of peak oxygen consumption. Both measurements have been used successfully to evaluate objective exercise limitation in patients with PAH of various etiologies, including congenital heart disease.<sup>4</sup> Reduced peak oxygen consumption and 6-minute walk distance are associated with impaired prognosis in patients with PAH.<sup>65–67</sup>

In cyanotic patients, however, early termination of exercise may be related to an increase in right-to-left shunting and arterial hypoxemia<sup>68</sup> rather than to ominous pathophysiological abnormalities including poor ventricular function, autonomic nervous dysfunction, or myocardial ischemia. In addition, chronic cyanosis represents a multiorgan disease and is associated with abnormalities such as systemic endothelial dysfunction,<sup>69</sup> and these factors may confound the prognostic value of exercise capacity in Eisenmenger patients. As a consequence, the prognostic value of peak oxygen consumption in patients with PAH and congenital heart disease (in particular in cyanotic patients) deserves further scrutiny. Currently, the 6-minute walk test represents the preferred method to assess exercise capacity and appraise therapeutic effects in patients with PAH. The 6-minute walk test is robust and currently is the only exercise test modality approved by the Food and Drug Administration as an end point for prospective clinical trials in this setting.<sup>70,71</sup> It should be considered seriously for the periodic assessment of the adult with congenital heart disease and PAH.

#### **Transthoracic Echocardiography**

Echocardiography is the preferred imaging modality for initial screening of all patients and should be used to systematically delineate underlying cardiac anatomy, cardiac defects, levels of shunting, and ventricular function. It enables estimation of subpulmonary ventricular pressure (from Doppler pressure gradients across the tricuspid valve) and provides indispensable information on whether the systemic-to-pulmonary shunt is nonrestrictive (by assessing the size and Doppler pressure gradient across the defect) as well as on the direction of flow.

#### **Cardiac Catheterization**

Cardiac catheterization is a key part in the evaluation of patients with PAH. It is often required to establish the diagnosis of PAH and to assess severity of pulmonary vascular disease. When pulmonary arterial pressures are assessed, careful exclusion of potential anatomic confounders (such as distal pulmonary artery or pulmonary venous stenosis) is mandatory. Depending on the individual case and on the available noninvasive imaging, it provides complemen-

tary invasive hemodynamic data and determines the potential vasoreactivity of the pulmonary vascular bed (with the use of 100% oxygen via a rebreathing mask, inhaled nitric oxide, intravenous adenosine, or prostacyclin). Pulmonary vasoreactivity was recently shown to have prognostic value for adult patients with Eisenmenger physiology.<sup>72</sup> It must be emphasized, however, that advanced therapies for PAH have a combined vasodilative and antiproliferative effect. Thus, there is also evidence to suggest that pulmonary hemodynamics and clinical status may improve irrespective of the response to acute vasodilator testing.<sup>73,74</sup> Cardiac catheterization provides diagnostic and prognostic information, but an absent or a negative pulmonary vasoreactivity study should not preclude initiation of disease-targeting therapy.

#### **Cardiac Magnetic Resonance Imaging or High-Resolution Computed Tomography**

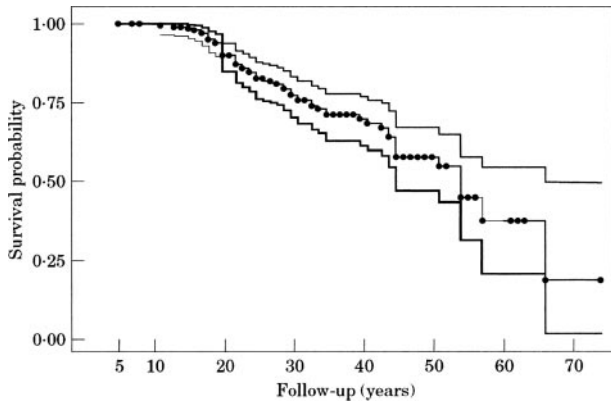
Magnetic resonance imaging can be used to determine the exact intracardiac anatomy and confirm the location and size of intracardiac or extracardiac communications, especially in patients with inadequate echocardiographic windows. Furthermore, it provides additional information on right ventricular function and depicts the pulmonary vascular bed.

High-resolution computed tomography is especially useful to assess pulmonary arterial thrombi (Figure 1A and 1B) and to exclude intrapulmonary hemorrhage or infarction in patients with PAH.<sup>75</sup> It is also the imaging modality of choice for assessing the lung parenchyma.

#### **Routine Laboratory Testing**

Investigations should include full blood count and biochemistry (comprising electrolytes, urea and creatinine, liver function tests, and uric acid). Assessment should particularly focus on hemoglobin concentration and iron status. The latter should be assessed by measuring transferrin saturation or serum ferritin (in clinically stable patients). Iron deficiency is common in patients with Eisenmenger syndrome and is most likely multifactorial. Consumption of iron stores occurs as a result of excessive erythropoiesis in all patients, whereas menorrhagia, gastrointestinal blood loss, and limited dietary intake or malabsorption may also be contributory in some patients. It is noteworthy that iron deficiency in this setting cannot be extrapolated from routine hematologic parameters. The expected pattern of microcytosis and hypochromia may be found in as few as 16% of cyanotic patients with iron deficiency. Instead, patients often present with hyperchromia and/or macrocytosis possibly related to coexistent folate or vitamin B deficiency.<sup>76</sup> Hypoglycemia is not uncommon and usually represents an artificially low blood glucose level due to augmented *in vitro* glycolysis as an effect of the increased red cell mass. This potentially misleading result can be avoided by adding sodium fluoride in the laboratory tube.<sup>77</sup>

Additional tests, such as pulmonary function testing, overnight oximetry for sleep apnea (particularly common in patients with Down syndrome), ventilation-perfusion lung scintigraphy, and blood screening for connective tissue disease may be particularly useful in patients in whom there is apparent discrepancy between underlying congenital heart disease and severity of PAH to exclude additional causes of PAH. In addition, given the increased potential for transfu-



**Figure 4.** Survival probability (including confidence intervals) as a function of age in patients with Eisenmenger syndrome. From Daliento et al.<sup>24</sup> with permission of the publisher. Copyright © 1998, the European Society of Cardiology.

sion exposure in this patient population and its relationship to development of PAH, HIV testing should be considered in selected patients.

### Survival and Risk Stratification

Idiopathic PAH represents a life-threatening disease with devastating prognosis and a reported median survival of 2.8 years.<sup>78</sup> Survival is clearly better in patients with PAH associated with congenital heart disease.<sup>24,79</sup> Many of these patients survive into their third or fourth decade if managed appropriately (Figure 4).<sup>24</sup> Survival rates at 30, 40, and 55 years of age were 75%, 70%, and 55%, respectively, in the study by Cantor and colleagues.<sup>48</sup> It has been speculated that 2 potential mechanisms account for these superior survival prospects compared with idiopathic PAH. First, in PAH associated with congenital heart disease, the right ventricle is subjected to high pressures from birth or from infancy and therefore may be better trained to support systemic pulmonary pressures, reducing the incidence of early right ventricular failure. Second, in patients with idiopathic PAH, pulmonary hypertension per se limits pulmonary and thereby systemic blood flow during exercise.<sup>80</sup> In contrast, patients with PAH and associated shunts maintain or increase their systemic cardiac output during exercise by shunting right to left, albeit at the expense of cyanosis. Consequently, atrial septostomy allowing for right-to-left shunting has been used successfully in selected patients with idiopathic PAH suffering from recurrent syncope and may have a similar hemodynamic benefit.<sup>81</sup>

Risk stratification, although increasingly required for consideration of emerging therapies, is not straightforward in this patient group because of its great heterogeneity, combined with a relatively low annual mortality rate. Available data suggest that low functional class, history of arrhythmia, right ventricular dysfunction, ECG evidence of right ventricular hypertrophy, and increased blood creatinine and uric acid levels predict poor outcome in patients with Eisenmenger syndrome.<sup>24,48,82,83</sup> Survival prospects are significantly poorer in patients with complex underlying cardiac defects and those with Down syndrome (who are subjected to additional morbidity).<sup>24</sup> In addition, noncardiac surgery and pregnancy (the

latter with a maternal mortality rate between 30% and 50%) carry a high mortality risk in this population.<sup>84,85</sup>

### Therapy

Traditionally, treatment options for patients with PAH associated with congenital heart disease were limited to palliative measures and heart-lung transplantation for highly selected patients. In brief, the mainstay of care has generally been not to destabilize the balanced systemic and pulmonary circulation.<sup>77</sup> This therapeutic nihilism, however, has been challenged recently by the advent of effective drugs for the treatment of PAH.<sup>8,9,10,11</sup> These therapies may also be applicable to selected patients with PAH and congenital heart disease, and recent results are encouraging.<sup>41,74</sup>

### General Management

Patients with PAH and congenital heart disease should undergo periodic assessment by cardiologists trained and experienced in the treatment of patients with adult congenital heart disease. Specific management strategies in patients with Eisenmenger syndrome include the following.

#### *Preservation of Fluid Balance and Avoidance of Dehydration*

The balance of fluids should be preserved, and dehydration should be avoided.

#### *Treatment of Iron-Deficiency Anemia*

Iron deficiency is of clinical importance because it limits exercise tolerance and increases the risk of stroke in these patients.<sup>86,87</sup> Iron deficiency should therefore be treated promptly with oral iron supplementation (or intravenous, if oral therapy fails).

#### *Relief of Hyperviscosity Syndrome*

When phlebotomy is deemed necessary, it should be performed by withdrawing 250 to 500 mL of blood, with appropriate intravenous volume replacement and the incorporation of air filters. Routine phlebotomy in cyanotic patients with congenital heart disease and PAH is, however, contraindicated and should be discouraged because it may impair oxygen transport capacity, reduce exercise tolerance,<sup>87</sup> induce iron deficiency,<sup>24</sup> and increase the risk of stroke.<sup>88</sup> If phlebotomy is performed, iron status should be monitored closely, and iron supplementation should be provided. In our experience, the vast majority of patients with cyanotic congenital heart disease and chronic compensated secondary erythrocytosis without previous phlebotomies do not exhibit overt hyperviscosity symptoms.

#### *Contraception and Avoidance of Pregnancy*

Pregnancy is associated with high maternal and fetal mortality and should be strongly discouraged. Maternal mortality has been reported to be as high as 50%, and spontaneous abortion has been reported to occur in 40% of pregnancies.<sup>89–91</sup> Discussion of future pregnancies and contraception should begin in adolescence to avoid unplanned pregnancies.

No available contraceptive method is optimal in this setting. Combined oral contraceptives (containing progesterone and estrogen) carry an increased risk for thrombosis and are therefore not recommended. Progesterone-only contra-



ceptives, without thrombophilic properties, are also not recommended because of their higher failure rate compared with combined oral contraceptives.<sup>92</sup> The use of an intrauterine coil impregnated with progestogen (eg, Mirena coil) offers acceptable efficacy and safety and should be considered. Laparoscopic sterilization represents an alternative but carries a significant surgical risk. In addition, the use of a progesterone subdermal implant has been suggested, although more data in this population are required.

If pregnancy occurs and abortion is declined, a multidisciplinary approach including experienced cardiologists, obstetricians, and anesthesiologists is clearly required.<sup>93</sup> Deaths usually occur in the postpartum, so close supervision is required 1 to 2 weeks after delivery.

#### **Antiarrhythmic Therapy**

Arrhythmias are common<sup>24</sup> and generally poorly tolerated in patients with Eisenmenger physiology. Although available data are contradictory and the predictive value of arrhythmia needs further evaluation,<sup>24,48,82</sup> prompt restoration and maintenance of sinus rhythm are important therapeutic goals. Furthermore, the role of implantable cardioverter-defibrillators in this patient group should be investigated because sudden cardiac death appears to be the most common mode of death.<sup>94</sup>

#### **Anticoagulation**

Large intrapulmonary thrombi occur in up to a third of adult patients with Eisenmenger physiology.<sup>58,59</sup> There is a paucity of data on the effect of anticoagulation in patients with intrapulmonary thrombosis, and therapy decisions are usually empirical. Thus, arguments have been made both in favor of and against anticoagulation in this setting.<sup>50</sup> In our practice, we recommend outpatient therapy with warfarin for patients with pulmonary thrombosis and absent or only mild hemoptysis. Whether routine prophylactic anticoagulation with warfarin (a common practice for other forms of PAH) or antiplatelet therapy is warranted in patients with congenital heart disease and PAH remains unknown. Anticoagulation with warfarin, whether prophylactic or for other reasons (such as supraventricular arrhythmia or ventricular dysfunction), needs slow and careful titration. In addition, special blood tubes adjusted for elevated hematocrit levels are required, and involvement of a hematologist in this respect is advisable.

#### **Oxygen Therapy and Air Travel**

Oxygen therapy is occasionally prescribed in cyanotic patients with PAH and is associated with improved subjective status in some. However, available data suggest that long-term nocturnal oxygen therapy does not improve symptoms, exercise capacity, and outcome in adult patients with Eisenmenger syndrome.<sup>95</sup> Routine use of long-term oxygen therapy can thus not be recommended particularly because it has a drying effect and predisposes some patients to epistaxis. Cabin pressures in commercial airplanes are maintained at levels corresponding to  $\approx 2000$  m of altitude throughout the flight. This mildly reduced barometric pressure is generally well tolerated by congenital heart disease patients with PAH, and air travel is therefore not contraindicated.<sup>96,97</sup> Adequate preparation and avoidance of stress are advisable, however.

Furthermore, dehydration during long flights should be avoided.

#### **Transplantation**

Heart and lung transplantation or lung transplantation in combination with repair of the underlying cardiac defect represents a therapeutic option for selected patients. Successful transplantation improves symptoms and quality of life in highly symptomatic patients with PAH and congenital heart disease.<sup>98,99</sup> However, because natural survival prospects are far better compared with idiopathic or other forms of PAH,<sup>79</sup> patient selection and timing of transplantation remain challenging. In practice, transplantation is currently restricted to highly symptomatic patients and those in whom life expectancy is considered short.

Additional management strategies include avoidance of strenuous exercise and competitive sports, meticulous endocarditis prophylaxis, annual immunization against influenza and pneumococcal infections and careful planning and intraoperative monitoring during noncardiac surgery, which carries significant mortality risks in this population.<sup>85</sup>

#### **Disease-Targeting Therapies**

Different drugs, including prostacyclin in various forms, nitric oxide, phosphodiesterase inhibitors such as sildenafil, and endothelin-receptor antagonists such as bosentan, have been demonstrated to be beneficial in patients with idiopathic PAH.<sup>99</sup> Until recently, there was little evidence to show efficacy of these drugs in patients with congenital heart disease or Eisenmenger syndrome. Furthermore, worsening right-to-left shunting due to concurrent reduction in systemic vascular resistance was assumed.

Recently, prostacyclin analogues have been shown to improve functional capacity, oxygen saturations, and pulmonary hemodynamics in patients with congenital heart disease and PAH.<sup>100,101</sup> However, prostacyclin administration is invasive, and prolonged intravenous therapy is associated with frequent complications such as sepsis and line dislocation. Overall, oral therapies are preferred in patients with PAH and congenital heart disease as opposed to intravenous agents that may be applicable to patients with idiopathic PAH and poor short-term prognosis. Only preliminary data on the efficacy of oral (beraprost) and subcutaneous (treprostinil) prostacyclin analogues are available. Subgroup analysis on the effect of beraprost in patients with PAH showed no significant improvement in exercise tolerance in patients with conditions other than idiopathic PAH (including congenital heart disease).<sup>102</sup> In contrast, Simonneau et al<sup>103</sup> demonstrated that subcutaneous treprostinil is beneficial in patients with PAH independent of underlying etiology.

Inhalation of nitric oxide has been shown to reduce total pulmonary vascular resistance in 30% of patients with Eisenmenger syndrome.<sup>104</sup> The same group showed more recently that responsiveness to inhaled nitric oxide is associated with a midterm survival benefit in patients with PAH and congenital heart disease.<sup>72</sup> There are, however, administration challenges with nitric oxide, although delivery systems are improving. Furthermore, anecdotal evidence suggests that

nitric oxide and inhaled iloprost may be advantageous for use during pregnancy and the peripartum.<sup>93,105</sup>

Sildenafil, a phosphodiesterase-5 inhibitor, was shown to be effective in reducing pulmonary vascular resistance and improving functional class and 6-minute walk test in patients with idiopathic PAH.<sup>106,107</sup> Its oral route of administration makes it attractive for potential use in patients with congenital heart disease and PAH. A recently published double-blind, randomized, placebo-controlled study demonstrated that sildenafil is safe and improves exercise capacity over the short term and midterm in patients with PAH of various etiologies.<sup>108</sup> In contrast, the safety and efficacy of sildenafil in patients with PAH and residual shunting or Eisenmenger syndrome have not yet been established. Preliminary results from 2 small open-label studies including 4 patients with Eisenmenger syndrome seem encouraging<sup>41,107</sup>; however, sildenafil should not be used routinely in patients with Eisenmenger syndrome until blinded, placebo-controlled data become available.<sup>109</sup>

Bosentan, a dual-receptor endothelin antagonist, has been demonstrated to reduce pulmonary arterial pressure, decrease pulmonary vascular resistance, and attenuate pulmonary fibrosis and inflammation.<sup>15</sup> Its efficacy in patients with idiopathic PAH has been confirmed by 2 randomized controlled trials.<sup>10,11</sup> Several intention-to-treat open-label pilot studies<sup>110–113</sup> and a recent randomized placebo-controlled study<sup>74</sup> have shown that oral bosentan therapy is effective in improving 6-minute walk distance and pulmonary hemodynamics in adults with Eisenmenger physiology. Furthermore, it does not disrupt the balance between the systemic and pulmonary vascular circulation and has the same safety profile as reported in other groups of PAH. Therefore, bosentan appears to be a promising treatment option for symptomatic patients with PAH and congenital heart disease.

Additional studies addressing long-term efficacy are required before the general use of these drugs can be recommended in patients with PAH and congenital heart disease. In addition, the impact of advanced therapies on clinical outcomes in patients with PAH and congenital heart disease is unknown. Because annual mortality rates are relatively low in this patient population, composite clinical end points or surrogate markers of outcome such as 6-minute walk test distance, ventricular function, or natriuretic peptides may serve as meaningful alternatives in future studies.<sup>70</sup>

Surgical reduction of pulmonary blood flow, enabling pulmonary vascular remodeling, has been reported anecdotally in Eisenmenger patients. Batista et al<sup>114</sup> described a young patient with advanced PAH in whom surgical correction of the underlying atrial and ventricular septal defect became possible after pulmonary artery banding for 1 year. Pulmonary artery banding, however, is problematic in patients with PAH associated with congenital heart disease; pulmonary vascular resistance improves only in a minority of patients after pulmonary artery banding, and even if it does, the decrease in pulmonary resistance is relatively small.<sup>115</sup> Furthermore, even successful banding may fail to induce regression of pulmonary vascular disease in patients aged >2 years.<sup>116</sup> Recently, successful correction of underlying cardiac defects under treatment with advanced therapies has

been described in adult patients with advanced PAH and congenital heart disease.<sup>117,118</sup> Because advanced therapies are increasingly used in this patient population, it is likely that a growing number of such patients will present and may be considered for corrective surgery. Generally, if advanced PAH is present, corrective surgery should be considered only for patients with evidence of pulmonary arterial reactivity and/or in the presence of a left-to-right shunting of at least 1.5:1.<sup>119</sup> Lung biopsy may provide additional information on severity of pulmonary vascular disease but should be undertaken only in specialist centers.

Pulmonary hypertensive crises remain a major complication after cardiothoracic surgery and are associated with considerable morbidity and mortality. Nitric oxide has been demonstrated to reduce the frequency of pulmonary vascular crises, improve oxygenation, and shorten time to extubation.<sup>120</sup> More recently, sildenafil alone or in combination with nitric oxide has also been shown to be beneficial in this setting.<sup>121,122</sup>

### Perspective

Improved understanding of the underlying pathophysiological mechanisms, earlier diagnosis, careful medical management, and the introduction of novel disease-targeting therapies are bound to improve quality of life and long-term survival prospects for patients with PAH and congenital heart disease. Further research elucidating underlying genetic predisposition and the complex interplay between genetic background and environmental triggers (cardiac lesion, pulmonary arterial pressures, and flow) will augment our understanding of etiology and disease progression. In addition, the long-term efficacy of disease-targeting therapies and the role of routine anticoagulation in these patients need to be addressed. Finally, there is a pressing need for education of general cardiologists, other medical groups, and the patients themselves on the issues discussed in this report.<sup>123</sup>

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