Editor's Memo

A New Source of Information for a New Era in Treatment

Ten years ago physicians treating pulmonary hypertension would have been amazed at today’s options for managing a disease that had a dismal prognosis. Progress has been swift, and we stand at the threshold of a new era in treatment. As our treatment options for pulmonary hypertension have expanded dramatically, so has our need for more information to keep pace with major advances.

Advances in Pulmonary Hypertension is committed to meeting your need for new information in a dynamic treatment arena. As the official journal of the Pulmonary Hypertension Association (PHA), it will draw on the expertise of the PHA’s Scientific Advisory Board, a group of specialists recognized internationally for their important contributions to research. Many of these leaders trained with Alfred P. Fishman, MD, the founder of the National Registry for Pulmonary Hypertension, whose career is chronicled in this premier issue.

As exciting as the last decade has been in expanding the spectrum of therapy, the years ahead look even more promising as we gather more data on the use of endothelin receptor antagonists and perhaps additional agents that will address the proliferative mechanisms of the disease. Our roundtable discussion in this issue and the review articles provide you with in-depth information to help guide your clinical decision making. The convenient pull-out algorithm is also a quick reference to help frame your choices in therapy. On behalf of the PHA, I welcome you to Advances in Pulmonary Hypertension and look forward to your comments and suggestions.

Please email me at tapso001@mc.duke.edu.

Victor F. Tapson, MD
Editor-in-Chief

Celebrating the Illustrious Career Of Alfred P. Fishman, MD

Founder of the Registry in Pulmonary Hypertension

As early as his residency, colleagues of Alfred P. Fishman, MD, recognized the first flashes of brilliance pointing toward a career that has taken him to the pinnacle of research in pulmonary hypertension. Soon after his residency, he introduced the artificial kidney in the United States and began investigative work in laboratories headed by physicians who won the Nobel Prize for their groundbreaking research. In a long and distinguished career, Dr Fishman is still recognized as one of the preeminent scholars in his field, the pioneer who organized the National Registry on Pulmonary Hypertension and the recent recipient of the Trudeau Award, the highest accolade given by the American Thoracic Society.

Dr Fishman received the award from Claude Lenfant, MD, Director of the National Heart, Lung, and Blood Institute.

After publishing a paper on the artificial kidney and seeing his research lead to the widespread use of dialysis, Dr Fishman was supported by the American Heart Association, which helped him in his studies at Harvard University, New York University, the University of Chicago, and Oxford University. He currently serves as William Maul Measey Professor of Medicine Emeritus at the University of Pennsylvania, Philadelphia. Throughout his career, his work has focused on the heart and kidneys and the interplay of these organs with the lungs. He found that the most intriguing aspect of (continued on page 8)
A New Classification of Pulmonary Hypertension

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Classification of Pulmonary Hypertension

Introduction
Because pulmonary hypertension can occur from diverse etiologies, a classification of the disease has been very helpful. The original classification, established at a World Health Organization (WHO) symposium in 1973, classified pulmonary hypertension into groups based on the known cause and defined primary pulmonary hypertension (PPH) as a separate entity of unknown cause. PPH was then classified into three histopathological patterns: (a) plexogenic arteriopathy, (b) recurrent thromboembolism, and (c) veno-occlusive disease. In 1998, a new classification for pulmonary hypertension was developed that focused on the biologic expression of the disease and etiologic factors in an attempt to group these illnesses on the basis of clinical similarities.1 This classification serves as a useful guide to the clinician in organizing the evaluation of a patient with pulmonary hypertension and developing a treatment plan. In addition, a functional classification (see Table) patterned after the New York Heart Association Functional Classification for heart disease was developed to allow comparisons of patients with respect to the clinical severity of the disease process.

Recently, parameters for normal pulmonary arterial systolic pressure derived by echo Doppler studies have been published which suggest that the upper limit of normal of pulmonary arterial systolic pressure in the general population may be higher than previously appreciated.2 Importantly, however, the study characterized changes based on age and found a modest increase in pulmonary arterial pressure with age similar to what exists in the systemic circulation.

There are patients whose resting hemodynamics are normal, but in whom marked elevations in pulmonary pressure occur with exercise. It has been presumed that this represents an early stage of pulmonary vascular disease. However, as patients may have a hypertensive response to exercise with respect to the systemic vasculature, a similar type of response can occur in the pulmonary vasculature. Thus, whether exercise induced pulmonary hypertension represents true pulmonary vascular disease or reduced compliance of an otherwise normal pulmonary circulation can be difficult to ascertain.

Pulmonary Hypertension—Diagnostic Challenges

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WHO Functional Classification of Pulmonary Hypertension

A. Class I – Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
B. Class II – Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
C. Class III – Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
D. Class IV – Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by any physical activity.
Patients with pulmonary arterial hypertension characteristically present with effort dyspnea that can have a slowly progressive course. The onset of right ventricular failure, manifest by a reduction in cardiac output and/or elevation in right atrial pressure, is usually associated with a marked clinical deterioration and poor prognosis. The rapidity in which this occurs in highly variable and is often related to the age of onset and associated conditions. Thus, patients with pulmonary arterial hypertension associated with congenital heart defects will more commonly have a slow, insidious onset of symptoms and develop right heart failure after decades, whereas patients with the CREST syndrome present later in life with a progressive downhill course.

**Primary Pulmonary Hypertension**
Patients with primary pulmonary hypertension (PPH) are subdivided into sporadic and familial. The diagnosis of familial PPH is made through a patient’s family history, as there are no clinical or pathologic features that separate these two entities. Although the prevalence of familial PPH had been published as being 12% at the time of the NIH Registry, this underestimates the true familial prevalence. Because of incomplete penetrance of the gene, it may skip several generations, which would not be uncovered unless the physician were to take an in-depth look at the patient’s family medical histories. The PPH-1 gene, which has been recently described, has been reported to be present in approximately half the patients with familial PPH. Those without the PPH-1 gene may have other genetic mutations that have not yet been discovered or may have a gene that cannot be determined by current techniques. Patients with sporadic PPH have also been noted to test positive for the PPH-1 gene in about 25%. These patients actually may be familial but characterized as sporadic because of the lack of a supporting family history, or may indeed represent point mutations.

**Collagen Vascular Disease**
Patients with pulmonary arterial hypertension related to the collagen vascular diseases will have clinical features representing both entities. It is most common for the collagen vascular disease to manifest itself years before the onset of pulmonary hypertension, but on occasion the opposite has occurred. Many patients with PPH will have elevated titers of antinuclear antibodies. Whether this represents a form fruste of a collagen vascular disease, or is just a clinical feature of PPH, has been debated. The high incidence of pulmonary hypertension in patients with CREST and scleroderma has supported the recommendation that these patients be screened periodically with echocardiography.

**Congenital Heart Disease**
Congenital systemic to pulmonary shunts can cause pulmonary hypertension believed to be related to the increased blood flow and pressure transmitted to the pulmonary circulation. In most instances this entity is reversible if detected early and the shunt is corrected. In some instances, however, pulmonary hypertension develops very rapidly at the early stages of the disease and precludes any surgical correction. Some patients present with a remote history of a patent ductus arteriosus that was ligated, or an atrial septal defect that was relatively small with coexisting pulmonary vascular disease. Whether the shunt and the pulmonary hypertension are related or coincidental has been a matter of debate. Right-to-left shunting through a patent foramen ovale needs to be distinguished from congenital heart disease. It is uncommon for a patent foramen ovale to be associated with significant right-to-left shunting at rest, but it can contribute to exercise-induced hypoxemia. When uncertainty exists, transesophageal echocardiography should distinguish a foramen ovale from an atrial septal defect. If necessary the distinction can be made during catheterization by sizing the defect with the balloon from a pulmonary artery catheter.

**Portal Hypertension**
The association between liver disease and pulmonary hypertension appears to be related to portal hypertension, and not to liver disease itself. Why portal hypertension leads to pulmonary hypertension has never been fully understood. Making the diagnosis of portal hypertension in a patient with pulmonary hypertension can be problematic. The diagnosis of portal hypertension, an elevation in portal pressure, can be made by direct wedge pressure determination of the portal vein at the time of cardiac catheterization. An elevation of portal pressure above 10 mmHg from a normal right atrial pressure defines portal hypertension. It has never been determined, however, what gradient is necessary to make this diagnosis in a patient with an elevated right atrial pressure that is commonly found in patients with pulmonary hypertension. Thus, the clinical diagnosis of portal hypertension may have to be made by other indirect determinations such as the presence of esophageal varices or an abnormal flow pattern in the hepatic veins determined by Doppler.

**HIV Infection**
It is well established that the presence of the HIV virus can induce pulmonary hypertension, probably through activation of cytokine or growth factor pathways. There has been no association made between the viral load or the type of antiviral therapy and the severity of the pulmonary hypertension. As antiviral therapy against HIV improves over time, it will be of interest to note whether or not the coexisting pulmonary hypertension resolves with treatment.

**Drugs/Toxins**
Although several drugs and toxins have been associated with the development of pulmonary hypertension, a causal relationship with many of these remains uncertain. The strongest association between drug ingestion and the development of pulmonary hypertension has been made with the fenfluramines. Although the syndrome is indistinguishable from primary pulmonary hypertension, our experience suggests these patients tend to have a more aggressive disease with a poorer prognosis than similar patients with PPH. This may be a result of the fenfluramines triggering a unique molecular pathway that produces pulmonary vasculopathy.

*CREST = calcinosis cutis, Raynaud’s phenomenon, esophageal dysmotility, scleroderma, telangiectasia*
Persistent pulmonary hypertension of the newborn is to be distinguished from congenital abnormalities of the heart and pulmonary vasculature. It represents an entity similar to PPH and is typically somewhat more responsive to acute and chronic vasodilator therapies. Untreated, it can be rapidly fatal.

Other Causes of Pulmonary Hypertension

Pulmonary Venous Hypertension

1. Left-sided atrial or ventricular heart disease
2. Left-sided valvular heart disease
3. Extrinsic compression of central pulmonary veins
   (a) Fibrosing mediastinitis
   (b) Adenopathy/tumors
4. Pulmonary veno-occlusive disease
5. Other

Pulmonary venous hypertension represents a clinical entity that has a pathophysiology and clinical course that is markedly different from pulmonary arterial hypertension. Orthopnea and paroxysmal nocturnal dyspnea are characteristic features, which may precede effort dyspnea. These patients often have a history of chronic congestive heart failure and/or recurring pulmonary edema, which then becomes obscured when right ventricular failure ensues.

Pulmonary venous hypertension is the most common cause of pulmonary hypertension in clinical practice. Because blood by necessity flows through the pulmonary vascular bed into the left heart, any elevation of the filling pressure of the left side of the heart will result in an increase in pulmonary artery pressure. Although often times this is quite apparent, there are some circumstances where the situation is confusing. For example, chronic pulmonary venous hypertension can lead to morphologic changes in the pulmonary arterial and venous bed resulting in further elevation of the pulmonary artery pressure beyond that which was initially a result of the elevated left-sided pressure, implying pulmonary vasoconstriction or a vasculopathy triggered by the elevation in pulmonary venous pressure. Often, the physician is confronted as to whether or not two processes are ongoing or the long-term result of a single process.

Another scenario is the patient who has a longstanding history of left heart disease who develops pulmonary hypertension and severe right heart failure. At the time of cardiac catheterization these patients may have a normal pulmonary capillary wedge pressure or left ventricular end diastolic pressure in the presence of a low cardiac output. Thus, they may have the hemodynamic profile of a patient with PPH because one is unable to determine what the left ventricular end diastolic pressure would be in the face of a normal cardiac output.

The diagnosis of pulmonary veno-occlusive disease can be difficult, since the pulmonary wedge pressure may be normal or elevated depending on the segment of the lung that is measured. In our experience these patients often have a very abnormal perfusion lung scan without any evidence of pulmonary thromboembolic disease. Another common, but inconsistent, feature is an elevation in pulmonary capillary wedge pressure following the challenge of an infusion of adenosine or prostacyclin at the time of catheterization.

Pulmonary Hypertension Associated With Disorders of the Respiratory System and/or Hypoxemia

1. Chronic obstructive pulmonary disease
2. Interstitial lung disease
3. Sleep-disordered breathing
4. Alveolar hypoventilation disorders
5. Chronic exposure to high altitude
6. Neonatal lung disease
7. Alveolar-capillary dysplasia
8. Other

Although hypoxemia may coexist in all forms of pulmonary hypertension, it is the hallmark of these conditions. These patients are often dyspneic at rest as well as with minimal activity, with only subtle clinical features of pulmonary hypertension. Supplemental oxygen will usually provide substantial clinical improvement.

A subset of patients present with severe elevations in pulmonary artery pressure beyond those typically seen in these disease entities. Whether this represents an extreme manifestation of the underlying disease or a different disease process characteristic of pulmonary arterial hypertension that has been triggered by a common pathway is currently unknown. Clinically, it can be difficult to sort out the basis of a patient’s complaint of dyspnea. In addition, even successful treatment of the pulmonary hypertensive component of the problem may not render the patient clinically improved if the hypoxemia persists. Of great concern is that some therapies directed toward the pulmonary hypertension can worsen gas exchange and make the hypoxemia even worse.

Pulmonary Hypertension Due to Chronic Thrombotic or Embolic Disease

1. Thromboembolic obstruction of proximal pulmonary arteries
   (a) Pulmonary embolism (thrombus, tumor, ova and/or parasites, foreign material)
   (b) In-situ thrombosis
   (c) Sickle-cell disease

These patients often present with clinical signs and symptoms that are indistinguishable from pulmonary arterial hypertension. Unless a thorough evaluation is conducted to exclude these diseases, patients may be misdiagnosed and inappropriately treated. Chronic proximal thromboembolic obstruction of the pulmonary arteries is a well characterized clinical entity that has been extensively studied. Because it is potentially reversible, it must be excluded in every patient who presents with pulmonary hypertension irrespective of the lack of an antecedent history of deep vein thrombosis or pulmonary thromboembolism.

Obstruction of the distal pulmonary arteries can be either
Advances in Pulmonary Hypertension

Embolic or thrombotic. Recurrent microthromboembolism does not appear to be a clinical entity, since current evidence points to thrombosis in situ as being responsible for the thrombotic changes noted in the arteriolar bed in patients with pulmonary arterial hypertension. Thrombotic obstruction, however, can occur anywhere from the pulmonary capillary bed to the main pulmonary arteries and may reflect a continuum of a disease process. This makes it difficult to ascertain the cause of pulmonary hypertension in a patient with clear evidence of pulmonary thromboembolism involving a relatively few number of vessels. It appears that in some of these patients thrombotic obstruction of the pulmonary arteries leads to chronic pathologic changes in the uninvolved vasculature. Diffuse pulmonary embolism can occur on rare occasions from metastatic tumors, parasitic disease, or from foreign material through intravenous injection.

Pulmonary Hypertension Due to Disorders Directly Affecting the Pulmonary Vasculature

1. Inflammatory
   (a) Schistosomiasis
   (b) Sarcoidosis
   (c) Other
2. Pulmonary capillary hemangiomatosis

These very rare entities require a high index of suspicion in order for a diagnosis to be made. Schistosomiasis, for example, is probably the most common cause of pulmonary hypertension worldwide, although it is virtually never seen in Westernized countries. It should be kept in mind when patients are referred from underdeveloped countries as a potential underlying etiology.

Sarcoidosis can cause extensive destruction of the pulmonary parenchyma and pulmonary vascular bed and can cause pulmonary hypertension merely by lung destruction and resulting hypoxemia. In addition, these patients may develop pulmonary hypertension presumed to be on the basis of involvement of the pulmonary circulation from the sarcoid process. It is unlikely that this is due to local granuloma formation within the pulmonary vasculature and is more likely the result of growth factors triggering the same process that is seen in pulmonary arterial hypertension. Some of these patients may respond very favorably to long-term intravenous epoprostenol.15

Pulmonary capillary hemangiomatosis is an extremely rare disorder involving the pulmonary capillary bed that can present in different stages. It is often associated with frequent hemoptysis, severe pulmonary hypertension, and a progressive fatal course in a short period of time. The diagnosis can be made with pulmonary angiography in the hands of an experienced radiologist. PH

References
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“The PHA conference is an excellent forum for the exchange of medical and scientific information, but I find the meeting’s greatest value to be on a personal level. As I marvel at how well patients and their families cope with a very challenging chronic illness, I return home with a renewed perspective on what is truly important in life—family, friends, and working together to help each other.”

David B. Badesch, MD
Professor of Medicine
University of Colorado Health Sciences Center

“This is an unparalleled opportunity for patients, physicians, nurses, scientists and others to see each other as real people with a common passionate interest...rather than just as patients, physicians, or nurses. This is an environment where goals are inspired and work gets done.”

Michael McGoon, MD
Pulmonary Hypertension Clinic Director
Mayo Clinic

“The PHA Conference is a unique forum that gains energy from the interaction of patients, family members, and health professionals concerned with pulmonary hypertension.”

C. Gregory Elliott, MD
Chief, Pulmonary Division
LDS Hospital
University of Utah School of Medicine
Advances in Pulmonary Hypertension

(Alfred P. Fishman, continued from page 2)

this interplay—and one that raised implications for therapy in humans—could be found in the African lungfish and its ability to achieve a state of suspended animation for several years without the need of food or water.

“We wanted to know whether you could take patients who were on a downhill course—as in pulmonary hypertension—and slow their metabolism down and bring them to a state of suspended animation, like the lungfish, until you could bring therapies to bear on them,” said Dr Fishman. “We wanted to study the control, and the pulmonary circulation in very primitive animals because we might get some clues regarding their nerve supply, their hormones or other factors at work. All the way through, my research has been oriented to how we might learn lessons from comparative physiology and pathology.

“Based on the animal models, the most important issue was whether there was a way to drop the metabolism so that we would not be in as much of a hurry or as desperate when we got a patient with pulmonary hypertension. When we began working with patients with pulmonary hypertension, the patients had a lifespan of a year. But we could see only one or two patients a year.”

The big break came when the National Registry was established and Dr Fishman gained access to more pulmonary hypertension patients. By the time the registry was closed, 300 patients had been enrolled. “We were able to see which drugs work, and suddenly we had 18 centers working together; but most importantly, we created a pathology center at the University of Pennsylvania, so that all the data from autopsy or biopsy are analyzed by one pathologist. Right now everybody is concerned about remodeling—but you couldn’t think about that without the pathology.

“We need to explore the mechanisms by which one develops occlusion of the vessel,” added Dr Fishman. “They close because the linings proliferate. There are certain stages when the vessel is so scarred that you can’t reverse it. But there are many proliferative lesions that might be stopped or reversed. One thing seems to be true—if you can drop the pressure and keep it down, the vessels start to reverse their proliferative changes. A key question is whether the antiproliferation is working because you are relieving vasoconstriction or are you starting another process which undoes the proliferation? So remodeling in the pulmonary circulation must be examined. It is not easy to do and we will have to go primarily to animal models, although there are a few human cases that have been studied, who came to autopsy. Apparently you can reverse many of these changes, but the secret of how you do it, other than by dropping the pressure, is not known.”

Dr Fishman urged physicians to suspect pulmonary hypertension at an earlier stage. One of the problems is that the disease does not manifest itself clearly except by fatigue, shortness of breath, and a sense of deconditioning that may appear in someone 20, 30, or 40 years of age. If he were to suggest how training programs for physicians might be improved, he suggested that programs include molecular biology, genetics, and developmental biology “because until we understand growth and development we can’t understand why blood vessels close. You need to go back to the fundamental process that you see during developmental biology. Why does a lung become a lung? Why does the lining stay flat? There must be susceptibility genes. That’s why the studies on familial pulmonary hypertension are so important. The period of training could be a very rewarding one because timing is absolutely right for developmental biology, molecular cell biology, and genetics. Without that, you cannot approach pulmonary hypertension in the future.” PH

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Pulmonary Hypertension: A Patient’s Survival Guide—Second Edition

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Abstract
The endothelin system has been extensively studied over the last several years. It is clear that endothelin-1 (ET-1) is a key mediator in pulmonary vascular biology and physiology. Abnormal increases in ET-1 production and decreased pulmonary clearance appear to play a major pathogenetic and perpetuating role in the pulmonary hypertensive process, through their vasoconstrictive, smooth muscle cell proliferative and profibrotic effects. The degree of overexpression of ET-1 may correlate with the severity of pulmonary hypertension (PH). Advances in understanding the role of ET-1 in pulmonary hypertension have driven the development of endothelin receptor antagonists. One such agent, bosentan (Tracleer), is FDA approved for pulmonary arterial hypertension. Bosentan was approved following two randomized, placebo-controlled, double-blind studies that both showed marked improvement in exercise capacity after treatment with bosentan. The beneficial effects of bosentan appear to be sustained in most patients followed for as long as 22 months. Other uses for endothelin receptor antagonists are being examined, such as in combination with epoprostenol (Flolan) or in pediatric PH patients.

One of the most exciting developments in the treatment of pulmonary arterial hypertension in recent years is the approval of the first oral agent specifically indicated for the treatment of pulmonary hypertension, the dual endothelin receptor antagonist bosentan. This article will review the importance of the endothelin system in pulmonary arterial hypertension and the role of inhibiting this system as a treatment modality in pulmonary arterial hypertension.

Biology of ET-1
ET-1 is a 21-amino acid peptide discovered in 1988. ET-1 is produced in high concentrations within human lung. High-affinity binding sites for ET-1 are found throughout the lung parenchyma, predominantly on small pulmonary arteries and arterioles, but also on bronchial smooth muscle. Two receptor subtypes, ETA and ETB, have been described; the proportion and distribution of these subtypes vary among species. In human pulmonary artery, the ETA receptor subtype appears to be most predominant. At the capillary level, both ETA (30%) and ETB (70%) receptors are found. In addition to being the predominant producer of ET-1, the human lung appears to clear ET-1, under normal conditions. Thus, there is no net arteriovenous difference in ET-1 levels.

Fig. 1—Illustration of the actions of endothelin-1 (ET-1) on vascular smooth muscle cells. In addition to contraction, ET-1 can mediate smooth muscle cell relaxation through release of PG2 and nitric oxide (NO).
of importance when the contribution of ET-1 to the pathogenesis and progression of pulmonary arterial hypertension (PAH) is considered.

Abnormalities in the Endothelin System in Pulmonary Hypertension
Numerous studies have confirmed the prominent role of abnormalities in ET-1 in the pulmonary hypertensive process. Patients with primary pulmonary hypertension (PPH) have been shown to have elevated circulating levels of ET-1, with higher arterial than venous levels, suggesting increased pulmonary production. Some investigators have found that levels of ET-1 correlate with the severity of pulmonary hypertension. Immunostaining studies have demonstrated increased expression of ET-1 in the muscular pulmonary arteries of PPH patients as well as in the plexiform lesions often seen in this disease (Figure 2). The degree of immunoreactivity in these vessels has been found to correlate with the pulmonary vascular resistance. Treatment of PPH with epoprostenol has been shown to decrease the production of ET-1, suggesting improvement in endothelial function.

Although less studied in other forms of PAH, increased ET-1 levels have been noted in patients with PH associated with systemic lupus erythematosus (SLE) and scleroderma as well as congenital heart disease-associated PAH. Other forms of pulmonary hypertension have also been associated with ET-1 increases. For example, Cody et al. found high plasma ET-1 levels in patients with congestive heart failure. In addition, PH due to chronic hypoxic lung disease, notably COPD and interstitial pulmonary fibrosis (IPF), has also been reported. In IPF, Giaid and coworkers found increased expression of ET-1 in airway epithelium and type II pneumocytes compared with controls. In IPF patients with PH, increased ET-1 and mRNA were present in endothelial cells. Finally, in the pulmonary vasculopathy that develops in association with chronic pulmonary arterial obstruction, increased ET-1 immunoreactivity has been noted in an animal model of pulmonary embolism. Notably, postobstructive pulmonary vasculopathic changes were inhibited by the dual receptor antagonist bosentan.

Endothelin Receptor Antagonists
Because of the clear importance of ET-1 in the spectrum of pulmonary hypertensive disorders, the potential use of endothelin antagonists is obvious. The dual receptor antagonist bosentan has received the most study. Both intravenous and orally active endothelin receptor antagonists have been developed. Oral bosentan has been studied in two randomized, placebo-controlled, double blind studies.

The first study enrolled 32 patients with either PPH or PAH associated with scleroderma. Patients were all in modified New York Heart Association functional class III at the onset of the study. Patients had been maximally treated and were stable on conventional therapy, including calcium channel antagonists and diuretics. Two thirds of patients received 62.5 mg of bosentan for 4 weeks followed by 125 mg of bosentan for 8 weeks. One third received placebo. The primary efficacy endpoint was a 6-minute walk distance. Patients receiving bosentan walked an average of 70 meters farther after 12 weeks (Figure 3) while placebo patients had a decline in walk distance. In addition, bosentan-treated patients had improvements in dyspnea score and functional class (Figure 4) compared with placebo patients. Pulmonary hemodynamic measurements revealed decreases in pulmonary arterial pressure and pulmonary vascular resistance and increase in cardiac output after 12 weeks of bosentan, compared with worsening of pulmonary hemodynamics in placebo patients. All these changes in treated patients were highly significant compared with placebo.

In this study the only significant adverse effect noted was an increase in hepatic transaminases in 2 patients treated with bosentan. These abnormalities, however, resolved with either discontinuation or dose reduction.

On the basis of the results of this pilot study, a large study (BREATHE-1) was conducted. In BREATHE-1, 213 patients
were randomized to receive either 125 mg bid or 250 mg bid of bosentan or placebo in a 1:1:1 ratio. Patients with PPH or connective tissue disease-associated PH (scleroderma or SLE) were included. Patients in WHO functional class III or IV were enrolled. The primary endpoint, a 6-minute walk distance, was evaluated at 16 weeks. Bosentan-treated patients walked 36.4 meters further at 16 weeks compared to a 7.8 meter reduction in walk distance in the placebo group, for a treatment effect of 44.2 meters (CI: 21-67 meters, \( P = .0002 \)). Clinical worsening, defined by death, premature withdrawal from study, hospitalization for worsening of PAH or institution of epoprostenol occurred in 37% of placebo-treated patients, compared with 11% of bosentan-treated patients (\( P = .0015 \)). Functional class improved in significantly more treated patients than placebo patients. Dose-related increases in hepatic transaminases occurred in 11% of patients, but resolved with discontinuation or dose reduction. No other significant adverse effects were noted.

On the basis of these two studies, bosentan was approved by the FDA and is currently commercially available. The indications for the drug are pulmonary arterial hypertension and functional Class III or IV (PPH, PH associated with HIV, anorexigens, connective tissue disease, congenital heart disease, liver disease). It is recommended that liver function be monitored monthly in all patients, and there are strict warnings about using approved birth control in women. The recommended dose is 125 mg bid.

Other aspects of bosentan efficacy are being studied. BREATHE-2 is examining the combination of epoprostenol and bosentan in PAH. Patients who are initially given epoprostenol are randomized to receive either bosentan or placebo and the primary endpoint is a 6-minute walk distance at 12 weeks. BREATHE-3 is studying bosentan in pediatric patients with pulmonary hypertension.

Another oral endothelin antagonist, the ETA-specific receptor antagonist sitaxsentan, is under study. An uncontrolled trial of sitaxsentan in 14 patients with PAH demonstrated improvement in pulmonary hemodynamics at 12 weeks.\(^{19}\) A randomized, placebo-controlled trial is underway.

Comment

The approval of bosentan for the treatment of pulmonary arterial hypertension has heralded an exciting new era. This drug represents not only an entirely new class of pharmacologic agents but also the first oral treatment specifically indicated for pulmonary hypertension.

Where does bosentan fit into the overall scheme for treating pulmonary hypertension? We still believe that the first step in determining proper therapy is an acute vasodilator test with invasive hemodynamic monitoring. We use either inhaled nitric oxide or intravenous prostacyclin as acute testing agents. For the approximately 20% of patients who demonstrate significant acute pulmonary vasoreactivity, oral calcium channel antagonists remain first-line treatment. However, it should be noted that the long-term efficacy of these agents is variable; some patients respond partially and others lose responsiveness. Therefore, close monitoring and consideration of the addition of or change to bosentan should be utilized in this group.

For the 80% of patients who are not calcium blocker candidates, bosentan is the agent of choice, provided patients are not in decompensated, functional class IV right ventricular failure. Such patients (severe edema, syncope, etc.) should be treated promptly with intravenous epoprostenol; this intervention can be life-saving. The results of the BREATHE 2 trial should help answer the question of whether patients initially treated with epoprostenol should have bosentan added. A related question is whether bosentan should be added to the regimen of patients receiving epoprostenol who, in some cases, have been taking the drug for years. The concept of combination therapy with agents attacking different pathogenetic mechanisms of the disease is an attractive one. However, there are no data and no study currently addressing this issue. Our approach is to add bosentan to virtually all patients receiving epoprostenol. The hope is that bosentan will allow dose reduction of epoprostenol, thereby reducing side effects. It is certainly possible that, in some cases, one will be able to discontinue epoprostenol.

Finally, can the use of endothelin antagonists be expanded to PAH patients with earlier stage, milder disease, or those with other forms of pulmonary hypertension, such as that associated with lung disease (COPD, pulmonary fibrosis) or chronic pulmonary emboli? As these groups have been shown to have similar abnormalities in the ET-1 system, it seems logical that endothelin antagonism might have benefit. Given the favorable safety profile of the drug, off-label use for these patients is likely. Hopefully, subsequent data will help define additional roles for this exciting new therapy.

References


(continued on page 17)
1. Warfarin therapy should be undertaken if deemed safe. The generally accepted INR range is 1.5-2.5. Diuretics, digoxin, and oxygen are utilized on an individual basis.
2. Right-heart catheterization is essential in determining initial and sometimes subsequent therapy. This, together with WHO classification, echocardiographic data and exercise testing are used in treatment decisions. The rate at which symptoms are progressing may play a role in the level of aggressiveness with therapy. The terms IIIa and IIIb denote early, stable class III patients and advanced class III patients, respectively.
3. Unresponsive class I-II patients are individualized; one option is enrollment in clinical research trials as in class IIIa. For vasoreactive patients, calcium channel blockers (CCB) alone may be appropriate when the vasodilator response is exceptional.
4. In those who respond to CCB, but suboptimally, or who respond but clinically worsen, oral bosentan (Tracleer) should be strongly considered. This drug is approved for WHO class III-IV patients. There is no clear consensus on the use of this drug as it relates to presence or absence of vasodilator response. Bosentan (Tracleer) should not be used in setting of liver disease.
5. Treprostinil (Remodulin) is an investigational subcutaneous prostacyclin analogue (approvable letter for class II-IV PAH), and iloprost (not available in U.S.) is an investigational inhaled prostacyclin analogue. Other investigational agents may be considered in stable class II-III patients in the setting of clinical research trials.
6. Epoprostenol (Flolan) is the FDA-approved intravenous prostacyclin for class III-IV patients and is the most effective form of therapy in these individuals. Bosentan is appropriate for most class IIIa patients prior to considering epoprostenol, but in class IIIb-IV patients, epoprostenol is preferred. The distinction between class IIIb and class IV is essentially arbitrary as these patients are generally handled in the same manner. The relative roles of bosentan and treprostinil are not well defined and the latter awaits final approval. Combined therapy with the addition of bosentan and/or sildenafil could be considered but would be investigational; clinical trials are ongoing or planned.
7. Very few centers have extensive experience with atrial septostomy. When utilized, this is intended to serve as a bridge to transplantation. The timing of lung transplant referral is individualized at different centers. This depends in part upon the waiting time at the listing institution.


When we are talking about therapeutic options for these patients, we are considering that many of the therapeutic options that we’ve learned the most about from treating patients with primary pulmonary hypertension may also be efficacious for these other forms of pulmonary arterial hypertension, although our experience is much less. As Dr Rubin has said, there have recently been dramatic improvements in treatment options for patients with primary pulmonary hypertension, but if we want to review briefly how we have gotten to this point, which we are very excited about, and what the future holds, we should first review the treatment options available prior to the availability of the novel therapeutic options we will be discussing. There really weren’t any options until the late 1970s. With the introduction of vasodilators to treat systemic hypertension, we began looking at vasodilators to treat pulmonary arterial hypertension as well. These efforts focused primarily on calcium channel blockers in the early 1980s, and they have been demonstrated to be efficacious in patients who respond with acute short-acting vasodilator testing, eg, inhaled nitric oxide, intravenous prostacyclin, or intravenous adenosine. If we see a very significant fall in the pulmonary artery pressure with acute testing, these patients are very likely to also have that same response when they are treated with long-term calcium channel blockade therapy, such as amlodipine or nifedipine. The proportion of patients with primary pulmonary hypertension who demonstrate this response is probably only about 20%, and in our experience, the proportion of those patients who continue to do exceedingly well on calcium channel blockers over 5 to 10 years decreases to approximately 75% of the original responders. For the patients who could not be treated with a calcium channel blocker in the 1980s, several studies were begun using chronic intravenous prostacyclin, or epoprostenol, initially with the thinking that these patients would not respond significantly, but we wanted to try to use chronic intravenous epoprostenol as a bridge to transplantation. In the late 1980s, at least 40% of patients were dying awaiting heart-lung or lung transplantation so we started using intravenous epoprostenol as a bridge. Surprisingly, we saw a number of patients markedly improve clinically and hemodynamically as well as having improved survival, which led to epoprostenol being the first FDA approved therapy for the treatment of primary pulmonary hypertension in 1995. Why epoprostenol significantly improved a number of patients when they had no acute response remains unclear, but recent research focusing on an antiproliferative effect of epoprostenol in addition to its vasodilator and antiaggregatory effects may be why epoprostenol works chronically. That takes us up to what Dr Rubin began discussing. So, up until this point our options for primary pulmonary hypertension patients were chronic oral calcium channel blockade in approximately 20% of patients, and the remaining 80% were started on epoprostenol. The results with the other types of patients we talked about, particularly patients with collagen vascular disease and congenital heart disease, show a much less efficacious response with calcium channel blockers.

Dr Galiè: Regarding “background” therapy, I would like to mention oral anticoagulant therapy that has been used in patients with pulmonary arterial hypertension since the 1980s. Even if the evidence of efficacy of oral anticoagulant therapy is based on retrospective and uncontrolled studies, this form of treatment is largely utilized by clinicians. In all the controlled clinical trials on new treatments in pulmonary arterial hypertension, more than two thirds of patients were receiving anticoagulant treatment.

Dr Rubin: To summarize very briefly, the calcium channel blockers were advanced in their time, but only for a limited

(continued on back cover)
Since 1996 Gentiva Health Services has been the leader and pioneer in the treatment of pulmonary arterial hypertension in the home.

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number of patients, and as Dr. Barst pointed out, the acute responsiveness doesn’t guarantee chronic responsiveness in calcium blockers. For the nonresponders, the development of intravenous prostacyclin was a dramatic advance, but even with that, the long-term outlook remained limited for many patients. Long-term responsiveness to prostacyclin certainly does occur, but the mode of delivery, the complexity of the drug, and the side effects have really been limiting factors. And finally, transplantation, typically lung transplantation, has been an option for a select few patients who have failed to respond to medical therapy, but the availability of organs has really been limited. Long-term complications after transplantation, typically chronic rejection and opportunistic infections have hampered its long-term efficacy in many patients. All that has prompted efforts to develop new therapies or modify existing therapies into modalities that are easier to deliver and more efficacious. There have been several studies of late that have demonstrated encouraging positive findings. The most recent one is the development of endothelin-receptor antagonists for the treatment of pulmonary hypertension. Endothelin is a vasoconstrictor and mitogen that is produced by the vascular endothelium and is produced in excess in the pulmonary vascular endothelium of patients with pulmonary hypertension. There are now drugs that are blockers of the endothelin receptor that have been studied in patients with pulmonary hypertension. There are two types of endothelin receptors: endothelin A or ETA and endothelin B or ETB receptors. The first drug that has been extensively studied and now FDA approved in pulmonary hypertension is the nonselective ETA and ETB receptor blocker bosentan (Tracleer). It is an orally active drug that has been demonstrated in two randomized placebo-controlled, double-blind trials to produce improvement in a variety of parameters of clinical significance in pulmonary hypertension, pulmonary artery hypertension, although it has been primarily studied, thus far, in patients with either primary pulmonary hypertension or pulmonary hypertension associated with connective tissue diseases. This has now opened up the opportunity to treat patients with an orally active drug even if they are not vasoreactive, even if they cannot be treated with calcium channel blockers. There are ongoing studies now using more selective endothelin receptor blockers, ETA receptor blockers, in particular, to see whether selectivity confers preferential effects compared with nonselective blockade. But this also creates questions. And among the questions that have to be addressed are which patients should be treated with endothelin-receptor blockers, at this point, and when?

Dr Barst: These are very important questions and I’d like to reiterate what Dr. Rubin said at the opening of the discussion and that is, who should treat these patients and where should they be treated? One of our concerns is that with the availability of several of these novel therapeutic agents, in particular the ease of therapy, eg, oral therapy, more and more physicians have the opportunity to treat patients with pulmonary arterial hypertension without having to send them to centers that have significant experience and expertise in the treatment of pulmonary arterial hypertension patients. In the past, when patients were in need of chronic intravenous epoprostenol, or Flolan, most patients were sent to centers because of the need for nurses to teach the families and the patients how to take care of their Flolan, their central venous lines, and mixing and delivering of the drug therapy. One concern that I think many of us have is that not uncommonly patients are referred to us with the diagnosis of primary pulmonary hypertension, and, in fact, they have another etiology for their pulmonary hypertension, and the therapy, assuming the diagnosis is primary pulmonary hypertension, may be the wrong therapy for that patient. A classic example of this is patients who are presumed to have primary pulmonary hypertension and upon further evaluation turn out to have chronic thromboembolic disease as the etiology of their pulmonary arterial hypertension, which is very often amenable to surgery, with excellent results with thromboendarterectomy. We certainly would like to treat these patients with surgery if that is indicated, as opposed to treating them with any of our medical therapies. As Dr. Rubin said earlier, our therapeutic options have improved and although the palliative effects of the therapies have markedly improved over the past decade, we still are only palliating these patients; we are not curing them. For example, if a patient truly has chronic thromboembolic disease, it is not uncommon that these patients can be “cured” with effective surgery. So we really want to be very, very careful that we are making the right diagnosis. The second point is that, not uncommonly, these patients are presumed to have primary pulmonary hypertension when they may have subtle findings of left ventricular dysfunction with pulmonary venous hypertension and secondary pulmonary arterial hypertension. It is a concern to many of us that if patients are initially evaluated by a physician who does not have a great deal of experience with pulmonary arterial hypertension, patients may be misdiagnosed. All patients need a thorough evaluation, which includes a right heart catheterization. The consensus is that patients absolutely need a right heart catheterization to make sure that they don’t have some component of left ventricular dysfunction or elevated pulmonary venous pressure. Nea on exertion, if an echocardiogram suggests there may be pulmonary arterial hypertension, the patient may then be told he/she has primary pulmonary hypertension. If the patient does not have primary pulmonary hypertension, we are doing him/her a terrible disservice. Even though some clinicians may say that since we now have an agent such as bosentan, which can be given orally twice a day, if the echo suggests pulmonary hypertension, let’s just try bosentan, I believe this is doing the patient a disservice, and we should try to strongly recommend that we think this is inappropriate and we want to avoid it. With regard to the questions that Dr Rubin raised about whom we should treat with bosentan, we are in a very
exciting time, but that means that we have a lot of unknowns. Whether patients who are very reactive and responsive and to date have been treated efficaciously with calcium channel blockers would respond as well or better if they were on an endothelin-receptor antagonist is unknown. Would such patients respond better if they were on a combination? There are many questions that these advances have opened up for us, and I think it behooves us to carefully evaluate who should be treated with which therapies. And hopefully, with many of the physicians who treat pulmonary arterial hypertension patients, we will be able to do further clinical trials evaluating what combination therapies may be better for subsets of selected patients versus other subsets. I believe many of us feel that even when we try to use the most homogeneous group of patients (for clinical trials), eg, patients with primary pulmonary hypertension, there are subsets within that disease. I suspect that we will find that, for example, selective ETA receptor antagonists may be more efficacious for a certain subset as opposed to a dual endothelin-receptor antagonist for other subsets.

**Dr Galiè:** I agree with the concept that if a treatment is easy to administer it can be more often given without a correct indication. For example, we are aware that not more than 20% of pulmonary hypertension patients are “responders” to acute vasoreactivity testing and have the indication for chronic calcium channel blockers treatment. Nevertheless, the percentage of patients on this form of oral therapy as assessed in recent trials is about 50%. We need to consider that the therapy of patients with pulmonary arterial hypertension requires a complex strategy that starts from correct diagnosis and appropriate prescriptions and continues in the monitoring of treatment effects and side effects. I strongly believe that this strategy is better accomplished if the patient is followed up in specialized centers with experience in all the resources now available, from the simpler to the more complex ones.

**Dr Rubin:** At this point, which patients would you start treating with an endothelin-receptor blocker?

**Dr Barst:** With the initial evaluation, if a patient has a dramatic response to acute vasodilator testing, I think the standard of therapy is that we start that patient on a chronic calcium channel blocker. What defines a “response” remains controversial. The definition of a significant response depends upon the percentage decrease in mean pulmonary arterial pressure as well as the absolute pressure that the mean pulmonary arterial pressure falls to. We usually start chronic calcium channel blockade if patients have a very reactive response with short-acting vasodilator testing, as well as with acute testing with calcium channel blockers. We also routinely repeat a right heart catheterization one year after starting a patient’s treatment, and if we have a patient who started receiving chronic calcium channel blockade, even if they significantly improved clinically, if we do not see a significant improvement in pulmonary hemodynamics at repeat study, we would go down the treatment algorithm to see what we could add to that patient’s medical regimen. And I think, certainly, when we have an oral agent available, such as bosentan, it is worth considering as opposed to adding Flolan to their calcium channel blockade therapy.

**Dr Galiè:** Are you talking about pediatric patients or adult patients?

**Dr Barst:** Most of what I am talking about is with respect to adult patients.

**Dr Rubin:** Dr Galiè, how would you approach therapy in a patient who is not vasoreactive acutely?

**Dr Galiè:** The problem is availability here in Europe of the endothelin receptor antagonist bosentan. Hopefully, it will be available late in spring. It is now available in France, as anticipated treatment, and in Italy for selected patients.

**Dr Rubin:** Let us make the assumption that you have several medications available, which would include an endothelin antagonist and would also include the oral prostacyclin analogue, beraprost, which you have studied, and also the aerosolized prostacyclin analogue iloprost, and also include the subcutaneous analogue, trepostinil. Readers should recognize that the availability of these agents is somewhat variable from country to country. In the US bosentan is available, prostacyclin intravenously is available, trepostinil is still under FDA review, and beraprost and iloprost as of right now are not available. In Europe things are a little different. Let’s say that you have all of those available and you have obviously extensive familiarity with the experience thus far with those drugs. Where do you go?

**Dr Galiè:** Of course, in class IV patients, I would use epoprostenol because of the rapidity and reliability of this form of treatment. In class III, the most relevant patient population, I think I would first try one of the two orally available drugs, the endothelin-receptor antagonist bosentan or the prostacyclin analogue beraprost. The advantage of bosentan is that the administration is only twice a day, compared with four times a day for beraprost. Actually, I have seen favorable results with both drugs and I would try one of the two. I would discuss with the patient the side effects of the two drugs, and possible personal preferences. Some individual clinical characteristics could be of help: in a patient with a tendency to have head-ache, I would exclude beraprost, and in a patient with moderate liver function abnormalities, I would avoid bosentan as the first choice. We need more time to define the effect of these two treatments over the long term; this is very important information we still lack. In case of intolerable side effects with these oral compounds, a minimally invasive alternative is the subcutaneous infusion of trepostinil by means of small portable pumps. I have observed favorable results with this treatment, even though some patients may have local pain at the infusion site that can prevent its use. A suitable option is also represented by inhaled iloprost which is available in some European countries. The data of several uncontrolled experiences and of the randomized AIR study confirm efficacy of this treatment in class III and IV patients. Compliance to inhaled iloprost can be influenced by the number of required
Dr Barst: In addition to care in the up-titration of Flolan, I think it is exceedingly important for us to assess whether or not the combination is in fact more efficacious. Even though from a theoretical standpoint it makes sense to combine two drugs that work by different mechanisms, or we think work by different mechanisms, such as endothelin receptor antagonists and epoprostenol or a prostacyclin analogue, it is extremely important for us to determine efficacy by doing clinical trials. We are just beginning to look at combination therapy with an endothelin-receptor antagonist and intravenous epoprostenol. Whether or not the combination results in improved efficacy remains unknown. There is currently a small, double-blind, randomized controlled trial evaluating whether or not bosentan plus Flolan is safe and more efficacious than Flolan alone, but this will be with only a small number of patients, a total of 30 patients, and the results of this will not be available until midyear.

Dr Rubin: Is there a rationale in the responders that you are going to treat with calcium blockers? You mentioned that some of those, maybe a quarter, maybe more, lose the response over time. Is there a rationale for also at the same time combining another oral medication, such as either bosentan or any other endothelin blocker, or beraprost to their regimen?

Dr Barst: There certainly is a rationale, but all of us realize that very often when we have a rationale and we have a hypothesis, that when we do a clinical study, the data do not always turn out to be what we had anticipated. I certainly think, as Nazzareno said earlier, that how sick a patient is will determine what additional therapy we may want to treat with, or if we want to stop the calcium channel blockade and switch therapies. Very often, patients who start with chronic calcium channel blockade and then lose effectiveness with that therapy remain in WHO functional class III, and it is very appealing to start another oral agent such as an endothelin-receptor antagonist or an oral prostacyclin analogue such as beraprost to avoid, or at least defer, starting intravenous epoprostenol. One point that we haven’t yet addressed that is often raised by patients is “will I ever be able to come off Flolan?” To date, even though there has been the rare patient who has been weaned off Flolan or transitioned from Flolan to a more palatable therapy, this is exceedingly rare, and we still discuss with patients that “if we are starting you on Flolan, you have to anticipate that you may be on this very long term, including indefinitely.” Therefore, if we can treat a patient and improve his or her quality of life, and even at a minimum maintain hemodynamics without Flolan, very often this is in the patient’s best interests as more and more novel therapeutic options are becoming available. The really important question is, for the patient who is an acute responder over the long term, would that patient do better on an oral agent such as bosentan or beraprost as opposed to calcium channel blockers? That is an important question to answer.

Dr Galie: I agree with you Robyn, because in the small number of patients who have responded to chronic calcium antagonists, some effects of these drugs seem to be still present, even if the patient clinically deteriorates. I have had a couple of experiences in which I had to transition a patient on Flolan, but I was unable to withdraw the calcium antagonist, even after I reached a very effective dose of Flolan. It seems that some patients, in any case, remain dependent upon the dose of calcium antagonists.

Dr Barst: Our experience is variable. Certainly, if we have patients who start chronic calcium blockade and do well, and then they subsequently deteriorate, depending upon how sick they are becomes the basis of how we decide if we continue the calcium channel blockade. If they have markedly deteriorated and have right heart failure, we stop the calcium blockade once they are taking a reasonable dose of Flolan, but I think it remains a very individual decision.

Dr Rubin: I believe that we have come back to other therapies, emerging therapies, particularly oral therapy. There have been some limited data now with phosphodiesterase inhibitors, and in particular, the one that is commercially available is sildenafil, or Viagra, which has been demonstrated to produce a preliminary vasodilator effect in experimental conditions and has been in some cases reported to be beneficial for patients with pulmonary hypertension. Where does sildenafil fit into your treatment algorithm?

Dr Galie: We still need a controlled clinical trial assessing the effects of sildenafil in pulmonary arterial hypertension. After the approval of bosentan in the United States, placebo controlled studies may be difficult to perform. In Europe until the middle of 2002 probably many of the new treatments will not be largely available and it would be possible to perform a placebo controlled study. If we demonstrate a beneficial effect of sildenafil, a new oral compound with a different mechanism of action will be available. This will give us further opportunities for treatment and combinations. In addition there have been some controlled and uncontrolled reports of efficacy of L-arginine supplementation in patients with pul-
Dr Rubin: So, at this point would you say that in the absence of more rigorous data that really neither of those yet fits into the recommended algorithm, but may in the future?

Dr Galiè: Correct.

Dr Rubin: Robyn?

Dr Barst: It is very important to avoid anecdotal reports, which may include placebo effects, as some of the reports that are coming out for sildenafil as well as arginine, because even if we believe these drugs are fairly “safe,” we don’t know what the long-term effects of sildenafil will be over years or perhaps decades, particularly if we consider starting therapy in childhood. I strongly recommend that physicians avoid empirically trying one of these drugs even if patients are very insulin, saying “I would like to try sildenafil” or “I would like to try this other oral agent.” If we do not demonstrate long-term, safety and efficacy of the various combinations of these newer therapies, we are again doing our patients a disservice. And this concerns me greatly. With many new oral agents available, many physicians may say to their patients, “You have some degree of pulmonary hypertension, let’s try this oral agent. If it doesn’t work, then we will send you to a center with more expertise in pulmonary hypertension.” We will be reversing the advances that have been made over the past several decades and we will once again only see patients at centers with expertise who have failed everything and are functional class IV patients by the time we see them. Although some of these new therapeutic options may be very efficacious, we need to demonstrate their safety and efficacy with controlled trials.

Dr Galiè: I agree.

Dr Rubin: Maybe we can provide some summary. The first question: Who should be treated with calcium channel blockers? Only those who demonstrate acute reactivity?

Dr Galiè: Yes.

Dr Barst: It has to be significant reactivity. The other important point to make is that there have been some letters to the editor and case reports of catastrophic results in patients who were initially empirically treated with chronic calcium channel blockade. We strongly advise against empirically starting treatment with on chronic calcium channel blockade. In addition to demonstrating lack of efficacy, there may be very significant safety issues as well.

Dr Rubin: Who should go directly to Flolan?

Dr Galiè: If a patient is class IV and we see this patient for the first time with a very high central venous pressure, low cardiac output, and signs of poor peripheral perfusion, I think that the most reliable treatment we have now is intravenous Flolan. We do not have data in this patient population on the efficacy of new treatments because class IV patients were excluded from most of the recent randomized trials. Only in the AIR study on inhaled iloprost were class IV patients included, and preliminary reports confirm efficacy in this population.

Dr Rubin: So a late class IV patient, with right heart failure, right now, I think we would all agree, that patient at the very least should be put on Flolan.

Dr Barst: I agree completely. The one other thought to mention is that patients have to be treated with a short-acting intravenous therapy and what we now have available is epoprostenol or iloprost. In the future, there may be other prostacyclin analogues or other agents that can be given intravenously. What is really important is that very sick patients are initiated on a short-acting intravenous therapy. We should caution readers that when we have a very sick patient who is in cardiogenic shock, epoprostenol is not an extremely good rescue therapy if we are not also maintaining the patient’s cardiac output with other inotropic agents.

Dr Rubin: Some of our colleagues who have some data and some experience would say that in that setting a suitable alternative may be aerosolized iloprost.

Dr Galiè: Yes, I agree. I wanted to mention this because in countries like Germany and Austria they have experience with aerosolized iloprost as rescue therapy in advanced class IV patients and this option seems to work in their hands. So, we can leave this option open to experienced centers.

Dr Rubin: The experience and the availability. So, we would say that class IV patients should be treated with a potent prostanoid, with intravenous Flolan, prostacyclin, or aerosolized iloprost, depending upon availability and experience.

Dr Barst: Yes.

Dr Galiè: Correct.
sibly in the future, both, of the orally active agents that have been rigorously studied so far.

**Dr Galiè:** Yes. I also would leave an option for subcutaneous treprostinil and inhaled iloprost because some patients cannot tolerate the new oral therapies. In addition, combination therapies may include an oral endothelin receptor antagonist and an inhaled or subcutaneous prostanoïd (also to avoid an excessive number of “pills” and improve compliance).

**Dr Barst:** I agree.

**Dr Galiè:** There is a problem related to patients in early class I and II, because we have few data on these patients. Only in the ALPHABET study on oral beraprost were class II patients enrolled, and the results were encouraging. Class I and II patients are not more than maybe 20% or 30%, at best, of the patient population we face in clinical practice, but we need to decide what to do with them. Is he or she leading a normal life? Shall we treat them prophylactically with the new oral drugs?

**Dr Rubin:** It’s a very interesting question. Nobody at this point has data. Clearly you have theoretic rationale and theoretic benefit. However, there are risks with these therapies and there are no data. So, I think it would be worth saying at this point that at least in the US, the FDA approval, the indication for bosentan, does not include patients who are functional in class I or II. Clearly, in the absence of data, that would be off-label use. Then, we would also say that while combination therapies directed at different targets of pathogenesis of the disease have appeal, theoretically, we have no long-term data or even short-term data, at this point, regarding efficacy. It is an area of study but as Nazzareno has emphasized, if one does do that it should be done very cautiously because of the potential for drug interactions and combining the hemodynamic effects of two different agents. Robyn, would you agree with that?

**Dr Barst:** Definitely. We did discuss early on the role or indications for transplantation. That is one additional question that many of us have a difficult time determining: when should a patient be listed, or when should he/she be transplanted? One of the issues is how the waiting time is determined. In the United States, timing of transplantation is determined by the length of time the patient has been on the waiting list and not by how ill the patient is. In our experience, when we have a patient who is class IV when initially seen, we have him/her evaluated and listed for transplantation. If that patient significantly improves, we subsequently take him/her off an active list, but we continue to have that patient hold on to the time that has been accrued. We have to look at what we think the long-term outlook is. We think that if we expect the patient to have a 2-year survival of less than 50%, he/she should remain on an active transplantation list. Unfortunately, I think we very often wait until a patient starts to deteriorate, and then it is often too late. This remains a very difficult point that we still do not have a handle on.

**Dr Galiè:** I completely agree with your last sentence. Unfortunately, for many patients transplantation remains a theoretical option because of the shortage of organs. So, usually, out of 10 patients who are on the waiting list, only 2 or 3 have the chance to be transplanted. So, it is an option, but it is still a theoretical option. We have to reduce the number of people on the waiting list for pulmonary hypertension to have the maximum possibility for these few patients to get an organ. The problem is that pulmonary hypertension patients compete with other lung indications, and usually these other indications have a shorter waiting time. The problem is very complex and I don’t know how to solve it. We could reliably utilize this option if the time on the waiting list is not more than 6 months; in this case, deteriorating patients can get a chance. The current mean waiting time of 12 or more months is too long for deteriorating patients, and it is very difficult to decide when to list the patient.

**Dr Rubin:** Our waiting time is over 2 years, so in a sense, it makes the decision easy. We list the patient immediately, as soon as it is clear that they are in functional class III and their survival is expected to be, untreated, shorter than the waiting time on the transplant list; then we initiate therapy. If they improve, as Robyn has said, then we would defer transplantation. If they don’t improve, then they have accrued, hopefully, sufficient time to come to the top of the list and we support them as best we can with therapies to bridge them to transplantation. But with that, the number of patients that we transplant for pulmonary hypertension has actually decreased, and it has decreased in the United States over the last several years with newer and more effective medical therapy, particularly Flolan.

**Dr Barst:** In conclusion, although in the 1970s survival for pulmonary arterial hypertension was horrific, it is certainly much better now. Despite the improvements over the past several decades, we still have a long way to go and it behooves us to carefully evaluate the novel therapies now becoming available to make sure that they are safe over the long term as well as efficacious. PH
Pulmonary Hypertension Roundtable

Inside the New Era in Treatment: Three Experts Analyze the Growing Spectrum of Therapy and Future Strategies

Three physicians addressed key concerns in the treatment of pulmonary hypertension in a discussion that ranged from special considerations in tailoring therapy to the role of new agents dramatically changing the algorithm for managing this disease.

The roundtable discussion was moderated by Lewis J. Rubin, MD, Professor of Medicine, University of California, San Diego, School of Medicine, and included Robyn Barst, MD, Professor of Pediatrics, Columbia University College of Physicians and Surgeons, New York, New York, and Nazzareno Galiè MD, Professor at the Postgraduate School of Cardiology, University of Bologna, Italy.

Dr Rubin: The treatment of pulmonary hypertension has evolved dramatically over the past decade and in particular is evolving remarkably at present. It is creating opportunities for us to better treat our patients and to treat our patients more easily, but it is also raising many challenges for us and our colleagues who care for these patients. It might be useful to address some of the common questions and challenges that are coming up with new treatments. Maybe we should start by addressing the first new treatment that has now become available, which is the oral endothelin blocker bosentan that is now FDA approved and the common question that I think we are all asked is who should we treat with bosentan, and secondly, who should be treating patients with bosentan?

Dr Barst: As background we should consider a consensus for a treatment algorithm for pulmonary arterial hypertension, prior to the availability of endothelin-receptor antagonists and prostacyclin analogues.

Dr Rubin: That’s great. Why don’t you start with that?

Dr Barst: I remember being at a symposium where my task was to talk solely about endothelin-receptor antagonists such as bosentan and at the end of the meeting everyone assumed that’s where you should start and there was no role for calcium channel blockers or some of the other standard therapies that we have used (prior to the availability of endothelin-receptor antagonists or other novel therapeutic agents). We are talking about patients who have pulmonary arterial hypertension, not just primary pulmonary hypertension. At a symposium sponsored by the World Health Organization (WHO) in 1998, there was a reclassification of patients who have pulmonary hypertension: experts from around the world agreed on a new diagnostic classification. If we focus upon the initial part of this classification, we decided that many patients could be classified as having “pulmonary arterial hypertension” because very often they were similar from a clinical standpoint as well as with respect to their pulmonary histopathology. This included patients who have primary pulmonary hypertension, sporadic and familial, as well as pulmonary arterial hypertension associated with collagen vascular disorders, congenital systemic to pulmonary shunts, HIV, portal hypertension, and appetite suppressants. So (continued on page17)