



#### Editorial Mission

*Advances in Pulmonary Hypertension* is committed to help physicians in their clinical decision making by informing them of important trends affecting their practice. Analyzing the impact of new findings and covering current information in the peer-reviewed literature, *Advances in Pulmonary Hypertension* is published four times a year. *Advances in Pulmonary Hypertension* is the official journal of the Pulmonary Hypertension Association.

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**Cover Photo:** Echocardiogram of an adult with an ASD: upper left, color flow doppler demonstrating bidirectional shunting across the ASD; lower left, 2-D echo demonstrating marked atrial and ventricular enlargement; right, doppler flow measurement of pulmonary artery pressure.

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## PAH-Associated Congenital Heart Disease: Finding Common Ground With Primary Pulmonary Hypertension



As we planned this issue on pulmonary arterial hypertension (PAH) in congenital heart disease and in children, we sensed the long shadows of physicians who have helped establish the parameters of its diagnosis. There were giants like Viktor Eisenmenger, who described the clinical features of a patient with PAH more than 100 years ago, and Paul Wood, who subsequently used the term “Eisenmenger syndrome” to describe PAH with reversal of a systemic to pulmonary shunt. As the nomenclature has evolved so has our understanding of the conditions seen in association with pulmonary hypertension.

A reclassification by the World Health Organization in 1998 brought us further along, as it emphasized similarities between pri-

mary pulmonary hypertension and PAH of certain known etiologies. An improved understanding of the mechanisms underlying the vascular changes in PAH has been an important factor in the emergence of new therapies. Notably, some medical therapies for the treatment of primary pulmonary hypertension may benefit patients with PAH associated with congenital heart disease. It is intriguing to find the diversity in the etiology of PAH and yet some uniformity in treatment approaches.

Our Roundtable Discussion so capably managed by Robyn Barst, MD, explored all of these issues. We have all recognized how difficult it may be to differentiate whether a patient with a congenital heart defect has Eisenmenger syndrome as opposed to primary pulmonary hypertension. The experts in pediatric cardiology we brought together for the Roundtable, as well as the authors of our articles in this issue, addressed this and many other difficult questions and present a comprehensive discussion of vital topics essential to our understanding of PAH in congenital heart disease. Hopefully, the insights presented will give us a clearer perspective on how to classify and treat patients who have these diseases.

Vic Tapson, MD  
Editor-in-Chief



### Profiles in Pulmonary Hypertension

## Remembering Paul Wood: Relentlessly Driven, Dazzling Diagnostician



Paul Wood, MD

Forty years after he died at the tragical early age of 54, the reputation of Dr Paul Wood as a showman and consummate physician, so dazzling in his ability to diagnose that he is recognized as one of the greatest diagnosticians ever, still serves as a reminder of what he means to contemporary cardiology. These diagnostic skills, combined with his quantitative approach to examination and clinical data, meticulously recorded on voluminous data cards, led to studies

that have become the foundation of current clinical understanding of septal defects, pulmonic stenosis, mitral stenosis, aortic stenosis, Eisenmenger syndrome, constrictive pericarditis, and surgery for congenital and acquired heart disease.

Driving himself relentlessly in his investigative work and expecting perfection from himself and his colleagues, he injected energy, enthusiasm, and an enormous capacity for work into everything that he did, according to Mark Silverman, MD, Professor of Medicine at Emory University, Atlanta, Georgia. As an historian, Silverman chronicled the brilliant career of the British physician whose reputation in Europe and the United States in the 1950s established him as a legend in the field of rheumat-

ic and congenital heart disease.<sup>1</sup> According to Silverman's research, Wood introduced physiology to the bedside, brought accuracy to the preoperative assessment of cardiac disease, and bridged the gap between early 20th century and modern cardiology.<sup>1</sup>

Wood's commanding personality—ranging from caustic and sarcastic to combative—often intimidated students and offended colleagues as he openly argued with himself and others to arrive at the correct diagnosis. His 1950 textbook, *Diseases of the Heart and Circulation*, still stands as a landmark in the cardiovascular literature and the Wood Unit, the value for vascular resistance, still reminds 21st century clinicians of his stature in the field. As early as the 1950s, Wood echoed the concerns of some latter day clinicians when he warned that bedside medicine was being replaced by an overreliance on technology: “Yet there is already plenty of evidence to show that we are in danger of losing our clinical heritage and of pinning too much faith in figures thrown up by machines. Medicine must suffer if this tendency is not checked,” he said.

Practicing in London during an era when echocardiography had yet to appear and when cardiac catheterization still meant right-heart catheterization, Wood made important observations on Da Costa's syndrome, the electrocardiogram in pulmonary heart disease, pulmonary vasoconstriction, and anticoagulation for coronary insufficiency. His major influence was his extraordinary bedside teaching during the days of unoperated upon and often advanced valvular and congenital heart disease. A bedside diagnosis was critical because a decision to operate hinged on clinical findings. Wood's method of teaching emphasized a gathering of 10 to 20 colleagues, residents, students, and clinical assistants around the bedside as he revealed his logic in arriving at a diagnosis and challenged them to offer their opinions.

Refusing resuscitation because he said he preferred to die rather than risk surviving without his full mental capabilities,

*(continued on page 10)*

# Pulmonary Hypertension in Children: New Insights Offer Opportunity to Reverse the Disease Process



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Severe, sustained pulmonary hypertension is potentially fatal. It is, however, time to adopt a more positive and aggressive approach to the management of pulmonary hypertension in children. Recent advances in genetics and cell biology provide insights into the pathogenesis of this disease. New therapies offer an improved quality of life and increased survival.

The sustained clinical and hemodynamic improvement seen in many adults and children with primary pulmonary hypertension (PPH) treated with continuous prostacyclin, and data from numerous experimental studies indicate that it is possible to arrest and perhaps even reverse the disease process. Potential reversal of the disease process is likely to be greater in the young, in whom the vasculature is still remodeling. Also, pulmonary vascular reactivity is greater in children than in adults with pulmonary hypertension, suggesting greater vasodilator responsiveness and the possibility of a better therapeutic outcome. When PPH is untreated, however, its natural history is significantly worse in children than adults, and even with treatment the disease is less predictable. Unfortunately, most children are referred late in the course of the disease, making it imperative to increase awareness of the condition and encourage early referral. It is unclear, however, why the clinical course varies considerably in different children.

Pulmonary hypertension is defined as a mean pulmonary arterial pressure > 25mm Hg at rest or 30mm Hg with exercise, although pulmonary hypertension in childhood is usually associated with considerably higher pressures. A new classification was proposed at a WHO Symposium in 1998, based on anatomy, clinical features and an appreciation of the commonality of at least some of the underlying mechanisms.<sup>1</sup> Primary pulmonary hypertension and pulmonary hypertension related to congenital heart disease, persistent pulmonary hypertension of the newborn (PPHN), connective tissue disease, HIV infection, drugs and toxins were grouped together as 'pulmonary arterial hypertension' (PAH). This new classification encourages the extension of therapeutic modalities known to be effective in PPH to other forms of pulmonary hypertension, in both adults and children. Further clarification is necessary in children with congenital heart disease. In these children PAH is usually caused and driven by a cardiac abnormality, which leads to the development of the Eisenmenger Syndrome. But in some children the abnormality is, and always has been, hemodynamically insignificant. Clinically these children behave as though they

have PPH, and should be treated as such.

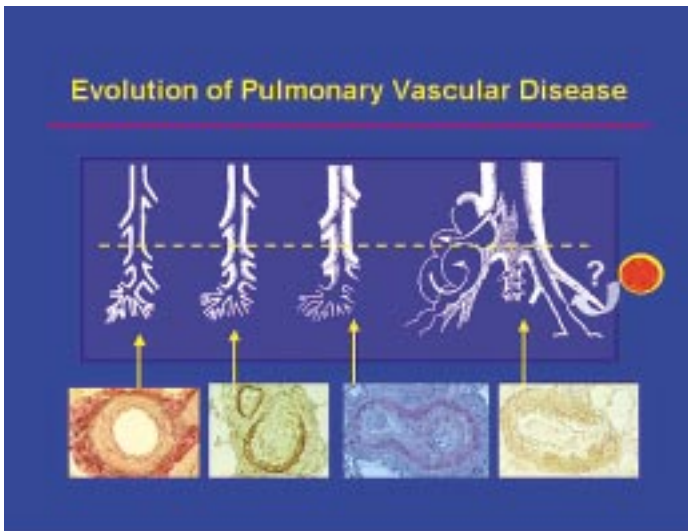
## Pathogenesis of Pulmonary Hypertension in Children

During the past few years we have gained considerable insight into the molecular mechanisms responsible for the development and maintenance of PAH, several of which suggest promising new approaches to therapy.<sup>2</sup> This review focuses on the pathogenesis of the more common forms of PAH in the young, PPH, PPHN, and pulmonary hypertension associated with congenital heart disease. Genetic studies have concentrated on familial PPH (FPPH) and the mutations recently identified in FPPH have not yet been sought systematically in other forms of pulmonary hypertension.

## PRIMARY PULMONARY HYPERTENSION: GENETICS

### Familial Primary Pulmonary Hypertension (FPPH)

Only 6% of cases of PPH have been reported as familial.<sup>3</sup> The disease is transmitted as an autosomal dominant trait, with incomplete penetrance. The chance of a person carrying a gene for FPPH developing the disease is higher in females (30%) than males (15%), and a female predominance is present from early childhood. FPPH shows gene anticipation, the disease frequently presenting at an earlier age in successive generations.<sup>4</sup> The FPPH locus maps to chromosome 2q31-32 and germline mutations have been identified in the bone morphogenetic protein receptor-II (BMPR2).<sup>5</sup> The BMPs form the largest group within the transforming growth factor-b (TGF-b) family of cytokines. The PPH disease-associated mutations identified would be expected to disrupt signaling pathways mediated by BMPR2, thereby removing a mechanism for keeping vascular remodeling in check and facilitating abnormal proliferation of pulmonary vascular cells. Mutation in another TGF-b family member, the Type I receptor gene, activin -receptor -like- kinase (ALK1) has been implicated in Hereditary Hemorrhagic Telangiectasia associated pulmonary hypertension.<sup>6</sup> It is likely that other PPH genes remain to be identified. BMPR2 mutations have not been identified in some 60% of FPPH cases, and most sporadic cases do not appear to harbor BMPR2 mutations. There are also families in whom pulmonary hypertension is associated with hemoglobinopathies and platelet storage defects.



**Fig. 1**—Cartoon illustrating the evolution of pulmonary vascular disease in the young. The interrupted line indicates the lines of transection through which the transverse tissue sections shown at bottom were taken.

Sporadic Primary Pulmonary Hypertension (PPH) BMPR2 defects have been described in 26% of sporadic cases of PPH, in some cases arising as “de novo” or spontaneous, mutations.<sup>7</sup>

### Pathobiology

Sporadic and familial PPH have the same pathological features. At autopsy, most adults and older children have advanced pulmonary vascular obstructive disease with plexiform lesions, and this picture can be seen before 3 years of age (**Fig. 1**). Monoclonal cell expansion is thought to lead to the production of plexiform lesions in a subset of adult patients with PPH.<sup>8</sup> In young children, the cellular changes can be restricted to severe pulmonary arterial medial hypertrophy with marked intimal proliferation, lesions that are more likely to be potentially reversible. The instigators of this process are uncertain. Loss of one normal BMPR2 allele does not, in itself, produce the phenotype. It is now thought that PPH affects those with a genetic predisposition to respond adversely to a variety of stimuli and that the clinical and structural findings represent the final common pathway.

The following are thought important in the pathogenesis of PPH:

- **Endothelial dysfunction:** Levels of circulating endothelin, a powerful vasoconstrictor and mitogen, are elevated and expression of endothelin converting enzyme is increased. Prostacyclin and nitric oxide, vasodilators with antiproliferative and antimigratory properties, are reduced.<sup>9</sup> Long-term treatment with prostacyclin or one of its analogues is a proven, effective therapy<sup>10</sup> while inhaled NO, NO donors, and the phosphodiesterase inhibitors are as yet unproved alternatives/adjuncts, unproven in terms of both efficacy and safety. Endothelin receptor antagonists have proved safe and effective in small trials, mostly in adult patients, and are being evaluated in younger patients.<sup>11</sup>
- **Intense vasoconstriction** is thought to be an early, common response to injury. Although pulmonary vascular disease is

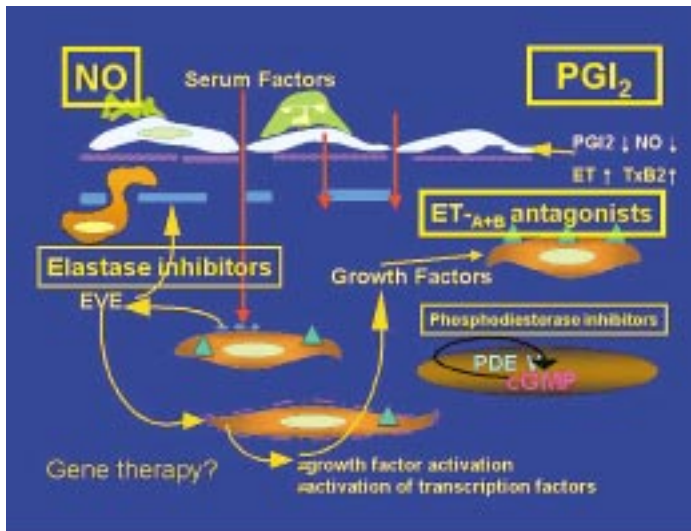
usually well advanced at presentation, the pulmonary vascular resistance falls in some patients on acute vasodilator testing, more often in children (50% to 60%) than in adults (20%).<sup>12</sup> Calcium channel blockers, an accepted, conventional therapy, prolongs survival in adults. Both hypoxia and anorexic agents, which can cause pulmonary hypertension, inhibit potassium currents in pulmonary artery smooth muscle cells causing membrane depolarization, which promotes an increase in intracellular calcium concentration and hence, vasoconstriction. Finding dysfunctional voltage-gated potassium channels in primary but not secondary pulmonary hypertension suggests that potassium channels may play a significant role in the pathogenesis of PPH. In terms of potential therapy, ATP-sensitive potassium channel openers probably offer the greatest promise since these agents are potent dilators of the pulmonary circulation and are still able to promote membrane hyperpolarization in proliferating smooth muscle cells.<sup>13</sup>

- **Platelet function:** The ratio of thromboxane to prostacyclin is increased, predisposing to vasoconstriction and platelet aggregation.<sup>9</sup> The role of serotonin in the pathogenesis of PPH is still uncertain, but elevated plasma levels and impaired platelet storage of serotonin can occur. Serotonin transporters are overexpressed on pulmonary arterial smooth muscle cells.<sup>14</sup> Elevated fibrinopeptide A levels and pathological studies indicate thrombosis in situ, and there is evidence of impaired local fibrinolysis. Anticoagulation increases survival in adults and is used in children.
- **Dysfunction of the immune system:** Pulmonary hypertension is a component of several autoimmune disorders, particularly scleroderma and appears to have an autoimmune origin in some children.

### PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

Failure of the pulmonary circulation to adapt normally to extra-uterine life causes PPHN. The condition can be idiopathic but this is rare, and it is more commonly associated with congenital and acquired hypoxic lung disease and congenital heart defects. The condition has a high morbidity and mortality despite the advent of inhaled nitric oxide therapy. Irrespective of etiology, during the first few days of life the intrapulmonary arterial wall structure is similar to that seen in fetal life and neonatal remodeling is impaired.<sup>15</sup> Functional studies demonstrate impairment of the NO pathway, sometimes a deficiency of the NO substrate L-arginine, increased levels of the endogenous inhibitor asymmetric dimethyl arginine, and persistently high circulating endothelin levels. Studies on *normal* animals reveal low NOS activity and relatively poor endothelial dependent relaxation at birth, and these systems fail to mature properly in PPHN.<sup>16</sup>

Different relaxation pathways (NO, prostaglandin, EDHF) mature at different rates and have different vulnerabilities to insult. Vasoconstrictor ET-A receptor density increases and endothelial vasodilator ET-B receptor density decreases.<sup>17</sup> Thus, failure to reduce the pulmonary vascular resistance after birth appears to involve a primary structural abnormality, failure of endothelial dependent +/- independent relaxation, and an



**Fig. 2—Cartoon illustrating factors driving the evolution of PAH and the rationale of present and potential therapies. Endothelial dysfunction reduces release of prostacyclin and nitric oxide, causes adherence of activated platelets and leukocytes, enhances release of thromboxane and endothelin, and contributes to loss of barrier function with leakage of serum factor into the subendothelium. This is thought to heighten activity of metalloproteinases (MMPs) (including the proteolytic enzyme endogenous vascular elastase [EVE] released from smooth muscle cells) to help induce structural remodeling, cause smooth muscle cell activation, disrupt the internal elastic lamina, and facilitate smooth muscle cell migration. MMPs also activate growth factors normally sequestered in the matrix in an inactive form. Increased tenascin expression is associated with cell proliferation, and its downregulation with apoptosis. Tenascin amplifies the proliferative response to epidermal growth factor and fibroblast growth factor (FGF)-2 in vitro. Expression of fibronectin is widespread and this glycoprotein can facilitate smooth muscle migration. Innermost smooth muscle cells cease to express many smooth muscle specific contractile and cytoskeletal proteins before migrating through gaps in the internal elastic lamina. Changes in phenotype are widespread. Phosphodiesterase (PDE) V inhibitors help sustain the level of intracellular cGMP.**

excess of vasoconstrictor activity. The rationale for giving NO and phosphodiesterase inhibitors is that there is an absolute or relative lack of the endogenous substance. Oxygenation usually improves with administration of NO and the availability of NO has reduced the need for extracorporeal membrane oxygenation. New strategies directed at antagonizing vasoconstriction and modifying smooth muscle cell cytoskeletal remodeling are indicated. Outcome depends on causality. Some babies who appeared to recover normally were later found to have persistent arterial medial hypertrophy.

The relationship between PPHN and PPH is uncertain but children who present with PPH during the first years of life frequently have a history that suggests that they were pulmonary hypertensive from birth. Occasionally an infant thought to have PPH is found to have a secundum atrial septal defect. This is usually an incidental, though protective abnormality, and should not be closed.

### Congenital Heart Disease

The rate at which pulmonary vascular disease develops in children with congenital heart disease depends on the type of intracardiac abnormality, but some exceptional children appear

to be genetically predisposed to develop an accelerated form of the disease. Endothelial cell damage, medial smooth muscle cell hyperplasia, hypertrophy and site-specific changes in cell phenotype are well described in early infancy<sup>2</sup> (Fig. 1). Respiratory unit arteries, about half of which normally form after birth, are reduced in size and number. This is the morphological substrate of pulmonary hypertensive crises, which most often occur in the presence of potentially reversible structural abnormalities. Endothelial dysfunction is present early.

In potentially operable children the relaxation response to acetylcholine is impaired, basal NO production may be elevated initially but then decreases, and the ratio of thromboxane to prostacyclin is elevated.<sup>18</sup> Impaired endothelial-dependent relaxation occurs later in association with elevation in resistance. Dilatation and plexiform lesions contain abundant VEGF, which may help ensure continued perfusion of the capillary bed since VEGF helps induce endothelium dependent relaxation.<sup>19</sup> VEGF is also a potent angiogenic factor. It co-localizes with TGF- $\beta$  in the arterial wall and TGF- $\beta$  upregulates its angiogenic activity in vitro. As intimal obstruction develops, flow becomes more turbulent and in vitro studies suggest that this is likely to unfavorably influence gene transcription. Laminar flow is associated with activation of genes such as eNOS and COX2 but turbulent flow is associated with the localized upregulation of VCAM-1 and ICAM-1, encouraging leucocyte recruitment and activation.<sup>20,21</sup> Changes in mechanical stress also alter expression of specific genes in the smooth muscle cell, such as PDGF.

*Postoperative pulmonary hypertension.* The patient with repaired congenital heart disease who has pulmonary hypertension effectively has PPH, with the added problem of a compromised myocardium. Survival is significantly worse in the untreated patient with PPH than in most patients with the Eisenmenger syndrome. Assuming that these patients cannot be helped by further surgery, they should generally be treated as though they had PPH, and without delay.

### Pathobiology: Targeting the Mechanisms of Disease

Clinical and experimental studies have identified potentially important structural and functional abnormalities,<sup>2</sup> but whether these are cause or consequence of the disease remains to be determined (Fig. 2). Experimental models of PPHN have demonstrated that the term “endothelial dysfunction” does not apply to all aspects of endothelial function, but to specific signal transduction pathways in certain segments or regions of the pulmonary vascular bed. Functioning pathways should be identified and exploited.

Strategies shown to be effective in attenuating the hypertensive response to hypoxia and/or monocrotaline in rats include endothelin receptor blockers, modulating potassium channels, inhibition of 5-lipoxygenase as activating protein serine elastase inhibitors,<sup>22</sup> inhaled nitric oxide, and inhibition of 3'5'guanosinemonophosphate-specific phosphodiesterase. In vitro studies indicate that there will be a role for smooth-muscle growth inhibitors. The approach to gene therapy has concentrated on the overexpression of vasodilator genes, principally NO and prostaglandin I synthase, and results are encouraging.<sup>23,24</sup>

Tackling the different facets of angiogenesis is problematic. Growth of new vessels is a priority in the young who have developed pulmonary hypertension before the lung fulfilled its

growth potential. Intratracheal (VEGF)<sub>165</sub> gene injection attenuated hypoxic pulmonary hypertension in rats, but the mechanism is uncertain.<sup>25</sup> VEGF may not stimulate growth of normal vessels and in man it is abundant in plexiform lesions, which some have described as a form of uncontrolled angiogenesis.<sup>8</sup> Evidence that advanced disease can be arrested has come from clinical experience with continuous intravenous prostacyclin therapy in PPH. Prostacyclin appears to act primarily by structurally remodeling the pulmonary vasculature rather than solely as a pulmonary vasodilator. Identifying a mutation in the BMPR2 receptor implicating defective control of vascular remodeling puts the structural abnormalities back in the forefront of research interest as being the prime mover in the pathogenesis, rather than being viewed always as the inevitable consequence of endothelial injury. New therapies will preferentially target the long-term control of vascular remodeling rather than vasoconstriction.

### Diagnosis and Clinical Investigation

In PPH, symptoms vary and are age related. Infants and young children may fail to thrive, tire easily, have exertional dyspnea, and, occasionally, chest pain. Symptoms suggestive of pulmonary hypertensive crises as well as syncope can occur at any age. The following tests are crucial:

1. Echocardiography, which clarifies intracardiac anatomy and excludes congenital heart disease. Estimation of the pulmonary arterial pressure, right atrial and ventricular cavity size, and ventricular function is essential.
2. Exercise test, a 6-minute walk test or surrogate according to age and capacity, to measure the degree of functional impairment. In PPH exercise capacity correlates with right atrial pressure, pulmonary arterial pressure, and cardiac index.
3. Pulmonary function tests.
4. Oxygen saturation measurements, including a sleep assessment.
5. Cardiac catheterization: Following a conventional study, acute vasodilator testing is carried out using 100% oxygen and short-acting vasodilators, such as inhaled nitric oxide, intravenous epoprostenol, and intravenous adenosine. Using measured oxygen consumption together with arteriovenous oxygen difference, cardiac output is calculated and pulmonary vascular resistance determined. A positive response to acute vasodilator testing means reducing the pressure and resistance to a value approaching normal in the presence of an unchanged or increased cardiac output. Atrial septostomy/septectomy should be considered at the time of diagnostic catheterization in severely ill children (particularly if there is a history of drop attacks) whose anatomy is such that there is no opportunity for right to left shunting to acutely decompress the right heart and improve systemic output. An open lung biopsy may be indicated in complex congenital heart disease, suspected venoocclusive disease, and vasculitis.

Tests carried out primarily to detect chronic thromboembolic disease are rarely indicated in childhood.

**The patient with repaired congenital heart disease who has pulmonary hypertension effectively has PPH, with the added problem of a compromised myocardium. Survival is significantly worse in the untreated patient with PPH than in most patients with the Eisenmenger syndrome. Assuming that these patients cannot be helped by further surgery, they should generally be treated as though they had PPH, and without delay.**

### Management of the Pulmonary Hypertensive Child

In patients with PPH treated with chronic vasodilator therapy the most important determinants of survival are (1) age, with a 5-year survival of 88% in children of less than 6 years of age, as compared with 25% for older children and (2) the acute response to prostacyclin, the 5-year survival being 86%, as compared with 33% for nonresponders.<sup>26</sup> In congenital heart disease, symptoms and signs reflect the natural history of pulmonary vascular disease with and without surgery in the different anomalies. Lessons learned in the management of children with PPH are now being applied to other forms of pulmonary hypertension in childhood.

#### PPH

Treatment for PPH is lifelong. The therapeutic regimen has to be individualized and adjusted according to changes in clinical and hemodynamic status. Children need close monitoring of the clinical course to ensure a satisfactory and sustained

response to treatment, with recatheterization if necessary. Optimizing the management of these patients markedly improves quality of life and survival. The principles of management are:

- Children with a positive response to acute vasodilator testing are given calcium channel blockers, usually nifedipine. Actuarial survival is increased in adults treated with this drug. But the magnitude of response that predicts long-term survival is unknown in the young, and repeat cardiac catheterization is necessary after several months to detect any deterioration. Loss of acute responsiveness demands urgent revision of therapy.
- Children unresponsive to acute vasodilator testing are not treated with calcium channel blockers, which can have adverse effects and precipitate or worsen right-heart failure. Older, compliant children in NYHA Class II can take nebulized iloprost, which has a similar molecular structure to epoprostenol. Regular, effective dosing (6-12 times a day) is difficult in young children. The dual endothelin receptor antagonist Tracleer (bosentan), efficacious in adults, is now being studied in children. The oral prostacyclin analogue beraprost sodium is efficacious in adults but recommended only for those with less severe pulmonary hypertension and is largely untested in children. The subcutaneous analogue of prostacyclin, treprostinil (Remodulin), is too painful for use in young children. The phosphodiesterase inhibitor sildenafil is untested, but its effect appears to be relatively short-lived in sick children. The proven treatment of choice for the very sick child is long-term intravenous epoprostenol (Flolan). The dose is titrated according to clinical response, subjective and objective. Children generally need much higher doses of epoprostenol than adults and can become very tolerant of the drug, requiring constant, aggressive, upward adjustment of their dosage. Despite the obvious logistical problems, infants and young children can be managed satisfactorily. The side effects experienced by children are sim-

ilar to those seen in adults.

- Supplemental domiciliary oxygen provides symptomatic improvement for those with systemic arterial desaturation.
- Anticoagulation: Warfarin rather than aspirin or dipyridamole is recommended to prevent thrombosis in situ, although aspirin is more tolerable in early infancy.
- Supportive medical therapy: Diuretics are indicated to control the fluid retention of right-heart failure but should be administered cautiously in very sick children, who need a high preload. Digoxin may be helpful in the treatment of right-heart failure.
- Atrial septostomy/ septectomy, if indicated.
- Organization of care in the community and contact with patients' support groups is essential.

**Screening and Genetic Testing.** All first-degree relatives are screened in FPPH. It is thought that an individual in a family with FPPH has a 5% to 10% lifetime risk of developing PPH.<sup>27</sup> Genetic testing entails DNA sequencing because mutations in the BMPR2 gene appear to be "private" to each family.

### Congenital Heart Disease

Correlating the physiological findings with structural observations in different types of intracardiac abnormality has improved the accuracy with which immediate and long-term outcome can be predicted with and without corrective surgery.<sup>28</sup> But prediction is still more difficult in younger children. The most crucial factor in determining late outcome is the age at which repair is carried out. Most children operated on by 9 months of age have a normal pulmonary vascular resistance one year after repair. After two years of age-resistance may fall, but not to a normal level. These observations indicate vessel wall remodeling toward normality, continued growth, and a demonstrable improvement in endothelial function.<sup>18</sup> Repairing an intracardiac abnormality in the presence of established disease accelerates the progression of disease and the onset of right ventricular failure and death. If there is doubt about the likely outcome of surgical repair, then an open lung biopsy should clarify the position.

Treatment for patients with classic Eisenmenger syndrome is empirical. Long-term oxygen treatment often gives subjective improvement. Dipyridamole is thought to reduce platelet aggregation but may also have a beneficial vasodilatory effect as a phosphodiesterase inhibitor. Anticoagulation is recommended. Phlebotomy with plasma dilution in those with a high hematocrit is not used routinely but may afford symptomatic relief to some patients. Frequent phlebotomy causing iron deficiency can increase the risk of cerebrovascular accidents.

Treatment with prostacyclin is tempting, but its efficacy is not proved in patients with classic Eisenmenger syndrome and it can cause systemic hypotension in the presence of pulmonary-systemic communication. Endothelin receptor antagonists are promising but still unproved therapies. Long-term administration of L-arginine might be helpful if it could be shown conclusively that these patients have a relative substrate deficiency of NO production. Calcium channel blockers are not used.

**Repairing an intracardiac abnormality in the presence of established disease accelerates the progression of disease and the onset of right ventricular failure and death. If there is doubt about the likely outcome of surgical repair, then an open lung biopsy should clarify the position.**

Finally, the only effective treatment for the very sick patient with pulmonary vascular disease of any etiology who has failed medical treatment is lung transplantation. This is not usually an option in young children. Since the results of lung transplantation are less than optimal, transplantation should be considered only when the expected survival on medical treatment is less than the expected survival after transplantation. In the future, we can hope that prompt early referral and effective treatment with the new and emerging therapies will postpone the need for transplantation indefinitely in many young people.

### Future Treatment Strategies

1. Maximize the effect of current therapies by investigating selective combinations of drugs for use at different stages of disease.
2. Elucidate the role of endothelin receptor antagonists and the extent to which they can replace or be used with intravenous prostacyclin and the different prostacyclin analogues.
3. Develop new, stable prostacyclin analogues with a longer half-life for oral and inhalational use and specific, long-acting phosphodiesterase V inhibitors.
4. Explore novel therapies, such as elastase inhibitors, gene therapy, and treatments based on exploitation of key signaling pathways identified by BMPR2 mutations in FPPH.
5. Stimulate growth of new, normal vessels, particularly in the young.

### References

1. Rich S. Primary Pulmonary Hypertension: Executive Summary from the World Symposium on Primary Pulmonary Hypertension 1998, Evian, France, 6-10 September 1998. Rich, S. 2002.
2. Haworth SG. Pulmonary hypertension in the young. *Heart* 2002;88:658-64.
3. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension: a national prospective study. *Ann Intern Med* 1987;107:216-23.
4. Loyd JE, Butler MG, Foroud TM, et al. Genetic anticipation and abnormal gender ratio at birth in familial primary pulmonary hypertension. *Am J Respir Crit Care Med* 1995;152:93-7.
5. The International PPH Consortium, Lane KB, Machado RD, Pauciulo MW, Thompson JR, Phillips III JA, et al. Heterozygous germline mutations in a TGF- $\beta$ -receptor, BMPR2, are the cause of familial primary pulmonary hypertension. *Genetics* 2000;26:81-4.
6. Johnson DW, Berg JN, Baldwin MA, et al. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. *Nat Genet* 1996;13:189-95.
7. Thompson JR, Machado RD, Pauciulo MW. Sporadic primary pulmonary hypertension is associated with germline mutations of the gene encoding BMPR-II, a receptor member of the TGF-B family. *J Med Genet* 2000;37:741-5.
8. Lee S-D, Shroyer KR, Markham NE, et al. Monoclonal endothelial cell proliferation is present in primary pulmonary but not secondary pulmonary hypertension. *J Clin Invest* 1997;101:927-34.
9. Christman BW, McPherson CD, Newman JH, et al. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. *N Engl J Med* 1992;327:70-5.
10. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional treatment for primary pulmonary hypertension. *N Engl J Med* 1996;334:296-301.

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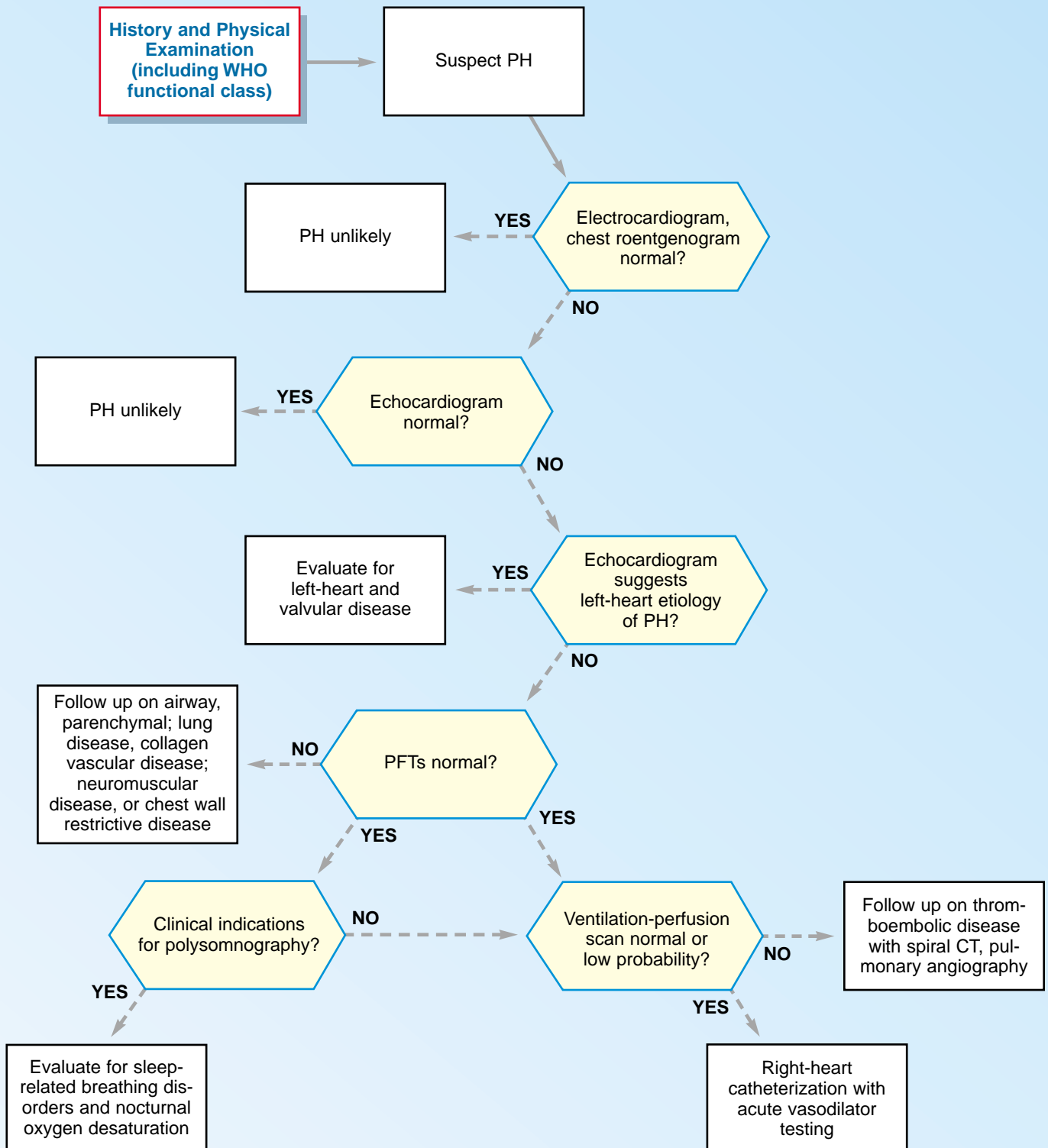
Clinical Algorithm

# Evaluation of Pulmonary Hypertension in Children

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11. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896-903.
12. Barst, R. J. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin. *Heart* 1997;77, 299-301.
13. Cui Y, Tran S, Tinker A, Clapp LH. The molecular composition of K(ATP) channels in human pulmonary artery smooth muscle cells and their modulation by growth. *Am J Respir Cell Mol Biol* 2002;26:135-43.
14. Eddahibi S, Humbert M, Fadel E, et al. Serotonin transporter overexpression is responsible for pulmonary artery smooth muscle hyperplasia in primary pulmonary hypertension. *J Clin Invest* 2001;108:1141-50.
15. Haworth SG. Pathobiology of pulmonary hypertension in infants and children. *Prog Ped Cardiol* 2001;12:249-69.
16. Tulloh RMR, Hislop AA, Boels PJ, et al. Chronic hypoxia inhibits postnatal maturation of porcine intrapulmonary artery relaxation. *Am J Physiol* 1997;272:H2436-H2445.
17. Noguchi Y, Hislop AA, Evans, J, et al. Increased plasma endothelin levels and endothelin receptor binding sites in neonatal pulmonary hypertensive pigs. *Am J Resp Crit Care Med* 1995;151:A517.
- Ref Type: Abstract
18. Adatia I, Barrow SE, Stratton PD, et al. Thromboxane A2 and prostacyclin biosynthesis in children and adolescents with pulmonary vascular disease. *Circulation* 1993;88:2117-22.
19. Ku DD, Zaleski JK, Liu S, et al. Vascular endothelial growth factor induces EDRF-dependent relaxation in coronary arteries. *Am J Physiol* 1993;265:H586-H592.
20. Resnick N, Gimbrone MA Jr. Hemodynamic forces are complex regulators of endothelial gene expression. *FASEB J* 1995;9:874-82.
21. Walpole PL, Gotlieb AI, Cybulsky MI, et al. Expression of ICAM-1 and VCAM-1 and monocyte adherence in arteries exposed to altered shear stress. *Arterioscler Thromb Vasc Biol* 1995;15:3-20.
22. Cowan KN, Heilbut A, Humpl T, et al. Complete reversal of fatal pulmonary hypertension in rats by a serine elastase inhibitor. *Nat Med* 2000;6:698-702.
23. Geraci MW, Gao B, Shepherd DC, et al. Pulmonary prostacyclin synthase overexpression in transgenic mice protects against development of hypoxic pulmonary hypertension. *J Clin Invest* 1999;103:1509-15.
24. Nagaya N, Yokoyama C, Kyotani S, et al. Gene transfer of human prostacyclin synthase ameliorates monocrotaline-induced pulmonary hypertension in rats. *Circulation* 2000;102:2005-10.
25. Partovian C, Adnot S, Raffestin B, et al. Adenovirus-mediated lung vascular endothelial growth factor overexpression protects against hypoxic pulmonary hypertension in rats. *Am J Respir Cell Mol Biol* 2000;23:762-71.
26. Barst RJ, Long W, Gersony W. Long-term vasodilator treatment improves survival in children with primary pulmonary hypertension. *Cardiol Young* 1993;3:89.
27. Morse JH, Knowles JA. Genetics of primary pulmonary hypertension. *Prog Ped Card* 2001;12:271-8.
28. Haworth SG. Pulmonary Hypertension, In: Moller JH, Hoffman JIE, eds. *Paediatric Cardiovascular Medicine*. Philadelphia, Pa:1998.

(continued from page 3)

Wood died of a myocardial infarction in July 1962, about a month after a speaking tour of the U.S. During that tour he met with J. Willis Hurst, Emeritus Chairman of Medicine at Emory. Hurst later credited his conversation with Wood as providing a major stimulus for Hurst and his colleagues to create the landmark text, *The Heart*, in 1966.

There was another side to Wood. Silverman reports that he was kind and considerate to each patient, and most seemed thrilled to be at the center of attention of a master physician. After his examination, he would explain his findings and prognosis to the patient,

expressing concern about his or her welfare but at the same time speaking bluntly and honestly.<sup>1</sup> Most of his graduate students, however, were cowed, awed and inspired by his dazzling ability to think and teach. Many used him as a role model and remained disciples to his teaching for the rest of their careers. In that sense, all who studied under or were influenced by him can be considered keepers of the flame of Paul Wood.


1. Silverman ME, Somerville W. To die in one's prime: the story of Paul Wood. *Am J Cardiol* 2000;85:75-88.

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  - Potential for serious liver injury: Liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter
  - Potential damage to a fetus: Pregnancy must be excluded and prevented; monthly pregnancy tests should be obtained
- Contraindicated for use with cyclosporine A and glyburide

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**Use of TRACLEER requires attention to two significant concerns: 1) potential for aminotransferase injury, and 2) potential damage to a fetus.**

**WARNING: Potential liver injury.** TRACLEER causes at least 2-fold (upper limit of normal) SUN elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly (see WARNINGS: Potential Liver Injury and DOSAGE AND ADMINISTRATION). To date, in a setting of close monitoring, elevations have been reversible, within a few days to 5 weeks, either spontaneously or after dose reduction or discontinuation, and without sequelae. Therefore, aminotransferases require close attention (see DOSAGE AND ADMINISTRATION). TRACLEER should generally be avoided in patients with elevated aminotransferase (> 3 x UN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual fatigue or fatigue or increase in bilirubin > 2 x UN), treatment should be stopped. There is no experience with the re-introduction of TRACLEER in these circumstances.

**CONTRAINDICATION: Pregnancy.** TRACLEER (bosentan) is very likely to produce major birth defects if used by pregnant women, as the effect has been seen consistently when it is administered to animals (see CONTRAINDICATIONS). Therefore, pregnancy must be excluded before the start of treatment with TRACLEER and prevented thereafter by use of a reliable method of contraception. Hormonal contraceptives, including oral, injectable and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in women receiving TRACLEER (see Precautions: Drug Interactions). Monthly pregnancy tests should be obtained.

Because of potential liver injury and as an effort to make the chance of fetal exposure to TRACLEER (bosentan) as small as possible, TRACLEER may be prescribed only through the TRACLEER Access Program by calling 1 866 381 346. Adverse events can also be reported directly on this website.

**INDICATIONS AND USAGE:** TRACLEER is indicated for the treatment of pulmonary arterial hypertension in patients with WHO Class II or III symptoms, to improve exercise ability and decrease the risk of clinical worsening.

**CONTRAINDICATIONS:** TRACLEER is contraindicated in pregnancy, with concomitant use of cyclosporins, with co-administration of glyburide, and in patients who are hypersensitive to bosentan or any component of the medication.

**Pregnancy Category X.** TRACLEER is expected to cause fetal harm if administered to pregnant women. The similarity of malformations induced by bosentan and those observed in embryonic 1 knockout mice and in animals treated with other endothelin receptor antagonists indicate that teratogenicity is a class effect of these drugs. There are no data on the use of TRACLEER in pregnant women. TRACLEER should be started only in patients known not to be pregnant. For female patients of childbearing potential, a prescription for TRACLEER should not be issued by the prescriber unless the patient signs the prescription that she is not sexually active or provides negative results from a urine or serum pregnancy test performed during the first 3 days of a normal menstrual period and at least 11 days after the last unprotected act of sexual intercourse. Following urine or serum pregnancy tests should be obtained monthly in women of childbearing potential using TRACLEER. The patient must be advised that there is a delay in onset of menses or any other reason to suspect pregnancy, she must notify the physician immediately for pregnancy testing. If the pregnancy test is positive, the physician and patient must discuss the risk to the pregnancy and the fetus.

**WARNINGS: Potential liver injury.** Bosentan in ALT or AST by more than 2 x UN were observed in 11% of bosentan-treated patients (N = 88) compared to 2% of placebo-treated subjects (N = 200). The combination of hepatocellular injury (increases in aminotransferases of > 3 x UN) and increases in total bilirubin (> 2 x UN) is a marker for potential serious liver injury. Elevations of AST and/or ALT associated with bosentan are dose-dependent, occur both early and late in treatment, usually progress slowly, or typically asymptomatic, and to date have been reversible after treatment interruption or cessation. These aminotransferase elevations may resolve spontaneously while continuing treatment with TRACLEER. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual fatigue or fatigue) or increase in bilirubin > 2 x UN, treatment should be stopped. There is no experience with the re-introduction of TRACLEER in these circumstances. Precautions: Liver Impairment TRACLEER should generally be avoided in patients with moderate or severe liver impairment; if available, TRACLEER should generally be avoided in patients with elevated aminotransferase (> 2 x UN) because monitoring liver injury in these patients may be more difficult.

**PRECAUTIONS: Hematology.** Change: Treatment with TRACLEER caused a dose-related decrease in hemoglobin and hematocrit. The overall mean decrease in hemoglobin concentration for bosentan-treated patients was 0.9 g/dL (range to end of treatment). Most absolute decreases in hemoglobin concentration were detected during the first few weeks of bosentan treatment and hemoglobin levels stabilized by 8-12 weeks of bosentan treatment. During the course of treatment the hemoglobin concentration remained within normal limits in 85% of bosentan-treated patients compared to 79% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhagic or hemolytic. If a marked decrease in hemoglobin concentration is checked after 1 and 3 months, and every 2 months thereafter, if a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.

**Information for Patients:** Patients are advised to consult the TRACLEER Medication Guide on the safe use of TRACLEER. The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases and urine or serum pregnancy testing and of avoidance of pregnancy. The physician should discuss options for effective contraception and measures to prevent pregnancy with these female patients (input from a gynecologist or similar expert or adequate contraceptive should be sought as needed).

**Drug Interactions: CYP Isoenzymes.** Bosentan is metabolized by CYP2C9 and CYP3A4. Inhibition of these isoenzymes may increase the plasma concentration of bosentan. Bosentan is an inhibitor of CYP3A4 and CYP2C9. Consequently, plasma concentrations of drugs metabolized by these two isoenzymes will be decreased when TRACLEER is co-administered. Concomitant Specific Interaction Studies have not been performed to evaluate the effect of co-administration of bosentan and hormonal contraceptives, including oral, injectable or implantable contraceptives. Since many of these drugs are metabolized by CYP3A4, there is a possibility of failure of contraceptives when TRACLEER is co-administered. Women should not rely on hormonal contraceptives alone when taking TRACLEER. Cyclosporin A During the first year of concomitant administration through concentrations of bosentan were increased by about 20-fold. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporin A. The concomitant administration of bosentan and cyclosporin A is contraindicated. Digoxin: An increased risk of elevated liver aminotransferase was observed in patients receiving concomitant therapy with glyburide. Therefore, the concomitant administration of TRACLEER and glyburide is contraindicated, and alternative hypoglycemic agents should be considered. Bosentan is also expected to reduce plasma concentrations of other oral hypoglycemic agents that are predominantly metabolized by CYP2C9 or CYP3A4. The possibility of increased glucose control in patients using these agents should be considered. Ketoconazole: Co-administration of bosentan (125 mg b.i.d.) and ketoconazole, a potent CYP3A4 inhibitor, increased the plasma concentrations of bosentan by approximately 2-fold. No dose adjustment of bosentan is necessary, but increased effects of bosentan should be considered. Simvastatin and Other Statins: Co-administration of bosentan decreased the plasma concentrations of simvastatin (a CYP3A4 substrate) and its active 5-hydroxy acid metabolite, by approximately 20%. The plasma concentrations of bosentan were not affected. Bosentan is also expected to reduce plasma concentrations of other drugs that have significant metabolism by CYP3A4 such as losartan and atorvastatin. The possibility of reduced drug efficacy should be considered. Patient using CYP3A4 metabolized drugs should have cholesterol levels monitored after TRACLEER is initiated to see whether the drugs show dosage adjustment. Warfarin: Co-administration of bosentan 500 mg b.i.d. for 14 days decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4 substrate) by 28 and 38%, respectively. Clinical experience with concomitant administration of bosentan and warfarin in patients with pulmonary arterial hypertension did not show clinically relevant changes in INR or warfarin dose (dosage up, and of the clinical studies), and the need to change the warfarin dose during the trial due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients. Diphenhydramine and Losartan: Bosentan has been shown to have no pharmacokinetic interactions with diphenhydramine and losartan but no effect on plasma levels of bosentan.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses about 8 times the maximum recommended human dose (MRHD) of 125 mg b.i.d., or a mg/kg basis. In the same study, doses greater than about 20 times the MRHD were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses about 8 times the MRHD. Impairment of Fertility/Endocrine Function: Many endothelin receptor antagonists have profound effects on the physiology and function of the testes in animals. These drugs have been shown to reduce sperm of the seminiferous tubules if the testes and to reduce sperm counts and male fertility in rats when administered for longer than 10 weeks. Therefore, testicular tubular atrophy and decreases in male fertility observed with endothelin receptor antagonists appear reversible. In fertility studies in which male and female rats were treated with bosentan at oral doses up to 25 times the MRHD on a mg/kg basis, no effects on sperm count, sperm quality, mating performance or fertility were observed. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as about 4 times the MRHD for two years but not at doses as high as about 50 times the MRHD for 6 months. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to about 75 times the MRHD or in dogs treated at 10 to 12 times the MRHD for about 18 weeks. There are no data on the effects of bosentan or other endothelin receptor antagonists on testicular function in man.

### Pregnancy, Teratogenic Effects, Category X

**PRECAUTIONS: Nursing Mothers:** It is not known whether this drug is excreted in human milk. Concomitantly drugs are used in human milk, breastfeeding while taking TRACLEER is not recommended. Pediatric Use: Safety and efficacy in pediatric patients have not been established. Use in Elderly Patients: Clinical experience with TRACLEER in subjects aged 65 or older has not included a sufficient number of such subjects to identify a difference in response between elderly and younger patients.

**ADVERSE REACTIONS:** Safety data on bosentan were obtained from 12 clinical studies (8 placebo-controlled and 4 open-label) in 777 patients with pulmonary arterial hypertension and other diseases. Treatment discontinuation due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent in bosentan (N= 870 patients) than in placebo (N= 240 patients). In this database the only cause of discontinuation > 1%, and occurring more often in bosentan was abnormal liver function. In placebo-controlled studies of bosentan in pulmonary arterial hypertension and for other diseases (primarily chronic heart failure), a total of 677 patients were treated with bosentan at oral doses ranging from 125 mg to 300 mg and 268 patients were treated with placebo. The duration of treatment ranged from 4 weeks to 8 months, for the adverse drug reactions that occurred in > 2% of bosentan-treated patients the only ones that occurred more frequently in bosentan than in placebo (2% discontinuation were headache (1% vs. 0%), fatigue (1% vs. 2%), abnormal hepatic function (0% vs. 2%), leg cramps (0% vs. 1%), and anemia (0% vs. 1%).

**INDICATIONS:** Bosentan has been given as a single dose of up to 2400 mg in normal volunteers, or up to 2000 mg/day for 2 months in patients, without any major clinical consequences. The most common side effect was headache of mild to moderate intensity in the comparative interaction study, in which doses of 300 and 600 mg b.i.d. of bosentan were given concomitantly with cyclosporin A, though plasma concentrations of bosentan increased 20-fold, resulting in severe headache, nausea, and vomiting, but no serious adverse events. All decreases in blood pressure and increases in heart rate were observed. There is no specific experience of overdosage with bosentan beyond the doses described above. Massive overdosage has not been reported in patients receiving active or placebo support.

**INDICATIONS AND ADMINISTRATION:** TRACLEER treatment should be initiated at a dose of 62.5 mg b.i.d. for 1 week and then increased to the maintenance dose of 125 mg b.i.d. Doses above 125 mg b.i.d. did not appear to confer additional benefit but increased the risk of liver injury. Tablets should be administered morning and evening with or without food.

### Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Abnormalities

ALT/AST levels	Treatment and monitoring recommendations
> 3 and < 5 x UN	Confirm by another aminotransferase test; if confirmed, reduce the daily dose or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate (see below).
> 5 and < 8 x UN	Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment (see below).
> 8 x UN	Treatment should be stopped and reintroduction of TRACLEER should not be considered. There is no experience with re-introduction of TRACLEER in these circumstances.

TRACLEER is re-introduced it should be at the starting dose, aminotransferase levels could be checked within 1 day and thereafter according to the recommendations above. If low aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual fatigue or fatigue) or increase in bilirubin > 2 x UN, treatment should be stopped. There is no experience with the re-introduction of TRACLEER in these circumstances. Use in Women of Childbearing Potential: TRACLEER treatment should only be initiated in women of childbearing potential following a negative pregnancy test and only in those who practice adequate contraception that does not rely only upon hormonal contraceptives, including oral, injectable or implantable contraceptives, but use a progesterone or similar agent, or adequate contraception should be sought as needed. Urine or serum pregnancy tests should be obtained monthly in women of childbearing potential using TRACLEER. Dosage Adjustment in Renally Impaired Patients: The effect of renal impairment on the pharmacokinetics of bosentan is oral and does not require dosage adjustment. Dosage Adjustment in Geriatric Patients: Clinical studies of TRACLEER did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in dose adjustment in elderly patients over the greater frequency of decreased renal, or cardiac function, and of concomitant disease or other drug therapy in this age group. Dosage Adjustment in Hepatically Impaired Patients: The influence of liver impairment on the pharmacokinetics of TRACLEER has not been evaluated. Because there is in vivo and in vitro evidence that the main route of excretion of TRACLEER is biliary, liver impairment should be expected to increase exposure to bosentan. There are no specific data to guide dosing in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function. TRACLEER should generally be avoided in patients with moderate or severe liver impairment. Dosage Adjustment in Pediatric: Safety and efficacy in pediatric patients have not been established. Dosage Adjustment in Patients with Low Body Weight: In patients with a body weight below 40 kg but who are over 17 years of age the recommended initial and maintenance dose is 62.5 mg b.i.d. Discontinuation of Treatment: There is limited experience with abrupt discontinuation of TRACLEER. No evidence for acute rebound has been observed. Nevertheless, it would be prudent to consider a gradual dose reduction (0.5 mg b.i.d. for 3 to 7 days) should be considered.

**HOW SUPPLIED:** 62.5 mg film-coated, oval, bisectate, orange/red tablets, embossed with identification marking "125" NDC 60215-10-06. 125 mg film-coated, oval, bisectate, orange-white tablets, embossed with identification marking "125" NDC 60215-100-06. Bottle containing 60 tablets.

U.S. only.

**STORAGE:** Store at 20°C - 25°C (68°F - 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). (See USP Controlled Room Temperature).

### References

1 Zimmerman HJ. Hepatotoxicity - The adverse effects of drug and other chemicals on the liver. Second ed. Philadelphia: Lippincott, 1985.

**Manufactured by:** Actelion Inc.  
Mossburn, Ontario, CANADA

**Marketed by:** Actelion Pharmaceuticals US, Inc.  
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Information for previous page: 1. Tracleer (bosentan) full prescribing information. Actelion Pharmaceuticals, Inc. 2004.

# Eisenmenger Syndrome in Adults: Strategies to Correct Congenital Defects Before Fixed Vascular Disease Develops

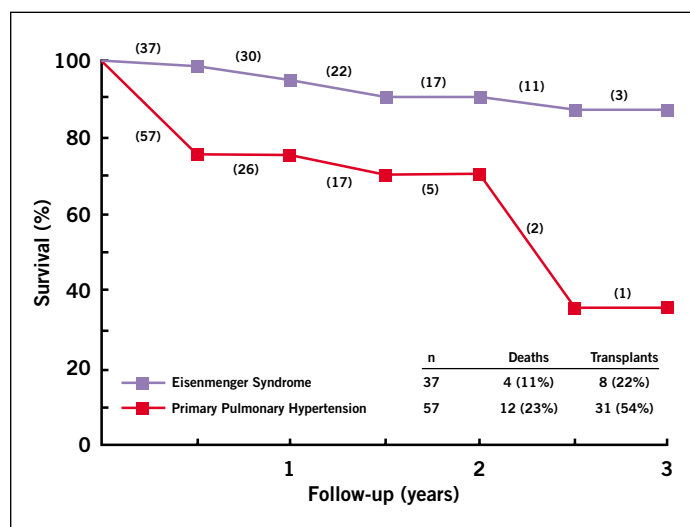


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New York

Congenital heart defects (CHDs) associated with large systemic-to-pulmonary shunts, (eg, atrial septal defect, ventricular septal defect, patent ductus arteriosus) can lead to pulmonary vascular disease, which is characterized by bidirectional shunting or reversal of the shunt. This phenomenon, which is associated with progressive cyanosis, polycythemia, and ultimately, functional limitation, was first described in 1897 by Viktor Eisenmenger and later termed the Eisenmenger syndrome (ES). If it is not corrected before fixed vascular disease develops, the patient is a poor surgical candidate as the failing right ventricle cannot tolerate closure of the defect. Approximately one third of all patients with CHD who have not undergone corrective procedures or who die of other causes, will die from pulmonary vascular disease.<sup>1</sup> The course of the disease, however, is usually more favorable than for patients with primary pulmonary hypertension (PPH). Today, while there have been many advances in our understanding of the pathophysiology and treatment of ES in adults, there is still no cure for this progressive condition once it is established, aside from lung or heart-lung transplantation which is associated with significant morbidity and mortality.<sup>2</sup>

## Natural History

The natural history of ES is highly variable, although overall survival is significantly better than for patients with PPH. Actuarial survival without transplantation is 97% at 1 year, 89% at 2 years, and 77% at 3 years for patients with ES and 77%, 69%, and 35%, respectively, for patients with PPH,<sup>3</sup> (Fig 1). Most patients survive into the third to fourth decade of life, and there are rare case reports of patients living into the seventh decade. The Second Congenital Heart Disease Natural History Study (1993) demonstrated that patients with ES can survive for several decades following diagnosis. In this study, 54% of 98 unoperated patients with ventricular septal defects and ES were alive 20 years after diagnosis.<sup>4</sup> Further, in a retrospective study of 109 adults with ES, the median survival was 52.6 years of age.<sup>5</sup> Some risk factors that have been associated with earlier mortality in ES patients have included trisomy 21, syncope, hemoptysis, elevated right atrial (RA) pressure, lower systemic arterial oxygen saturation, supraventricular arrhythmia, earlier age at presentation, electrocardiographic evidence of RVH, poor functional class, pregnancy, and ventricular or aortopulmonary shunt vs intraatrial shunt.<sup>5-7</sup>

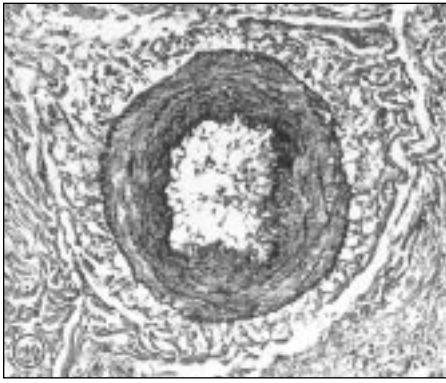


**Fig. 1—Kaplan-Meier survival of patients with Eisenmenger syndrome and PPH. Actuarial survival without transplantation is 97% at 1 year, 89% at 2 years, and 77% at 3 years for patients with Eisenmenger syndrome and 77%, 69%, and 35%, respectively, for patients with PPH. (Reprinted with permission: Hopkins WE, Ochoa LL, Richardson GW, Trulock EP. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. *J Heart Lung Transplant* 1996;15:100-5).**

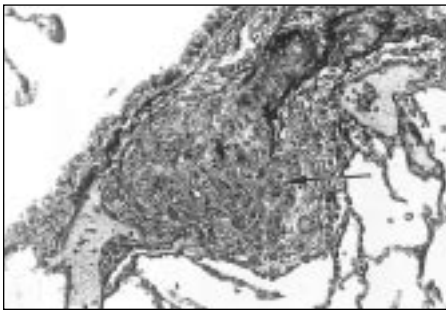
## Pathophysiology

The pathophysiologic mechanisms, which lead to the histopathologic changes seen in ES, are not completely understood. Increased shear stress, flow, and pressure contribute to the pathobiology of pulmonary vascular disease. In patients with large left-to-right shunts, the pulmonary vascular bed is subjected to ongoing shear stress. This leads to the histopathologic changes seen in pulmonary arterial hypertension (PAH), which include pulmonary arteriolar medial hypertrophy, intimal fibrosis, and plexiform lesions (Figs. 2, 3).

In ES patients, this may be the result of increased flow across the pulmonary vascular bed causing peripheral extension of muscle from differentiating pericytes and intermediate cells in precapillary vessels. In addition, damage to the pulmonary vascular endothelium from a mechanical stretch injury sets a series of events in motion at the cellular level (implicated in the pathogenesis of pulmonary vascular disease).<sup>6,8</sup> As a result of these events, pulmonary vascular resistance increases and ulti-



**Fig. 2**—Transverse section of a muscular pulmonary artery with medial hypertrophy. The media occupies 30% of the cross-sectional area (VvG x100). (Reprinted with permission: Rubin LJ, Rich S, eds. *Primary Pulmonary Hypertension. Lung Biology in Health and Disease*. Vol 99. City, State. Marcel Dekker, Inc;Year:27,34).



**Fig. 3**—Plexiform lesions in a muscular pulmonary artery. Plexiform lesions (arrow) are shown arising from a stenotic muscular pulmonary artery and feeding into dilated thin-walled arteries (VvG x100). (Reprinted with permission: Rubin LJ, Rich S, eds. *Primary Pulmonary Hypertension. Lung Biology in Health and Disease*. Vol 99. City, State. Marcel Dekker, Inc;Year:27,34).

mately leads to a decrease in left to right shunting. Eventually, when the resistance becomes significantly elevated, shunting becomes bi-directional and at later stages becomes predominantly right to left. The long-term outlook for patients with elevated pulmonary vascular resistance who undergo closure of their defect(s) is worse than for unrepaired ES patients with the same lesion(s).<sup>9</sup> This may be related to the absence of a communication between the right and left circulations, which may serve as a “pop-off valve” in patients who are at risk for pulmonary hypertensive crises.<sup>10</sup> Systemic cardiac output is greater in patients with ES than in those with PPH, presumably secondary to the presence of their pop-off valve. In contrast to PPH patients, right ventricular function is typically preserved and heart failure is uncommon in patients with ES, until the end stages of the disease.<sup>11,12</sup>

## Diagnosis

**Clinical History/Symptoms:** Timely diagnosis of a large systemic to pulmonary shunt is critical in the prevention of ES. Defects closed within the first two years of life are unlikely to lead to pulmonary vascular obstructive disease.<sup>4</sup> Infants with large, unrestrictive defects usually present initially with signs of congestive heart failure, and failure to thrive. Following years of continued exposure to high shear stress from the left to right shunting, the pulmonary vascular resistance increases, usually to systemic levels, leading to reversed shunting. Cyanosis then follows, which can be severe. In rare cases, the history of congestive heart failure or failure to thrive in infancy is absent. In these patients, reversal of flow may have occurred within the first two years of life. This group may represent a subset of patients who may have never had the normal physiologic fall in the pulmonary vascular resistance after birth or perhaps may represent a subset of patients with an increased susceptibility to pulmonary vascular disease.

Eventually, all adults with ES develop cyanosis and suffer from some of its inherent complications, eg, polycythemia,

headaches, blurry vision, cerebral abscesses and/or strokes. In addition, most patients develop progressive shortness of breath, dyspnea on exertion, and exercise intolerance. Patients may also complain of chest pain. Hemoptysis is more common with advancing age.

## Physical Signs

On physical examination, ES patients may appear cyanotic at rest. In the early stages of the disease, they may only develop cyanosis with exertion. Virtually all ES patients will become progressively more cyanotic with exertion. Clubbing of the digits may be present. Most patients have normal jugular venous pressure on physical examination. On cardiac examination a right ventricular lift, a loud, palpable single S<sub>2</sub>, a high-pitched diastolic murmur of pulmonary insufficiency, and a pansystolic murmur of tricuspid insufficiency may also be present. If there is congestive heart failure, peripheral edema, ascites, and hepatosplenomegaly may be present.

## Diagnostic Testing

The electrocardiogram in patients with ES typically demonstrates right axis deviation and right ventricular hypertrophy. A right ventricular strain pattern may also be present, with associated ST-T segment changes (**Fig 4**). The chest x-ray may demonstrate right ventricular enlargement and enlarged central pulmonary arteries with “pruning” of the peripheral pulmonary vessels. The peripheral pruning is usually a late finding. The central pulmonary arteries often appear severely enlarged in patients with atrial septal defects. Two-dimensional echocardiography may demonstrate any of the following: a dilated right ventricle and atrium, right ventricular hypertrophy, diminished right ventricular function, tricuspid regurgitation, pulmonary insufficiency, flattening or posterior bowing of the interventricular septum, and bidirectional or right-to-left shunting across the cardiac defect.

Right and left heart catheterization may be performed to assess “operability”. The patient is usually considered “inoperable” if the pulmonary vascular resistance is greater than 10 Wood units /m<sup>2</sup> despite the administration of acute pulmonary vasodilator agents such as inhaled nitric oxide, intravenous epoprostenol, intravenous adenosine, or inhaled iloprost.

Laboratory testing should include hemoglobin, hematocrit, and iron studies to determine the extent of polycythemia and need for supplemental iron. A coagulation profile should be performed at baseline prior to consideration of anticoagulation.

## Management

Although the etiology and natural history of PPH and ES are different, the histopathologic changes are virtually identical. This has prompted adaptation of some of the treatment strategies for PPH for ES patients.

**Supplemental oxygen:** Supplemental oxygen therapy should be considered for patients with ES. Although recent data from

**Table—Hemodynamic effects of long-term continuous intravenous epoprostenol (PGI<sub>2</sub>) in patients with pulmonary arterial hypertension associated with congenital heart defects (n=16)**

	Baseline	Chronic PGI <sub>2</sub> (1-year follow-up)	P value
PAPm (mmHg)	77 ± 20	61 ± 15	<0.01
CI (L/min/M <sup>2</sup> )	3.5 ± 1.6	5.9 ± 2.7	<0.01
PVRi (U*M <sup>2</sup> )	25 ± 13	12 ± 7	<0.01
MVO <sub>2</sub> (%)	64 ± 7	70 ± 8	<0.01
RAPm (mmHg)	6 ± 5	8 ± 4	NS

(Adapted with permission from Rosenzweig EB, et al. *Circulation* 1999;99:1858-65). Abbreviations: PAPm=mean pulmonary arterial pressure, CI=cardiac index, PVRi=pulmonary vascular resistance index, MVO<sub>2</sub>=mixed venous saturation, RAPm=mean right atrial pressure.

one small study demonstrated that supplemental oxygen did not offer a survival benefit for adult patients with ES,<sup>13</sup> previous studies have demonstrated that the use of supplemental oxygen in children with pulmonary vascular disease during sleep may slow the progression of polycythemia.<sup>14</sup> There is also evidence that desaturation may occur in the supine position because of VQ mismatch<sup>15</sup> and that the use of supplemental oxygen attenuates these changes.

In addition, patients who have significant desaturation with activity during exacerbations of heart failure, infections, or air travel because of increased oxygen extraction, in the setting of fixed oxygen delivery, may benefit from supplemental oxygen during exercise.

**Digitalis and diuretics:** The efficacy of inotropic agents for right-heart failure remains controversial. There have been reports of increased cardiac output with the use of digitalis in patients with PPH.<sup>16</sup> Thus, there may be a role for digitalis for ES patients with diminished right ventricular function.

Diuretics may be useful for patients with ES and severe right-heart failure to relieve hepatic congestion and/or increased intravascular volume.

**Anticoagulation:** Patients with ES are at risk for thromboembolic events and even a small pulmonary embolus can be life-threatening in patients who cannot vasodilate or recruit additional pulmonary vessels normally. Although there have been no adequate studies to demonstrate the efficacy of anticoagulation for patients with ES, most experts recommend anticoagulation; however, the risk of bleeding, particularly hemoptysis, needs consideration. If warfarin is used, the aim is to maintain the international normalized ratio (INR) at 1.5 to 2.0 for most patients, with a higher INR for patients who are hypercoagulable.

**Phlebotomy:** Phlebotomy with replacement of fluid may be helpful for cyanotic CHD beyond infancy in which severe hypoxemia has led to a large increase in red cell mass. When a hema-



**Fig. 4—12-lead electrocardiogram from an adult patient with the Eisenmenger syndrome. The electrocardiogram illustrates right axis deviation and right ventricular hypertrophy.**

tocrit reaches the 65% to 70% range, or if the patient is symptomatic with a lower hematocrit, eg, blurry vision or headaches, exchange transfusion with plasma or crystalloid is indicated to lower the hematocrit to the 50% to 60% range. This must be done carefully since simply removing blood can decrease systemic vascular resistance and result in a sudden hypoxic event. Fortunately, many patients with ES tend to stabilize their hematocrit in the 60% to 65% range for many years or even decades, and no longer require phlebotomy. One must also follow iron stores, which often become depleted, leading to a decrease in the circulating blood volume and increased viscosity.<sup>17</sup> Supplemental iron therapy is indicated for iron deficiency even if a patient is polycythemic to avoid a hyperviscosity syndrome related to iron deficiency in the setting of polycythemia.

**Vasodilator/antiproliferative therapies:** Pulmonary vasodilator therapy has been used for the treatment of PPH based on the premise that pulmonary vasoconstriction plays a role in the development of the pulmonary vascular disease. Patients with ES may also benefit from vasodilator/antiproliferative therapies such as intravenous epoprostenol, previously reserved only for PPH patients<sup>18</sup> (Table).

In our center, prior to initiation of pulmonary vasodilator therapy, ES patients undergo cardiac catheterization with acute pulmonary vasodilator testing. If patients respond to acute vasodilator testing with a fall in pulmonary vascular resistance of >30% following the administration of inhaled nitric oxide (80 ppm) or intravenous epoprostenol, and demonstrates a similar response to acute testing with sublingual calcium channel blockade, they can be offered treatment with long-term oral calcium channel blockade, if they are not in significant right-heart failure (mean RAP > 15 mmHg, C.I.<1.5 L/min/m<sup>2</sup>). This is based on previous studies of patients with PPH that demonstrate acute pulmonary vasoreactivity and subsequent clinical and hemodynamic improvement, as well as increased survival with long-term oral calcium channel blockade.<sup>19</sup> It should be noted that our experience has demonstrated significantly lower acute response rates for ES patients than for patients with PPH. In a small study from our institution, only 7% of 94 patients (including 27 adult patients) with PAH associated with CHD responded to acute vasodilator testing.<sup>20</sup> None of the “responders” were adult patients. For those symptomatic patients with ES who do not respond to acute vasodilator testing, treatment options include long-term intravenous epoprostenol therapy or



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lung or heart-lung transplantation.

Continuous intravenous epoprostenol therapy has been used successfully in patients with PAH and associated CHD. In a report from our institution of 20 patients (including 6 adult patients) with PAH associated with CHD (10 operated and 10 with residual shunts), who were not responsive to acute vasodilator testing, there were improved hemodynamics, and quality of life following one year of treatment with continuous intravenous epoprostenol.<sup>18</sup> Notably, in patients with residual shunts, we did not see an increase in right-to-left shunting, nor did we see a fall in systemic arterial blood pressure with long-term epoprostenol. These 10 patients with residual shunts had a significant improvement in oxygen delivery while receiving long-term epoprostenol.<sup>18</sup> McLaughlin et al, also reported improved hemodynamics with continuous intravenous epoprostenol in a study of patients with PAH that included 7 patients with CHD.<sup>21</sup> Unfortunately, the use of continuous intravenous prostacyclin has several associated risks, including the risk of thromboembolic events to the systemic circulation in the setting of ongoing pulmonary-to-systemic shunting. Although the data are limited, for patients with CHD, an alternative to continuous intravenous epoprostenol is the use of a subcutaneous prostacyclin analogue, such as treprostinil,<sup>22</sup> which avoids the risks associated with a central venous catheter.

### Transplantation

While successful heart-lung transplantation and lung transplantation with repair of CHD have been available for over 20 years, there are several limitations to these procedures. Patients with ES have the highest perioperative mortality and the lowest 1-month survival rates among all lung transplant recipients.<sup>23</sup> In addition, a limited number of centers can perform the procedures and care for the patients following transplantation, and the availability of suitable donors is limited. Further, the high incidence of bronchiolitis obliterans in the transplanted organs of these patients (25 to 40%) is of great concern.<sup>23</sup> For at least 5 years, single and bilateral lung transplantations have been performed increasingly in patients with pulmonary vascular obstructive disease including patients with severe right ventricular failure.<sup>2</sup> Thus, lung transplantation with repair of the CHD appears to be the surgical procedure of choice for virtually all patients in whom left ventricular function is maintained despite severe right ventricular failure. Currently, the overall 1-year, 5-year, and long-term (9-year) survival for lung transplantation for recipients with all forms of lung disease is 71%, 49%, and 20%, respectively. For patients with ES, the 1-year and 5-year survival following lung transplantation is worse, 52% and 39% respectively.<sup>23</sup> Recent data suggest that patients with ventricular septal defects have the best prognosis and that, for patients with ES secondary to a ventricular septal defect, heart-lung transplantation may offer a survival benefit.<sup>24</sup> For patients with ES, we often defer transplantation for many years based on overall risk-benefit considerations. For ES patients, we generally reserve transplantation for those patients who are very symptomatic despite optimal medical management, in whom long-

**The endothelin-receptor antagonists bosentan and sitaxsentan have been shown to improve exercise capacity, hemodynamics, and WHO functional classification in patients with PPH, PAH associated with collagen vascular disorders, and PAH with associated CHD.**

term survival is unlikely, ie, patients in whom likelihood of 2-year survival is less than 50%.

### General Measures

Adults with ES must be advised to avoid situations that could exacerbate their pulmonary vascular disease. For example, exercise should be guided by symptoms, with self-limits placed. Avoidance of travel to high altitudes should be advised. In addition, because flight cabins are not usually pressurized to sea level, we recommend the use of supplemental oxygen during air flight to avoid exacerbation of pulmonary hypertension.

Pregnancy, oral contraceptives, hormone replacement therapies, and appetite suppressants should be avoided. Pregnancy can be fatal for patients with ES both in the course of delivery and

in the postpartum period. During pregnancy, the SVR can fall considerably and lead to increased right-to-left shunting with worsening hypoxemia, which can be dangerous for both the mother and fetus. Similarly, hemorrhage and anesthetic agents may have the same effects on SVR during the peripartum period. Thromboembolic events have also been associated with up to 43% of all maternal deaths in ES.<sup>25</sup> The practice at our institution is to firmly advise against pregnancy, as the risk for maternal death is approximately 30% to 50% in the peripartum period.<sup>25</sup> In addition, because of the increased risk of thromboembolic events, which may be associated with oral contraceptives and hormone replacement therapies, we advise against oral contraceptive therapies for all of our ES patients and suggest barrier methods or tubal ligation as alternatives.

### Future Directions

There are several novel therapeutic agents that are currently being evaluated and/or considered for clinical investigation for patients with PAH, alone as well as in combination. These include endothelin-receptor antagonists, prostacyclin analogues, elastase inhibitors, inhaled nitric oxide, phosphodiesterase-5 inhibitors, eg, sildenafil, and angiotensin-converting enzyme inhibitors.

### Endothelin Receptor Antagonists

Endothelin-1 (ET-1), a very potent vasoconstrictor, is elevated in patients with PPH, and correlates inversely with prognosis.<sup>26</sup> Plasma ET-1 levels are also elevated in patients with ES.<sup>27</sup> The endothelin-receptor antagonists bosentan and sitaxsentan have been shown to improve exercise capacity, hemodynamics, and WHO functional classification in patients with PPH, PAH associated with collagen vascular disorders, and PAH with associated CHD.<sup>28-32</sup> Future prospective studies, which will include a greater number of patients with CHD, will be critical for determining whether this class of drug is also effective for patients with ES.

**Other novel therapeutic agents:** Other novel therapeutic agents, including oral and inhaled prostacyclin analogues, elastase inhibitors, inhaled nitric oxide, phosphodiesterase inhibitors, and angiotensin-converting enzyme inhibitors, are being investigated in patients with PAH and may show promise for the long-term management of ES.

While there have recently been many advances in the understanding of the pathobiology and management of adults with ES, there is still no cure for this disease. By furthering our understanding of the disease, we anticipate that more advances will continue for patients with ES, thereby improving the long-term outlook for these patients.

## References

1. Friedman WF, (ed). Proceedings of the National Heart, Lung, and Blood Institute Pediatric Cardiology Workshop: Pulmonary Hypertension. *Pediatr Res* 1986;20:811-24.
2. Keck BM, Bennett LE, Rosendale J, Daily OP, Novick RJ, Hosenpud JD. Worldwide thoracic organ transplantation: a report from the UNOS/ISHLT International Registry for Thoracic Organ Transplantation. *Clin Transplant* 1999;35-49.
3. Hopkins WE, Ochoa LL, Richardson GW, Trulock EP. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. *J Heart Lung Transplant* 1996;15:100-5.
4. Kidd L, Driscoll DJ, Gersony WM, Hayes CJ, Keane JF, O'Fallon WM, Pieroni DR, Wolfe RR, Weidman WH. Second natural history study of congenital heart defects. *Circulation* 1993;87(suppl 1):38-51.
5. Cantor WJ, Harrison DA, Moussadji JS, et al. Determinants of survival and length of survival in adults with Eisenmenger syndrome. *Am J Cardiol* 1999;84:677-81.
6. Granton JT, Rabinovitch M. Pulmonary arterial hypertension in congenital heart disease. *Cardiol Clin* 2002;20:441-57.
7. Young D, Mark H. Fate of the patient with Eisenmenger's syndrome. *Am J Cardiol* 1971;28:658-69.
8. Haworth SG. Pulmonary vascular disease in ventricular septal defect: structural and functional correlations in lung biopsies from 85 patients, with outcome of intracardiac repair. *J Pathol* 1987;152(3):157-68.
9. Somerville J. How to manage the Eisenmenger syndrome. *Int J Cardiol* 1998;63:1-8.
10. Sandoval J, Gaspar J, Pulido T, Bautista E, Martinez-Guerra ML, Zeballos M, Palomar A, Gomez A. Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension. A therapeutic alternative for patients nonresponsive to vasodilator treatment. *J Am Coll Cardiol* 1998;32(2):297-304.
11. Hopkins WE, Ochoa LL, Richardson GW, Trulock EP. Hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. *J Heart Lung Transplant* 1995;14:536.
12. Hopkins WE, Waggoner AD. Severe pulmonary hypertension without right ventricular failure: the unique hearts of patients with Eisenmenger syndrome. *Am J Cardiol* 2002;89:34-8.
13. Sandoval J, Aguirre JS, Pulido T, Martinez-Guerra ML, Santos E, Alvarado P, Rosas M, Bautista E. Nocturnal oxygen therapy in patients with the Eisenmenger syndrome. *Am J Respir Crit Care Med* 2001;164(9):1682-87.
14. Bowyer JJ, Busst CM, Denison DM, Shinebourne EA. Effect of long-term oxygen treatment at home in children with pulmonary vascular disease. *Br Heart J* 1985;55:385-90.
15. Sandoval J, Alvarado P, Martínez-Guerra ML, Gómez A, Palomar A, Meza S, Santos E, Rosas M. Effect of body position changes on pulmonary gas exchange in Eisenmenger's syndrome. *Am J Respir Crit Care Med* 1999;159:1070-73.
16. Rich S, Seidlitz M, Dodin E, Osimani D, Judd D, Genthner D, McLaughlin V, Francis G. The short-term effects of digoxin in patients with right ventricular dysfunction from pulmonary hypertension. *Chest* 1998;114:787-92.
17. Perloff JK. Systemic complications of cyanosis in adults with congenital heart disease: hematologic derangements, renal function, and urate metabolism. *Cardiol Clinics* 1993;11(4):689-99.
18. Berman Rosenzweig E, Kerstein D, Barst RJ. Chronic prostacyclin therapy for pulmonary hypertension with associated congenital heart defects. *Circulation* 1999;99(14):1858-65.
19. Rich S, Kaufmann E, Levy P. The effects of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992;327:76-81.
20. Berman Rosenzweig E, Maislin G, Kerstein D, Tongers J, Barst RJ. Acute vasodilator response and survival in patients with pulmonary vascular disease and congenital heart defects. *Am J Respir Crit Care Med* 2000;161:A423.
21. McLaughlin VV, Genthner DE, Panella MM, et al. Compassionate use of continuous prostacyclin in the management of secondary pulmonary hypertension: a case series. *Ann Intern Med* 1999;130:740-3.
22. Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, Keogh A, Oudiz R, Frost A, Blackburn SD, Crow JW, Rubin LJ; Treprostinil Study Group. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002;165(6):800-4.
23. Trulock EP. Lung transplantation for primary pulmonary hypertension. *Clin Chest Med* 2001;22(3):583-93.
24. Waddell TK, Bennett L, Kennedy R, et al. Heart-lung or lung transplantation for Eisenmenger syndrome. *J Heart Lung Transplant* 2002;21:731-7.
25. Daliendo L, Somerville J, Presbitero P, Menti L, Brach-Prever S, Rizzoli G, et al. Eisenmenger syndrome. Factors relating to deterioration and death. *Eur Heart J* 1998;19:1845-55.
26. Galie N, Grigoni F, Bacchi-Reggiani L, et al. Relation of endothelin-1 to survival in patients with primary pulmonary hypertension. *Eur J Clin Invest* 1996;26(suppl 1):273.
27. Yoshiyoshi M, Nishioka K, Nakao K, et al. Plasma endothelin concentrations in patients with pulmonary hypertension associated with congenital heart defects. Evidence for increased production of endothelin in pulmonary circulation. *Circulation* 1991;84(6):2280-5.
28. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomized placebo controlled study. *Lancet* 2001;358:1119-23.
29. Barst RJ, Rich S, Widlitz A, Horn EM, McLaughlin V, McFarlin J. Clinical efficacy of sitaxsentan, an endothelin-A receptor antagonist, in patients with pulmonary arterial hypertension: open-label pilot study. *Chest* 2002;121(6):1860-8.
30. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, Pulido T, Frost A, Roux S, Leconte I, Landzberg M, Simonneau G. For the Bosentan Randomized Trial of Endothelin Antagonist Therapy Study Group. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896-903.
31. van Giersbergen PLM, Ivy D, Dingemans J, Widlitz A, Schmitt K, Doran A, Ngoc N, Gaitonde M, Bodin F, Barst RJ. Single- and multiple-dose pharmacokinetics of bosentan in pediatric patients with pulmonary arterial hypertension. *Clin Pharmacol Ther*, 2003 (in press).
32. Barst RJ, Langleben D, Frost A, Horn E, Oudiz R, Shapiro S, McLaughlin V, Hill N, Tapson V, Robbins I, Zwicke D, Duncan B, Frumkin LR for the STRIDE Study Group, Sitaxsentan, a selective ET-A receptor antagonist, improves exercise capacity and NYHA functional class in pulmonary arterial hypertension (PAH). *Am J Respir Crit Care Med* 2003 (in press).

# Pulmonary Arterial Hypertension in Congenital Heart Disease: Controversies and Consensus



Robyn Barst, MD



David Wessel, MD



Nancy Bridges, MD



Dunbar Ivy, MD

Four physicians discussed current and future strategies for the assessment and treatment of pulmonary arterial hypertension (PAH) related to congenital heart disease.

The roundtable discussion was moderated by Robyn Barst, MD, Professor of Pediatrics, Columbia University College of Physicians and Surgeons, New York, New York, and included David Wessel, MD, Professor of Pediatrics and Anesthesia, Harvard Medical School, and Senior Associate in Cardiology and Anesthesia at Children's Hospital, Boston; Nancy Bridges, MD, Chief of the Clinical Transplantation Section, National Institute for Allergy and Infectious Disease, National Institutes of Health, Bethesda, Maryland; and Dunbar Ivy, MD, Associate Professor of Pediatrics, Chief and Selby Rickenbaugh Chair of Pediatric Cardiology, Director of the Pediatric Pulmonary Hypertension Program, University of Colorado, and Denver Children's Hospital.

PAH is a known complication of congenital heart disease, particularly congenital heart defects characterized by chronic left-to-right shunting. In 1897, Viktor Eisenmenger described the clinical features of a patient with PAH and a right-to-left shunt. Paul Wood subsequently used the term "Eisenmenger syndrome" for patients with PAH that appeared to result from a systemic-to-pulmonary shunt. In 1998, the World Health Organization symposium on pulmonary hypertension (PH) reclassified various conditions seen in association with PH, with one of the five broad categories designated "PAH." This classification emphasizes the similarities between primary pulmonary hypertension (PPH) and PAH associated with other diseases, including congenital systemic-to-pulmonary shunts as well as PAH related to collagen vascular disorders, toxins, drugs, portal hypertension, and HIV. The World Health Organization reclassification reflects recent advances in the understanding of pulmonary hypertensive diseases and attempts to address the similarities between PPH and PAH associated with certain disorders (as stated above). Indeed, advances in the understanding of the mechanisms underlying the vascular changes in PAH have contributed to the development of successful therapeutic strategies. It appears that some of the medical therapies for the treatment of PPH may benefit patients with PAH associated with congenital heart disease. In this regard, although there is diversity in the etiology of PAH, the therapeutic literature supports some uniformity. It is our hope today to discuss

the similarities between PPH and PAH related to congenital heart disease with respect to diagnosis and assessment of PPH and PAH related to congenital heart disease as well as current and future strategies for the treatment of PAH related to congenital heart disease. In addition, in some cases, it becomes extremely difficult to differentiate if a patient with a congenital heart defect has Eisenmenger syndrome as opposed to PPH with a clinically and hemodynamically insignificant congenital systemic-to-pulmonary shunt.

**Dr Barst:** Perhaps we can start with what I think is a very difficult question: what are the similarities and differences between PPH versus PAH associated with congenital heart disease versus Eisenmenger syndrome? How would you classify a child who has PAH with a small ventricular septal defect (VSD), or PAH in a toddler who has an atrial septal defect (ASD)? Are these cases of Eisenmenger syndrome or should they be considered PPH with a clinically and hemodynamically insignificant shunt? Perhaps Dr Wessel could start. What are your thoughts on PPH versus what I refer to as PPH related to congenital heart disease and how do you distinguish that from Eisenmenger syndrome?

**Dr Wessel:** We occasionally see a disease that looks very similar to PPH but is found in association with the small and hemodynamically insignificant congenital heart lesions, such as an ASD or a VSD. In my mind I still think of that disease as primary pulmonary hypertension provided there is no reason to believe the defect was much larger in the past. However, I have been impressed over the years that there seems to be an abundance of ASDs in particular, that are found in conjunction with what we are otherwise viewing as PPH. So, I suspect that at some level there is a genetic or physiologic link between certain small defects and PPH. Nonetheless, I don't have a conceptual difficulty viewing PH in a child with a relatively small ASD or VSD as a variant of PPH. However, I think there are lots of other kinds of PH that I would not refer to as PPH because I believe in some fashion it is related to the underlying congenital heart disease and is therefore secondary to it. For example, we have all seen patients with some degree of mitral valve stenosis or abnormality of the mitral valve who have a left atrial pressure of only 9 or 10 or 11 mmHg and yet have half or greater than half systemic pressure in the pulmonary artery. So, I think those are ambiguous etiologies in some cir-

cumstances. The diseases include truncus arteriosus, transposition of the great arteries, and certain forms of double outlet right ventricle. Patients who have a physiologic abnormality associated with their defect for many weeks or months or even years but are viewed as repairable, may still have persistence of PH as part of that postoperative illness. I view this as secondary, not primary pulmonary hypertension.

**Dr Barst:** If we step back for a moment with regard to the classic Eisenmenger syndrome and your third category which is closest to Eisenmenger syndrome, I still think there is controversy. Do we say patients have Eisenmenger syndrome if they have an unrestrictive defect? If a patient has a post-tricuspid shunt that is unrestrictive, is that Eisenmenger syndrome? And then we have the other two categories that we should separate. I think it is important to try and define these three groups if we want to study these patients, particularly now that we have many more therapeutic options available. All drugs have some risk and toxicity and I think that we do our patients a disservice to demonstrate that drug x, y, or z is safe and efficacious for PPH and then start using these therapies for all patients with PH and congenital heart disease.

**Dr Bridges:** I think it is difficult to come up with a robust diagnostic classification as long as we are stuck with these syndromic, phenotypic categorizations. If we really could diagnose the disease we would be closer to knowing what to do with it. If one wants to use the term “Eisenmenger syndrome,” it seems most reasonable to take our definition from the two-part article by Paul Wood (*British Medical Journal*, 1958). He described it as “resulting from lesions that have an unrestrictive communication with exposure of the pulmonary bed to arterial pressure.” So he specifically left out things like partial veins or ASDs in his definition of Eisenmenger syndrome. It doesn’t advance our understanding to call something “Eisenmenger’s, but with this,” or “PPH, but with this.” Terms like “Eisenmenger syndrome” or “primary pulmonary hypertension” are arbitrary terms with standard definitions and they have to be used accordingly. One hopes that one day we will learn enough to know that they don’t exactly describe a specific physiologic entity.

**Dr Barst:** I agree. Paul Wood did not include pre-tricuspid shunt lesions in the definition of Eisenmenger syndrome. If we look at our experience with continuous intravenous epoprostenol in patients with PAH and a small VSD or ASD, ie, congenital heart defects that do not meet the definition of Eisenmenger syndrome, in general these patients have done better than when we have treated a patient with epoprostenol who has classic Eisenmenger syndrome, eg, unrepaired truncus arteriosus.

**Dr Ivy:** Robyn, I would agree. I think our patients who might be considered to have classic Eisenmenger syndrome, such as a large VSD, who are treated with epoprostenol do not show the same response as patients who have PPH or may have a small ASD or a small VSD. I would also agree with your comment that we may define Eisenmenger syndrome as a large post-tricuspid shunt (VSD, truncus arteriosus, or unrepaired large PDA). The effectiveness of therapy in patients with classic Eisenmenger syndrome is different from that in patients with a small defect

and maybe a PPH component.

**Dr Barst:** I think this is very important for us to discuss. Nancy, do you want to comment on this?

**Dr Bridges:** Yes I would. With regard to what Dave was saying about how he categorizes children who have both structural heart disease and pulmonary vascular disease, I would say that the way I look at it is very similar. Even within that group, where they clearly have significant structural heart disease associated with PH, there are still two subgroups because there are those in whom the pulmonary vascular disease can be reversed or halted by doing away with the hemodynamic derangement and then there are others where you can completely normalize their plumbing, but the pulmonary vascular disease continues to progress. So, even in this category of people who have significant structural disease, they don’t all have the same pulmonary vascular disease.

**Dr Barst:** I agree. And the most recent hypothesis for the pathobiology of PAH is a “genetic predisposition” and a “vascular injury,” with the vascular injury highly variable. Before we move on to some specific treatment strategies, I would like Dunbar to comment on his experience with large unrestricted defects at high altitude compared with when the patients go to sea level.

**Dr Ivy:** With regard to the effects of altitude on pulmonary hypertension, each patient has to be individualized in terms of treatment. Our general recommendation is that altitude may be detrimental in the presence of pulmonary vascular disease. As a rule we recommend that patients with significant pulmonary hypertension move to sea level to see if the pulmonary hypertension improves. If the pulmonary hypertension improves, we recommend that they stay at lower altitude. The response to altitude in the child with pulmonary hypertension is not predictable. The degree of pulmonary hypertension in some patients is not different between sea level or at moderate altitudes of 5,280 feet in Denver. However, some children with pulmonary hypertension may have clinical worsening on travel to altitude. We try to discourage patients from living at altitude with pulmonary vascular disease, but some families are not able to move and if there is no difference in their hemodynamics at sea level versus Denver, then we treat them as best we can. We strongly discourage our patients from traveling or living above 7,000 feet elevation.

**Dr Barst:** Thank you. Let’s move on to treatment strategies, which probably will also be controversial. I’d like to start by asking Dave his recommendations for the perioperative management of PAH. Although we used to perform cardiac catheterizations on all patients before surgery, we now rarely perform preoperative cardiac catheterizations unless it is an interventional cardiac catheterization. What do you think, Dave?

**Dr Wessel:** I think different centers have evolved slightly different strategies for the assessment of patients who they think are at some risk of having elevated pulmonary vascular resistance as a part of their congenital heart disease. In general, if patients come to us with a large lesion that should represent a large left-

to-right-shunt, and they have no signs or symptoms of congestive heart failure, that certainly raises a red flag that pulmonary vascular resistance may be elevated. Now how much one investigates that preoperatively in my mind depends in part on the age of the patients. If it is quite a young patient (in the first months of life) with a large defect and no evidence of congestive heart failure, I think the recommendation is still going to be intervene, operate on that patient; it doesn't necessarily mean that the child is going to have significant PH as a postoperative problem. Cardiac catheterization is not necessarily mandatory. However, in an older patient who comes to us with a larger lesion at the ventricular level or even the ductus level, if one sees PH either indirectly inferred by the echocardiogram or by the absence of signs and symptoms of congestive heart failure, then I think the burden is on us to quantify the pulmonary vascular resistance and the extent of the pulmonary vascular disease because it does have pretty substantial implications for postoperative morbidity, mortality and the long-term outcome. So, I would recommend that after a child gets substantially beyond the first year of life with evidence of elevated pulmonary vascular resistance, then before intervention we catheterize those patients or get a better handle on the quantitative aspects of pulmonary vascular resistance. I believe in testing for vasoreactivity because in PPH we know that these outcomes are related to the vasoreactivity of the patient during testing. I think that carries over to the perioperative period for the child with secondary pulmonary hypertension as well.

**Dr Barst:** Now what about those patients who have PAH out of proportion to their pulmonary venous hypertension? Is there an age at which you would not operate? Do you do preoperative cardiac catheterizations on these patients or do you just say, "We're going to operate because we know it is reversible and then we'll deal with the postoperative issues."

**Dr Wessel:** In general we would do a preoperative catheterization in those patients, usually because the disease that causes severe PH is one in which there is other physiologic information or an opportunity for intervention that requires catheterization. It has always been my impression (in children) that if one can repair the left-side heart disease, that the PH will not present a major problem and cause death. In the postoperative period it is treatable and generally worth the risk of intervention. The simplest answer to your question is that we are very optimistic that in children with PH related to left-side heart disease if one can intervene and repair the heart disease, then the PH generally regresses.

**Dr Barst:** Is there a PVRI that you consider "operable" versus "inoperable"? And if you do, are you calculating the PVRI using measured oxygen consumption or assumed oxygen consumption? Are there some times when you think it is important to leave a small interatrial communication as a "pop-off valve" in the immediate perioperative period?

**Dr Bridges:** If by doing vasodilator testing I can't get the PVR

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somewhere in the neighborhood of six Wood units indexed, I have not sent them for repair. What I have done in several of those cases is referred them for a pulmonary artery band if they have a lesion suitable for banding. So let's consider a patient with an unrestricted post-tricuspid valve shunt who has a baseline, indexed PVR of 12 Wood units, which I think we may all agree is not repairable, and with vasodilator testing I can reveal some reactivity, but still not to an indexed PVR below six Wood units. In such cases I have referred the patient for a pulmonary artery band and subsequently brought the patient back for reevaluation for complete repair. That approach has been very successful in some cases, in that the pulmonary artery pressure and PVR falls after the band, and the patient can go on to repair.

**Dr Wessel:** I think it depends in part on the level of the shunt (ie, atrial or ventricular) as well as the demonstrated reactivity. We might be more liberal with atrial level shunts and accept a higher PVR. Let's consider children with a large VSD, or truncus arteriosus, or AV canal, and a ventricular level shunt. We are probably a little bit less conservative than Nancy has described, but if we can get the pulmonary vascular resistance to less than 8 units, corrected for body surface area then we would be inclined to have a shunt undergo a surgical repair. If it is between 8 and 12 U/m<sup>2</sup>, then we want to assess not only their age, because in younger patients we are more likely to want to intervene than in older patients, but also their reactivity. I think to be fixed at 12 U/m<sup>2</sup> is a little bit different than to have a pulmonary vascular resistance that may start at 12 but drop down to 8 or 9 U/m<sup>2</sup>. Above 12 U/m<sup>2</sup>, I think that we are reluctant to operate. Then again there have been occasional younger children for whom we performed a repair in the operating room or placed a device in the cath lab to close the left to right shunt, even though the PVR was 12 U/m<sup>2</sup>. What I have tried to incorporate into our evaluation is whether we turn them into a left to right shunt during catheterization with vasodilator testing. So if a young patient has high resistance, but one can demonstrate by pulmonary vasodilator testing that one can turn the shunt into a left-to-right shunt I think that there are more opportunities for intervention and long-term therapy for PH. We do from time to time leave a small atrial septal communication when closing a large VSD in a high-resistance patient. Frankly, I don't think that helps so much minute to minute in the postoperative period as it might help during an acute decompensation or even resuscitation. I think that if one can provide an opportunity for blood to fill the left ventricle by going right to left at the atrial level, it provides a better opportunity to get through that acute decompensation or even resuscitation as opposed to being faced with completely separated circuits when there is a very intense pulmonary vasoconstriction and a right heart that just can't manage through the pulmonary hypertensive crisis.

**Dr Barst:** I completely agree with everything that has been said, including if a patient has borderline resistance, if we can decrease the shear stress or pressure, we are more aggressive about operating on these patients. We may leave an interatrial communication as a pop-off valve. The next question is since

we keep throwing around the term “vasodilator testing”, are you including oxygen as well as inhaled nitric oxide, aerosolized iloprost, intravenous epoprostenol, or intravenous adenosene?

**Dr Ivy:** We use measured oxygen consumption in all of these patients and we use a combination of oxygen and nitric oxide, as previously shown to be the most effective strategy by Dr Wessel.

**Dr Wessel:** In preoperative patients we have found that using nitric oxide and oxygen together gives us the best pulmonary vasodilating response.

**Dr Barst:** How confident are you that using a measured oxygen consumption in room air will be accurate for calculating PVRI with inhaled nitric oxide and supplemental oxygen?

**Dr Wessel:** PVR is a calculated variable and can have enormous error especially when oxygen consumption is assumed and not measured. That is why we must be flexible when determining operability. If one looks at all of the data that have been accumulated over the years with nitric oxide, it does appear that, in the absence of large changes in cardiac output, inhaled nitric oxide does not change oxygen consumption. There is much experience to substantiate this assumption. So I am reasonably confident that in the absence of extreme right-heart failure and very low cardiac output that giving NO to patients to breathe does not substantially change the oxygen consumption and introduce an error in PVR calculation that is based on a measured oxygen consumption at baseline before nitric oxide.

**Dr Bridges:** I agree with that. And I think there are two other things that may be worth saying here. One is that even the measured oxygen consumption that one gets in the cath lab is not completely accurate. I think we just have to remember that all of these measurements that we make in the cath lab are just estimates, or snapshots, even after we have done our best to create standardized conditions. And the second thing is that, from my view, almost all of the vasodilator testing that I do in the cath lab is done with very pragmatic endpoints in mind. For example, I know that in some labs, hyperventilation is used to test for pulmonary vasoreactivity. I don't see what the point of that is, frankly, because it is not a therapy that I am going to use in the postoperative period or for long-term therapy for the patient who is not having surgery. I try to use oxygen, I use nitric oxide, I use calcium channel blockers. I try to test with the same things that I think I might reasonably use for therapy for the patients.

**Dr Barst:** The therapies that we should discuss include calcium channel blockers, epoprostenol intravenously, treprostinil subcutaneously, oral beraprost, iloprost (which is available in Europe for both intravenous and inhaled administration), inhaled nitric oxide, oral endothelin-receptor antagonists, and oral phosphodiesterase inhibitors.

**Dr Ivy:** I would just like to start by saying that evaluation of PH is very important before even considering therapy. We have patients who have repaired congenital heart disease, who are

later found to have other exacerbating factors for pulmonary hypertension, such as thromboembolic disease, ulcerative colitis, or thyroid disease. The treating physician shouldn't assume that because the child has congenital heart disease, the congenital lesion is the only cause of the patient's pulmonary hypertension. With regard to therapy, we do not use calcium channel blockers in patients who are not reactive to short-acting vasodilators at cardiac catheterization, have low or borderline cardiac output, or have high right atrial pressure. We don't test calcium channel blockers in those patients. So, I think it is important for the general pediatric cardiologist who is going to perform vasoreactivity testing to use calcium channel blockers only in patients who are reactive.

**Dr Bridges:** I agree precisely with every single thing that Dunbar just said. That is exactly the way I approach patients. I still find it alarming how many pediatric cardiologists in the community are starting calcium channel blockade in the clinic after an echo. That is still a big, common practice and I think we really need to emphasize that that is not an appropriate practice. I think the other problem is that there are occasional patients who have a paradoxical response to calcium channel blockade. I haven't seen many, I think I have seen 3 in the last 10 years, but I have seen 3 patients whose PA pressure went up, whose PVR went up, and whose cardiac output went down when treated with calcium channel blockade. These were all patients who had a very nice response to nitric oxide. Dunbar, have you seen this?

**Dr Ivy:** Yes. I would agree. In patients reactive to acute vasodilator testing, we test the response to calcium channel blockers in the cath lab. We usually use IV diltiazem instead of nifedipine, just for ease of administration.

**Dr Barst:** OK, let's turn our attention to the various treatment options. We have soft retrospective and prospective data in PPH that anticoagulation prolongs survival in adult patients. We don't have those data in children. If we start off saying a very small percentage will respond favorably to calcium channel blockers, for those children that is wonderful, but let's discuss the other 80 to 90% of patients. Do you want to touch on anticoagulation, and then move on to other therapies with vasodilator and perhaps antiproliferative effects?

**Dr Bridges:** I generally anticoagulate my patients unless I have a very good reason not to. And that is regardless of the etiology of their PH, as long as we are talking about PAH. The only exception that I make to this is in the case of young toddlers because of the risk of a bleeding event in association with a fall, and the difficulty of monitoring their anticoagulation. I will wait until they are a little older before I anticoagulate them.

**Dr Barst:** You are right. We don't have data. But I think all of us are seeing patients who are having significant episodes of hemoptysis. So I think we need to be careful about “assuming” that we should use anticoagulation in patients with PAH associated with congenital heart disease the same way we do with PPH.

**Dr Bridges:** Assuming that they have appropriate levels of anti-

coagulation, an INR of 2 to 2½, do we really think that is a cause of any of the hemoptysis? Hemoptysis is a part of the disease.

**Dr Barst:** Yes, absolutely, but if a child has hemoptysis, are you continuing them on low-dose anticoagulation, since we think that the hemoptysis is part of their underlying disease, or are you doing something else?

**Dr Wessel:** We certainly study patients who are having acute hemoptysis to investigate whether there are collaterals that can be identified that are contributing to the symptoms. I think it is a little bit hard when you actually get there and you start looking at collaterals and deciding which ones to embolize. I'd like to outline an algorithm for the care that we are gradually evolving for patients with PPH or perhaps repaired congenital heart disease where there's still persistence of PH. First we test them in the cath lab and look for vasoreactivity. If they are very good responders we put them on a calcium channel blocker and evaluate them closely over the next few months to see if there is a sustained reduction in pulmonary artery pressure. If they're not dramatic responders, then we go to the other therapies. I think there is a reasonable basis now for discussing the use of continuous IV prostacyclin that could be offered to the child. If there were a reason not to use a central venous line and continuous IV epoprostenol, then we would consider some of the other alternatives. The next option usually is other FDA-approved therapies for certain kinds of adult PH disease. Bosentan is an example but our experience is mixed and preliminary. Beyond that we get into more investigational therapy and we have offered families inhaled nitric oxide for long-term administration or I think we may see emerging the opportunity to use phosphodiesterase inhibitors in outpatients. Most of these patients who are not in the infant or toddler group we anticoagulate. We may modify that in Eisenmenger patients with hemoptysis.

**Dr Barst:** Are we helping these patients with these treatments, particularly Eisenmenger patients who have an 80% 5-year survival and a 40% 25-year survival without treatment? Are there subgroups that we need to evaluate to determine the overall risk-benefit considerations for these various treatments versus no treatment?

**Dr Wessel:** As everyone knows, the majority of advances in the treatment of PH in adults have been a result of properly designed clinical trials. We do not have placebo-controlled trials to guide our therapy in patients with Eisenmenger syndrome. We extrapolate in part from adult PPH work and studies by Dr Barst. So I would say that we don't know if we are helping. It would be crucial, especially in most pediatric diseases, that we start proper trials because we're taking clues from our adult patients but we're not certain that children will react the same way. I am pleased to say that trials with sildenafil, endothelin-receptor blockers, and inhaled nitric oxide are under way in children.

As we move forward I think it's important that we have a more aggressive attitude toward intervening with these patients. We are now seeing treatments for patients referred to us as "Do Not Resuscitate" status because there is thought to be no therapy. Yet they've had sometimes spectacular results from existing lines of therapy for treatment of their pulmonary hypertension.

**Dr Barst:** I would remind everyone that for the FDA-approved therapies, even though several, i.e., treprostinil and bosentan, are approved for the broad category of PAH, epoprostenol and bosentan were not evaluated in patients who have PAH associated with congenital heart defects. And I think that's very unfortunate. It behooves us to make sure we are doing "no harm" using these therapies in PAH patients with associated congenital heart disease.

**Dr Bridges:** I think one thing that we have to be conscious of in making individual treatment decisions for patients who have residual significant structural lesions and pulmonary vascular disease is that if they're getting worse because of myocardial failure rather than increasing cyanosis, they are not, in my opinion, candidates for vasodilator therapy. In other words, if I do a heart catheterization on one of these patients who, say, has an unrepaired VSD or an unrepaired canal and they have a right atrial pressure of 15, a QP/QS less than one, and low systemic cardiac output, I don't really think that vasodilator therapy of any sort is going to be helpful for any of those patients. I think that sort of myocardial failure is really a harbinger of very end-stage disease in such patients.

**Dr Wessel:** I want to underscore the comments that were made about the true Eisenmenger population in patients who have right-to-left shunting and a significant degree of cyanosis. This is a patient population that has not been well studied and we need to be most cautious about these new therapies in that patient population. The subgroup that Nancy has just described with significant heart failure in association with it is one in which we should be especially cautious about these therapies because we do have a bit of natural history data for Eisenmenger syndrome that I think may be a little bit different from the adult or PPH. We know that historically one can survive several years with Eisenmenger's physiology and we have to be very cautious about introducing new therapies that are systemic vasodilators when we have an open unrestricted defect and the potential to go right to left.

**Dr Barst:** We haven't seen any clinically significant right-to-left shunting but I agree that we need to be cognizant of this potential adverse effect with vasodilator therapy in patients with Eisenmenger syndrome. We must remember that without treatment(s), Eisenmenger patients often live into their 20s, 30s and beyond. Nancy, would you address timing of transplantation and outcome?

**Dr Bridges:** There are two issues when you're looking at thoracic organ replacement in people with coexisting congenital heart disease and pulmonary vascular disease. First is the technical set of issues. It's obviously much more straightforward when you're considering lung transplantation for a person with PPH; these patients rarely need heart replacement. You need to be sure that you have a good understanding of the technical risks associated with transplantation for this particular patient and make a very careful decision about what sort of thoracic organ

replacement will be done, heart and two lungs, heart and one lung, or heart repair plus one or two lungs. It's a very individualized decision. And then there are the physiological considerations: at what point have patients with Eisenmenger syndrome definitively failed all the available medical therapies, making it appropriate to go on to transplantation? I still pretty much use the hallmark in most cases of progression of heart failure. If we have tried all of the available vasodilator and anticongestive therapies and demonstrated that they are not useful for the patient or that they were useful and the patient is no longer responding and I start to see the progression of heart failure, I think that is the appropriate time to list the patient. If you have a patient you know is going to need replacement of both the heart and the lungs, then obviously you need to list earlier because the waiting time will be longer.

**Dr Ivy:** In discussing a pediatric algorithm, treatment of patients who are not responsive to acute vasodilator testing depends on clinical status and functional class. My algorithm would continue that if a child presents with congestive heart failure with a nonreactive pulmonary vascular bed, I think that epoprostenol is the standard of care for that patient and we would consider listing for transplantation. If the patient is non-reactive but with normal cardiac output and right atrial pressure and no sign of congestive heart failure, then other therapies may be considered, such as treprostinol, sildenafil, bosentan, or perhaps long-term inhaled nitric oxide. I would agree with Dr Bridges entirely.

**Dr Barst:** Would each of you like to comment on where you think we should be headed in the future? I think we do these patients a disservice when we treat all patients with PAH and associated congenital heart defects the same, regardless of age, congenital heart defect and its associated physiology, as well as how symptomatic the patient is from his or her PAH. We still don't know if the "disease" is the same or different in various

patients with PAH and associated congenital heart disease.

**Dr Ivy:** I would reiterate that it is very important that we start multicenter randomized trials in children with these newer agents.

**Dr Wessel:** As we move forward I think it's important that we have a more aggressive attitude toward intervening with these patients. We are now seeing treatments for patients referred to us as "Do Not Resuscitate" status because there is thought to be no therapy. Yet they've had sometimes spectacular results from existing lines of therapy for treatment of their pulmonary hypertension. It is our obligation to really exhaust all those forms of medical treatment and then consider more heroic efforts like transplantations. It is also important to inform the medical and patient communities that trials and treatments do exist for them.

**Dr Bridges:** I agree with everything that's been said and I would add that it's important both for those of us who are more specialized in seeing patients with PH and the general pediatric cardiologist to view each patient with an open mind. As I've had more patients with PH referred to me, I've found that there are more variations of the disease than I originally recognized and it's easy to be too quick to categorize the patient. That's a mistake. We need to start out with the view that we do not know the disease and make sure the evaluation is complete and the approach to therapy is flexible. Given how much ignorance we still have about the patients we are treating, we need to remain humble when faced with this disease.

**Dr Barst:** I think it is also important for us to collaborate with our colleagues in adult cardiology as more and more children with congenital heart disease are surviving into adulthood. Each patient with pulmonary vascular disease deserves an individualized evaluation and treatment approach.

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