December 2003
Volume 7, Issue 10

CardiologyRounds™
www.cardiologyrounds.org

As presented in the Rounds of the Cardiovascular Division
of Brigham and Women's Hospital, Boston, Massachusetts

New therapies for pulmonary hypertension

By STUART R. RICH, MD

Pulmonary hypertension was once considered a progressive fatal disease for which there was no effective therapy. Over the past two decades, however, several new drugs have been developed that are effective in improving symptoms, exercise tolerance, and survival. Based on observations made during cardiac catheterization in the 1950s and 60s, pulmonary hypertension was perceived to be a disease of chronic vasoconstriction in the pulmonary vascular bed. This led to the development of vasodilators as therapy. More recently, however, new insights in the molecular biology of the vasculature have revealed that pulmonary arterial hypertension (PAH) is a chronic disease of uncontrolled endothelial and smooth muscle cell proliferation that produces, in addition to vasoconstriction, medial hypertrophy, concentric laminar intimal fibrosis, vascular occlusion, and localized areas of neovascularization known as plexiform lesions (Figure 1). As a consequence of the progress made in the science of pulmonary vascular disease, drug therapies have been targeted towards halting the progression, with the goal of inducing regression of the vascular disease. Recently approved therapies for PAH reflect this knowledge and are the focus of this issue of *Cardiology Rounds.*

Clinical classification

PAH refers to any elevation in pulmonary arterial pressure above normal. The presence of pulmonary hypertension may reflect a serious underlying pulmonary vascular disease that can be progressive and fatal or it may simply be an obligatory passive elevation in pulmonary artery pressure in response to elevated filling pressures in the left heart. Consequently, an accurate diagnosis of the cause of PAH in a patient is essential in order to establish an effective treatment plan. In addition, therapies that may be beneficial in some types of PAH may be harmful in others.

In 1998, a new classification for pulmonary hypertension was developed at the World Symposium on Pulmonary Hypertension co-sponsored by the World Health Organization (Table 1). The classification catalogued clinical conditions based on common pathobiological features to serve as a guide in the clinical assessment and treatment of these patients. This review will focus on the treatment of PAH, with particular attention to primary pulmonary hypertension (PPH, Table 2).

Acute testing with vasodilators

Several vasodilators are of value in the assessment of pulmonary vasoreactivity in patients with PAH.

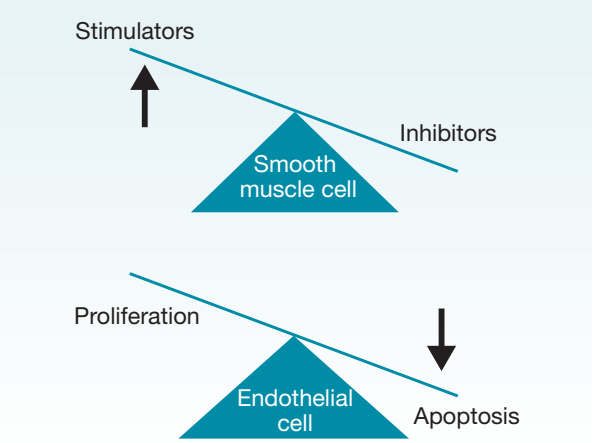
Adenosine – an intermediate product in the metabolism of adenosine triphosphate – has potent vasodilator properties through its action on specific vascular receptors. Adenosine is believed to stimulate A_2 type endothelial cells and vascular smooth muscle receptors that induce vascular smooth muscle relaxation by increasing cyclic adenosine monophosphate. In patients with PAH, adenosine has been shown to be a potent vasodilator and is predictive of the chronic effects of intravenous prostacyclin and oral calcium channel blockers.[1] Adenosine has an extremely short half-life (<5 seconds) and

Brigham and Women's Hospital
Fax: (617) 732-5291 Website: www.heartdoc.org

The editorial content of *Cardiology Rounds* is determined solely by the Cardiovascular Division of Brigham and Women's Hospital. This publication is made possible by an educational grant.

Cardiology Rounds **is approved by the Harvard Medical School Department of Continuing Education to offer continuing education credit**

Figure 1: Imbalance of vascular growth in pulmonary hypertension



its rapid dissolution provides a safety net should any adverse side effects occur. It is administered intravenously as an infusion in doses of 50 µg/kg/min and titrated upward every 2 minutes until uncomfortable symptoms develop (eg, chest tightness or dyspnea).

Epoprostenol has been used as an acute test of vasoreactivity in patients with PAH.[2] Like adenosine, its short half-life allows it to be discontinued if any acute adverse effects result. Also, similar to adenosine, it is administered incrementally, at 2 ng/kg/min and increased every 15 to 30 minutes until systemic effects (eg, headache, flushing, or nausea) occur that limit the acute dose titration. Favorable acute effects from epoprostenol are predictive of a favorable response to oral calcium channel blockers.

Adenosine and epoprostenol possess potent inotropic properties in addition to their ability to vasodilate the pulmonary vascular bed. When using these drugs for the acute testing of patients, particular attention must be paid to changes in cardiac output that occur in association with the changes in pulmonary arterial pressure. An increase in cardiac output with no change in pulmonary arterial pressure results in a reduction of the calculated pulmonary vascular resistance and may be erroneously interpreted as a vasodilator response.

Nitric oxide (NO) is also a useful drug to test pulmonary vasoreactivity.[3] Because NO binds very rapidly and with high affinity to hemoglobin and is thereby inactivated, inhalation of NO gas results in selective pulmonary vascular effects without influencing the systemic circulation.[4] Inhalation of NO by patients with PAH has been shown to produce an acute reduction in pulmonary vascular resistance, similar to that achieved with intravenous adenosine. NO has also been shown to predict the effectiveness of calcium channel blockers. However, NO differs from adenosine and epoprostenol in that it has little effect on cardiac output. It is usually given via a facemask at 20-40 ppm.

It is important to make a hemodynamic assessment of the entire circulatory system when determining the influence of drugs in these patients. Small changes in pulmonary artery pressure may be due to variability and not direct drug influence. Changes in pulmonary vascular resistance cannot be directly measured, but are computed by the change in pulmonary pressure and cardiac output simultaneously. Thermodilution cardiac output is the method that is most commonly used in these patients, but it can be associated with large errors in reproducibility. As a result, particular care should be taken in the methodology of thermodilution when used in these patients. In addition, when an underlying right-to-left shunt exists, the Fick determination of cardiac output is required.

Changes in pulmonary capillary wedge pressure (PCWP) can have important influences on the determination of pulmonary vascular resistance. A drug that produces an increase in PCWP secondary to increased cardiac output may be the first sign of impending left ventricular failure and an adverse drug effect, even though the calculated pulmonary vascular resistance may be lower and suggest a beneficial effect. The right atrial pressure reflects the filling characteristics of the right ventricle. A right atrial pressure increase in the face of rising cardiac output suggests right ventricular diastolic dysfunction. The resting heart rate is a physiological parameter of marked importance in patients with congestive heart failure. Treatments that cause an increased heart rate are likely to yield deleterious long-term results. Finally, systemic arterial oxygenation should also be evaluated. Vasodilator drugs can result in vasodilatation of blood vessels supplying poorly ventilated areas of the lung and worsen hypoxemia, an effect that is particularly noticeable in patients with underlying chronic lung disease.

Table 1: Classification of pulmonary hypertension[22]

World Health Organization 1998
1. Pulmonary arterial hypertension
2. Pulmonary venous hypertension
3. Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
5. Pulmonary hypertension due to disorders directly affecting the pulmonary vasculature

Table 2: Pulmonary arterial hypertension[22]

- Primary pulmonary hypertension
  - – Sporadic
  - – Familial primary
- Pulmonary hypertension associated with:
  - – Collagen vascular disease
  - – Drugs/toxins
  - – Portal hypertension
  - – HIV infection
  - – Congenital systemic to pulmonary shunts
  - – Persistent pulmonary hypertension of the newborn

Chronic therapy of PAH

Anticoagulants

Oral anticoagulant therapy is widely recommended for patients with PAH, although its clinical efficacy as a therapy is difficult to prove. A retrospective review of patients with PPH monitored over a 15-year period at the Mayo Clinic suggested that patients who received warfarin had improved survival over those who did not. The influence of warfarin therapy has been investigated in patients with PPH who failed to respond to high doses of calcium channel blockers.[5] Significant improvement in survival was observed in patients who received anticoagulation, with a 1-year survival rate of 91% and a 3-year survival rate of 47%, as compared with 1- and 3-year rates of 62% and 31%, respectively, in patients who did not receive anticoagulants. The current recommendation is to use warfarin in relatively low doses, as recommended for the prophylaxis of venous thromboembolism, with the international normalized ratio maintained at 2.0 to 3.0 times control.

Given its inhibitory effects on smooth muscle proliferation, heparin might be a better anticoagulant in PPH, although its use is more difficult. With the recent advent of low-molecular-weight heparins requiring once-a-day administration without the need for adjusting the dose to its antithrombotic effect, treatment with these agents is becoming a more viable alternative.

Vasodilator therapy

Because of early reports showing a reduction in pulmonary artery pressure following the acute administration of vasodilators, it was presumed that vasodilators would be the mainstay of treatment in patients with PAH. This presumption, however, has not been supported by the published literature. Vasodilators are effective in a subset of patients with PAH, but the many complexities surrounding vasodilator administration make their use in these patients very difficult.

Vasodilators work through the final common cellular pathway causing a reduction in intracellular calcium in vascular smooth muscle cells. The same mechanism is also attributable to cellular growth inhibition. Indeed, almost all vasodilators have been shown to possess growth inhibitory properties on smooth muscle cells in cultures. It is likely that the chronic effects of these agents in PAH represent both mechanisms.

Among the vasodilators prescribed to patients with PAH, calcium channel blockers appear to have the widest usage. Early studies using conventional doses failed to demonstrate a chronic sustained benefit. Moreover, calcium channel blockers have properties that may worsen underlying PAH, including negative inotropic effects on right ventricular function and reflex sympathetic stimulation that may increase the resting heart rate. However, it has been reported that 10% to 20% of patients with PPH who are challenged with very high doses of calcium channel blockers may manifest a dramatic reduction in pulmonary artery pressure and pulmonary vascular resistance which, upon serial catheterization, has been maintained for over 5 years.[5] Importantly, the patient's quality of life is restored with improved functional class, and survival (94% at 5 years), is improved when compared with nonresponders and historical control subjects (36% survival at 5 years). This experience suggests that a select subset of patients with PPH have the ability to have their PAH reversed and their quality of life and survival enhanced.

It is unknown whether the response to calcium channel blockers identities 2 subsets of patients with PPH, different stages of PPH, or a combination of both. However, it is essential to point out that patients who do not exhibit a dramatic hemodynamic response to calcium channel blockers do not appear to benefit from their long-term administration. Unfortunately, it is a common practice for physicians to prescribe calcium channel blockers at conventional doses to all patients with PAH, often without hemodynamic guidance. This unfortunate practice may result in quicker deterioration in these patients and should be strongly discouraged.

Prostacyclins

In randomized clinical trials, continuous-infusion epoprostenol has been shown to improve quality of life and symptoms related to PPH, ie, exercise tolerance, hemodynamics, and survival.[6,7] The initial enthusiasm for epoprostenol was based on the demonstration of pulmonary vasodilator effects when administered to experimental animals with acute pulmonary vasoconstriction. The long-term effects of epoprostenol in PPH include its vasodilator and antithrombotic effects, but its effects may also be importantly related to its ability to normalize cardiac output. Patients may have a reduction in pulmonary vascular resistance of >50% even if no acute pressure effects are noted.

Epoprostenol is administered through a central venous catheter that is surgically implanted and delivered by an ambulatory infusion system. The delivery system is complex and requires patients to learn the techniques of sterile drug preparation, operation of the pump, and care of the intravenous catheter. Most of the serious complications that have occurred with epoprostenol therapy have been attributable to the delivery system, including catheter-related infections, thrombosis, and temporary interruption of the infusion because of pump malfunction. Anecdotal reports of rebound pulmonary hypertension occurring in patients experiencing an interrupted infusion suggest that great care must be taken to ensure that the infusion is sustained.

Side effects related to epoprostenol include flushing, headache, nausea, diarrhea, and a unique type of jaw discomfort that occurs with eating. In most patients, these symptoms are minimal and well tolerated. Chronic foot pain and a poorly defined gastropathy with prolonged use develop in some patients. To date, epoprostenol has been given to patients with PPH for over 10 years with sustained effectiveness. In some patients (Class IV) who are critically ill, it serves as a bridge to lung transplantation by stabilizing the patient to a more favorable preoperative state. Patients who are less critically ill may do so well with epoprostenol therapy that they may delay the need to consider transplantation, perhaps indefinitely.

Figure 2: Survival in PPH[10]

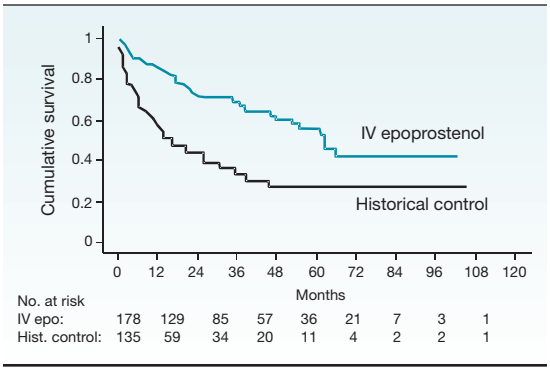
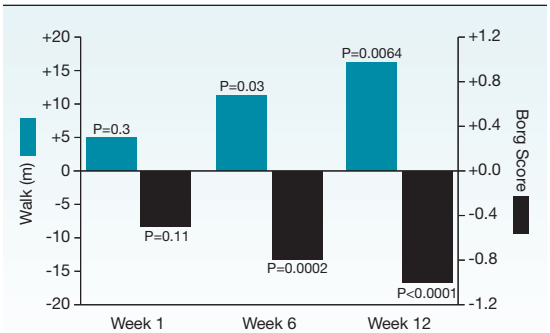


Figure 3: Effect of treprostinil on walk distance and symptoms in pulmonary hypertension[12]



A high-cardiac output state has been reported in a series of patients with PAH receiving chronic epoprostenol therapy and is consistent with the drug having positive inotropic effects.[8] Whether the effect is directly on the myocardium or indirectly via neurohormonal activation has not been determined. Although most patients with PAH have reduced cardiac output on initial examination, the development of a chronic high-output state could have long-term detrimental effects on underlying cardiac function. The follow-up assessment of patients receiving intravenous epoprostenol is quite variable from medical center to medical center, but it does appear important to determine periodically the cardiac output response to therapy in order to optimize dosing.[9]

Experiences with epoprostenol in PPH for >10 years have been reported by 2 large centers. Survival rates over 5 years were markedly improved compared to historical controls and the natural history predicted by the National Institutes of Health (NIH) Registry. Predictors of survival included New York Heart Association (NYHA) functional class, exercise tolerance, and acute vasodilator responsiveness. Both studies provided important data in identifying patients who would do well over the long-term vs. those in whom transplantation should be considered (Figure 2).[10,11]

Treprostinil is a recent FDA-approved stable prostacyclin analogue that shares pharmacologic actions that are similar to epoprostenol; however, it differs in that it is chemically stable at room temperature, has a neutral pH, and a longer half-life (3-4 hours). In a large randomized clinical trial in patients with PAH, treprostinil was effective in increasing the 6-minute walk test, symptoms of dyspnea associated with exercise, and hemodynamics.[12] The pharmacologic properties of treprostinil allow it to be administered through continuous subcutaneous infusion, thus eliminating the need for a central venous catheter and refrigeration during administrations. Infusion site pain was common (Figure 3).

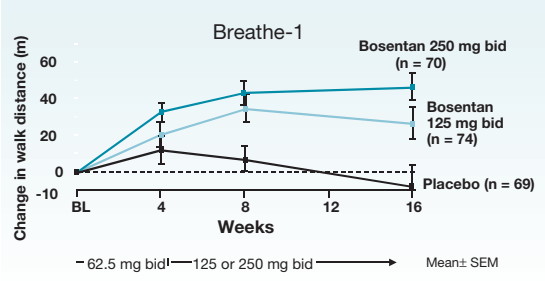
Iloprost is an analogue of prostacyclin that has been utilized via inhalation. In randomized clinical trials, inhaled iloprost was shown to have an acute effect on hemodynamics similar to inhaled nitric oxide.[13,14] When given chronically, patients reported an improvement in exercise, manifested by a 6-minute walk test, and in hemodynamics. Inhaled iloprost has advantages over intravenous epoprostenol in that it does not require a central venous catheter or infusion pump system with the attendant complications. However, due to the short half-life of iloprost, it requires frequent (up to 12 per day) inhalations that are very restrictive to patients on this therapy. Iloprost is not available in the United States.

Beraprost sodium is an orally active prostacyclin analogue that has been evaluated in randomized, double-blind, placebo-controlled, multicenter trials in patients with PPH. In one large European trial (the ALPHABET study), beraprost improved exercise capacity and symptoms over a 12-week period, but had no significant effect on cardiopulmonary hemodynamics or functional class.[15] A similar trial conducted in the United States, however, failed to show long-term efficacy beyond 12 weeks. Beraprost was associated with frequent side effects (ie, headache, flushing, and diarrhea) that has limited the ability to administer higher doses.

Endothelin receptor blockers

Bosentan is a non-selective endothelin receptor blocker that was recently approved as a treatment for PAH. In a 12-week, placebo-controlled trial of 32 patients with PAH, bosentan was superior to placebo in increasing the 6-minute walk distance and hemodynamics.[16] In a large, randomized, clinical trial, bosentan significantly improved the 6-minute walk distance after 16 weeks compared to placebo.[17] It was also shown to lengthen the composite endpoint of time-to-clinical worsening (including death, lung transplantation, hospitalization for pulmonary hypertension, lack of improvement) or worsening leading to discontinuation and the requirement for epoprostenol therapy. Importantly, there was a dose-dependent increase in hepatic transaminases noted with the medication, with significant elevations in 14% of the patients randomized to the higher dose (250 mg BID). The FDA approved bosentan at a dose of 125 mg twice a day for patients with PAH who are WHO Class III or IV (Figure 4).

Figure 4: Bosentan trial: effect on walk distance[17]



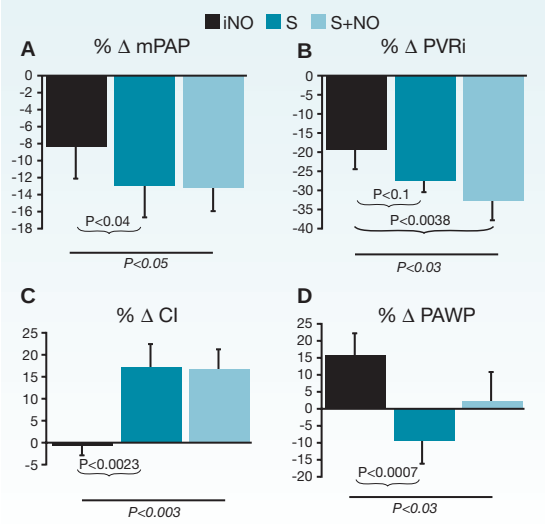
Phosphodiesterase-5 inhibitors

Sildenafil is a phosphodiesterase 5 (PDE5) inhibitor approved to treat erectile dysfunction. PDE5 inhibitors produce pulmonary vasodilation by promoting an enhanced and sustained level of cyclic GMP, an identical effect to inhaled NO. When tested as a single oral agent, sildenafil has been shown to be a potent and selective pulmonary vasodilator equally as effective as inhaled NO in lowering pulmonary artery pressure and pulmonary vascular resistance.[18] Sildenafil has a preferential effect on the pulmonary circulation because of the high expression of this isoform in the lung. Many anecdotal reports appear in the published medical literature on the success of sildenafil as an oral therapy for patients with PPH.[19-21] The safety and long-term effectiveness of sildenafil as a treatment of PAH is currently under investigation in large, randomized, clinical trials (Figure 5).

Selecting appropriate therapies

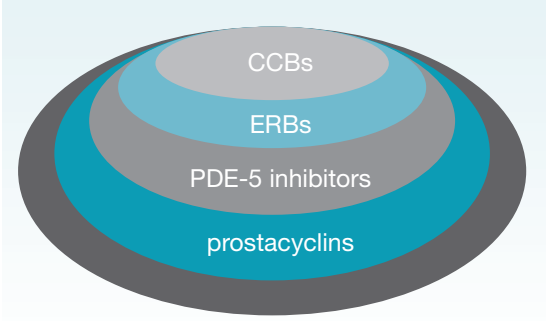
Since no head-to-head clinical trials have ever been performed on the different therapies for treating PAH, it remains uncertain as to which treatment should be

Figure 5: Oral sildenafil (S) vs. inhaled NO (iNO) in patients with PAH[18]



mPAP = mean pulmonary arterial pressure
CI = cardiac index
PVRi = pulmonary vascular persistance index
PAWP = pulmonary artery wedge pressure

Figure 6: Spectrum of Therapeutic Efficacy of PAH



CCBs = calcium channel blockers
ERBs = endothelin receptor blockers

considered first-line therapy. The data indicate that intravenous epoprostenol produces a greater improvement in symptoms, exercise tolerance, hemodynamics, and survival than any other therapy studied to date. Indeed, it would be considered the ideal treatment for patients with PAH were it not for the cumbersome and costly delivery system and associated complications. Subcutaneous remodulin is the only other FDA-approved prostacyclin for PAH. Although the delivery system is simpler, it is still a chronic infusion system with its own limitations of site pain.

Some physicians recommend oral therapy first because of the ease of administration. The concern with this approach, however, is that if a patient is treated with ineffective oral therapy, the disease may progress to a point that renders intravenous epoprostenol less effective.

In general, patients who present with less advanced symptoms or hemodynamics are offered oral therapy initially, whereas, those who present with advanced disease (Functional Class IV), or severe hemodynamic findings are usually placed on intravenous epoprostenol. This is a reasonable strategy provided the physician is thorough in the evaluation and follow-up care of the patient. Specifically, with the availability of oral therapy, it is essential that physicians not treat patients before establishing a definitive diagnosis, since all of these agents can have detrimental effects on patients with PAH related to left heart failure and/or lung disease. Secondly, it is essential to measure the efficacy of every treatment that is utilized. This does not necessarily mean serial right heart catheterizations. Indeed, exercise testing (whether using a 6-minute walk or a treadmill) is a proven, reproducible, and predictive measure of therapeutic efficacy. Establishing a baseline test allows the physician to make accurate assessments as to whether or not the therapy is helpful, harmful, or having no effect. We recommend monitoring the efficacy of treatments frequently with exercise testing until it is determined which therapy is best.

If a therapy is ineffective, it should be discontinued and the patient should be treated with another drug. Physicians too frequently add new therapies to existing failed therapies, not realizing that some of these treatments can have negative interactions and make the

patients worse. The wide spectrum of therapies available, however, should make it possible to improve the symptoms of virtually every patient with pulmonary arterial hypertension in this era (Figure 6).

References

1. Nootens M, Schrader B, Kaufmann E, et al. Comparative acute effects of adenosine and prostacyclin in primary pulmonary hypertension. *Chest* 1995;107:54-7.
2. Raffy O, Azarian R, Brenot F, et al. Clinical significance of the pulmonary vasodilator response during short-term infusion of prostacyclin in primary pulmonary hypertension. *Circulation* 1996;93:484-8.
3. Ricciardi MJ, Knight BP, Martinez FJ, Rubenfire M. Inhaled nitric oxide in primary pulmonary hypertension: a safe and effective agent for predicting response to nifedipine. *J Am Coll Cardiol* 1998;32:1068-73.
4. Krasuski R, Warner J, Wang A, et al. Inhaled nitric oxide selectively dilates pulmonary vasculature in adult patients with pulmonary hypertension, irrespective of etiology. *J Am Coll Cardiol* 2000;36:2204-11.
5. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992;327:76-81.
6. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996;334:296-302.
7. McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med* 1998;338:273-7.
8. Rich S, McLaughlin V. The effects of chronic prostacyclin therapy on cardiac output and symptoms in primary pulmonary hypertension. *J Am Coll Cardiol* 1999;34:1184-7.
9. Robbins IM, Christman BW, Newman JH, et al. A survey of diagnostic practices and the use of epoprostenol in patients with primary pulmonary hypertension. *Chest* 1998;114:1269-75.
10. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension. *J Am Coll Cardiol* 2002;40: 780-8.
11. McLaughlin V, Shillington A, Rich S. Survival in primary pulmonary hypertension. The impact of epoprostenol therapy. *Circulation* 2002;106: 1477-1482.
12. McLaughlin V, Gaine S, Barst R, et al. Efficacy and safety of treprostinil: an epoprostenol analog for primary pulmonary hypertension. *J Cardiovasc Pharmacol* 2003;41:293-299.
13. Hoeper M, Schwarze M, Ehlerding S, et al. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. *N Engl J Med* 2000;342:1866-70.
14. Olschewski H, Simonneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002;347:322-9.
15. Galie N, Humber M, Vachiery J-L, et al. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertesnion: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2002;39:1496-502.
16. Channick R, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001;358:1119-1123.
17. Rubin L, Badesch D, Barst R, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896-903.
18. Michelakis E, Tymchak W, Lien D, et al. Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension. *Circulation* 2002;105:2398-2403.
19. Sitbon O, Humbert M, Simonneau G. Primary pulmonary hypertension: current therapy. *Prog in Cardiov Diseases* 2002;45:115-128.
20. Wilkens H, Guth A, Konig J, et al. Effect of inhaled iloprost plus oral sildenafil in patients with primary pulmonary hypertension. *Circulation* 2001; 104:1218-1222.
21. Ghofrani HA, Rose F, Schermuly RT, et al. Oral sildenafil as long-term adjunct therapy to inhaled iloprost in severe pulmonary arterial hypertension. *J Am Coll Cardiol* 2003;42:158-64.
22. Rich S. Ed. Primary Pulmonary Hypertension. Executive Summary from the World Symposium on Primary Pulmonary Hypertension 1998. World Health Organiation. Reprints available via the Internet: http://www.who.int/ncd/cvd/pph.htm.

Stuart R. Rich, M.D. received his medical education from Loyola University, Stritch School of Medicine. He completed his residency at Washington University, Barnes Jewish Hospital, cardiology fellowship at the University of Chicago Hospitals. Dr. Rich has wide ranging interests in clinical cardiology and is a leading international expert in the evaluation and treatment of pulmonary vascular diseases. He is a Fellow of the American Heart Association, of the American College of Cardiology, of the American College of Chest Physicians and of the American College of Physicians. He presently serves as Professor of Medicine, the John H. and Margaret V. Krehbiel Professor of Cardiology at the Rush Medical College, Director of the Center for Pulmonary Heart Disease and Director of the Coronary Heart Disease Detection and Treatment Center at the Rush Heart Institute, Chicago, Illinois.

Dr. Rich has served as a consultant or received research grants from Actelion, Encysive, Inos, Myogen, and Pfizer and is currently Chief Medical Officer for United Therapeutics.

Brigham and Women's Hospital,
Cardiovascular Division website:
www.heartdoc.org

This publication is made possible by an educational grant from

Novartis Pharmaceuticals Corporation