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Treating pulmonary arterial hypertension: Cautious hope in a deadly disease

ABSTRACT

Advances have brought cautious hope for patients with this progressive and deadly disease. Intravenous prostanoids are still the most effective long-term medications, but oral options are available for select patients who are closely monitored. General internists and specialists in pulmonary, cardiac, and rheumatic diseases each have their role in managing these patients.

KEY POINTS

General health maintenance measures include aerobic physical activity, influenza and pneumococcal vaccinations, the cautious use of diuretics for symptoms of volume overload, oxygen supplementation to maintain saturation levels at 90% or above, and long-term anticoagulation therapy.

Calcium channel blockers should be used only for patients with demonstrated vasoreactivity during right-heart catheterization, with close monitoring for disease progression.

Epoprostenol (Flolan) is effective for severe disease but must be continuously infused. Once started, it must generally be continued for life. Treprostinil (Remodulin) is a longer-acting alternative that can be given subcutaneously or intravenously.

Oral and inhaled agents are appropriate for patients with less severe disease, and include bosentan (Tracleer), ambrisentan (Letairis), sildenafil (Revatio), and iloprost (Ventavis).

PULMONARY ARTERIAL HYPERTENSION is still considered to be progressive and incurable, but new treatments have been developed in recent years, and consensus conferences have made evidence-based recommendations to develop a standardized approach to therapy.[1–5]

Newer agents include prostacyclin analogues, endothelin receptor antagonists, and a class of drugs usually used for treating erectile dysfunction, phosphodiesterase type 5 inhibitors. Calcium channel blockers are being used less often than in the past.

In an earlier article in this journal,[6] we discussed the diagnosis of pulmonary arterial hypertension. In the pages that follow we focus on its management, with special emphasis on issues relevant to internists who help care for patients with this disease.

WHAT GENERAL CARE DO THESE PATIENTS NEED?

Patients suspected of having pulmonary arterial hypertension (**TABLE 1**) should be evaluated at a specialized medical center so that a correct diagnosis can be made and appropriate therapy started.[7,8] Optimal care requires collaboration between the patient, the community resources, and the resources at the pulmonary hypertension center.

All patients need good general medical care. The internist plays a critical role in their

*Dr. Minai has disclosed that he has received honoraria from the Actelion, Encysive, Gilead, Pfizer, and United Therapeutics corporations for consulting and speaking.

TABLE 1

Indications for referral to a pulmonary hypertension center

Unexplained dyspnea or chest pain on exertion with evidence of pulmonary hypertension by transthoracic echocardiography (without substantial left-sided cardiac disease or parenchymal lung disease)

Evidence of moderate to severe pulmonary arterial hypertension
Estimated pulmonary arterial systolic pressure > 45 mm Hg by transthoracic echocardiography
Symptoms consistent with New York Heart Association functional class II or higher
Syncope or near syncope

Clinical or echocardiographic evidence of right ventricular dysfunction
Lower extremity edema
Ascites
Right ventricular enlargement or systolic dysfunction on echocardiography

Parenchymal lung disease, such as chronic obstructive pulmonary disease or interstitial lung disease in a patient with pulmonary hypertension

Known pulmonary arterial hypertension with worsening disease despite therapy

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day-to-day care by instituting good health maintenance and providing a channel of communication between the patient and the pulmonary hypertension center (TABLE 2).

Close communiction between the patient, primary care physician, and pulmonary hypertension center is essential

Assess functional class. The American College of Chest Physicians recommends that a modified New York Heart Association (NYHA) functional classification system—known as the World Health Organization (WHO) functional classification system—be used to guide treatment for patients with pulmonary arterial hypertension. Patients in functional class I experience no limitation of their usual activity, those in class II have slight limitation, those in class II have marked limitation, and those in class IV cannot perform any physical activity without symptoms and possible signs of right heart failure.

Promote physical activity to promote cardiovascular health. Activity should be aerobic and limited by symptoms. Activities that cause excessive shortness of breath, dizziness, or chest discomfort should be avoided. Patients should not engage in activities that may abruptly increase intrathoracic pressure or cardiac work, such as lifting weights and pushing or pulling heavy objects.[9]

Prevent infections. No information exists about infection risk specifically in patients with pulmonary arterial hypertension, but we recommend that they receive influenza and pneumococcal vaccination, as is recommended for patients with advanced left heart failure and parenchymal lung diseases. Antibiotic prophylaxis should be provided before dental work and other invasive procedures according to the American Heart Association guidelines for preventing endocarditis.[10,11]

Treat volume overload. Loop diuretics and potassium-sparing aldosterone antagonists, when used with caution to avoid abrupt preload reduction, can be used to alleviate symptoms due to volume overload from right heart failure, including lower extremity edema, ascites, and hepatic congestion.

Prevent hypoxemia. Hypoxemia is a potent vasoconstrictor that can exacerbate pulmonary arterial pressures. Chronic hypoxia can both cause pulmonary hypertension and result from it. Oxygen saturation should be aggressively maintained at 90% or above—at rest and during exercise—to help reduce mean pulmonary artery pressures and improve cardiac hemodynamic variables. No consistent data are available on the effects of long-term oxygen therapy on pulmonary arterial hypertension.

Minai et al[12] recently found that nocturnal hypoxemia occurs in up to 70% of patients with pulmonary arterial hypertension who

The 'face' of pulmonary hypertension therapy

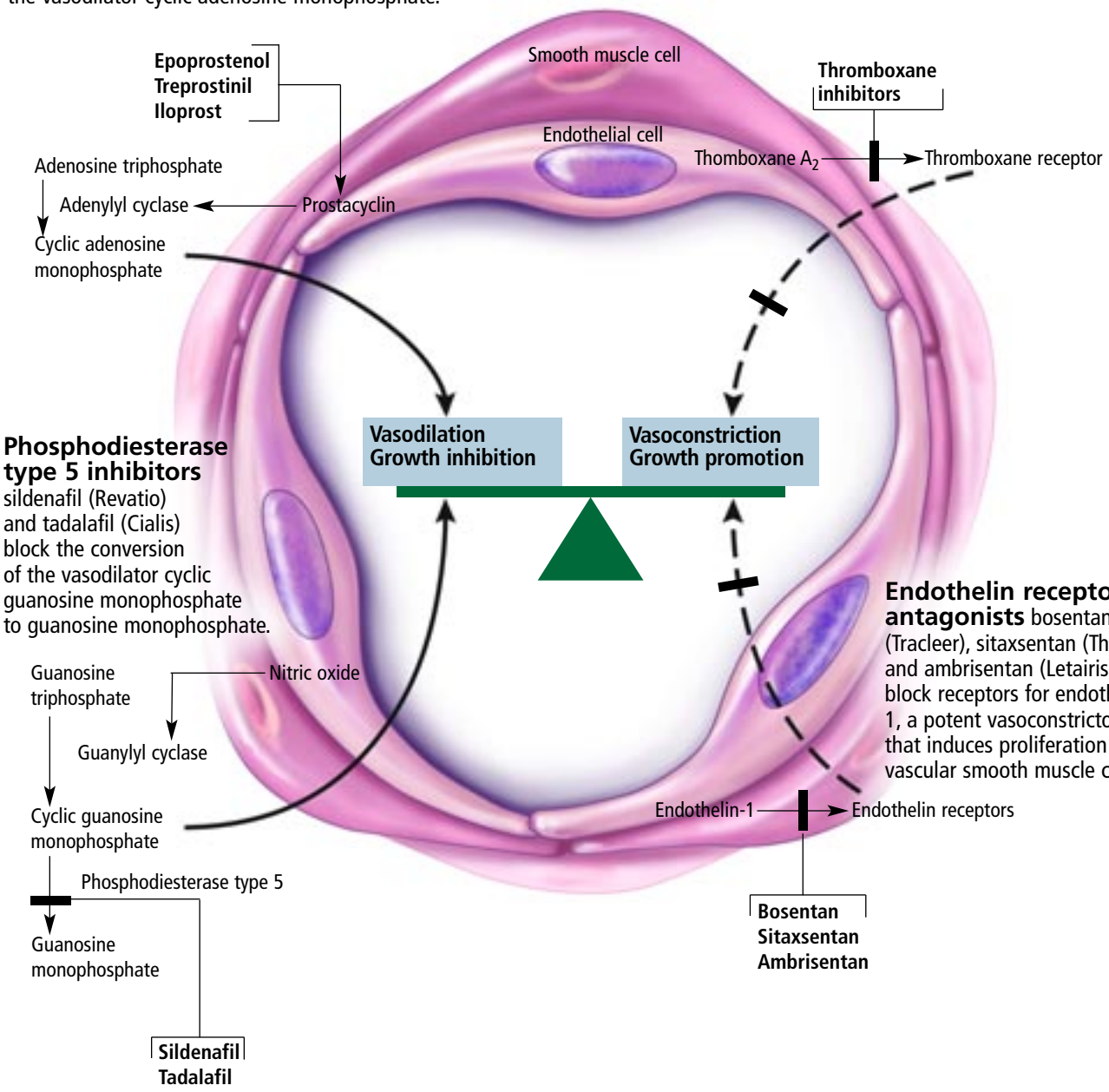
Pulmonary arterial hypertension is believed to be an imbalance favoring vasoconstriction over vasodilation, and growth over inhibition of growth. Various drugs target these processes in an attempt to restore the balance.

PROMOTING VASODILATION

Prostacyclin analogues epoprostenol (Flolan), treprostinil (Remodulin), and iloprost (Ventavis) mimic the action of prostacyclin, which activates adenylyl cyclase, promoting formation of the vasodilator cyclic adenosine monophosphate.

INHIBITING GROWTH

Thromboxane inhibitors may, in theory, prevent thromboxane-mediated vasoconstriction and growth.



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Medical Illustrator: Beth Halasz ©2007

FIGURE 1

TABLE 2

The internist's role in managing patients with pulmonary arterial hypertension

Initiates workup
Provides general medical care, including influenza and pneumococcal immunizations
Monitors fluid status, electrolyte levels, renal function, liver function tests, and anticoagulation
Assesses volume status, oxygenation
Refers patients to a pulmonary hypertension center when indicated

ADAPTED FROM RUBIN LJ, BADESCH DB. EVALUATION AND MANAGEMENT OF THE PATIENT WITH PULMONARY ARTERIAL HYPERTENSION. ANN INTERN MED 2005; 143:282–292.

have no evidence of parenchymal lung disease. Nocturnal hypoxemia was more common in patients with more severe right ventricular dysfunction. Of the patients who did not have desaturation with exertion, 60% had desturation at night. Because exertional hypoxemia cannot be used as a marker of nocturnal desaturation, all patients with pulmonary arterial hypertension should undergo nocturnal oximetry studies.

Calcium channel blockers are effective in only a small minority of patients

Prevent pregnancy. Pregnancy is risky for women with pulmonary arterial hypertension (see below). Therefore, women of childbearing age should use two forms of contraception, usually a barrier method plus an oral contraceptive with low or no estrogen. Depot shots of progestational contraceptives can also be used. Estrogen-containing contraceptives increase the risk of venous thromboembolism, and so high-dose preparations are not recommended for these patients.[13]

Cardiac glycosides lack evidence. Rich et al[14] found that giving digoxin intravenously to 17 patients with pulmonary arterial hypertension and right ventricular failure produced a modest but significant initial increase in cardiac output. However, no long-term safety or efficacy data exist regarding the use of cardiac glycosides in patients with pulmonary arterial hypertension and refractory right-sided heart failure, and their use is mostly based on clinician preference.

Atrial flutter and other atrial arrhythmias may also complicate advanced disease, and digoxin may help with rate control.[14]

Anticoagulation. Patients with pulmonary arterial hypertension are believed to have a limited cardiac reserve, and even a small thromboembolic event may have devastating consequences. Several retrospective studies suggest that long-term anticoagulation increases the survival rate in patients with idiopathic disease,[15,16] possibly by reducing the development of microscopic thrombosis in situ. These patients may also be at risk of thromboembolism, due to right ventricular chamber dilation, reduced overall level of activity, and implanted catheters.[15,16]

Although most evidence about anticoagulation is from patients with idiopathic disease, we believe that unless clear contraindications exist, anticoagulation should be standard therapy for all patients with pulmonary arterial hypertension, with a target international normalized ratio of 1.5 to 2.5.[3]

Anticoagulation can be safely withheld for 5 days before an invasive procedure such as dental work, heart catheterization, or surgery. Patients who are at increased risk of thrombosis or who have a history of chronic thromboembolic pulmonary hypertension should be covered with low-molecular-weight heparin during this time.

WHAT SHOULD BE DONE IN CASE OF SURGERY, AIR TRAVEL, OR PREGNANCY?

Patients should consult a pulmonary hypertension center before undergoing surgery, before travel by air to an altitude of more than 2,000 meters (6,562 feet), or if pregnancy occurs.

Surgery. Experts have long believed that patients with pulmonary arterial hypertension are at high risk of perioperative complications.[17] Minai et al,[18] in a study of 21 patients with pulmonary arterial hypertension undergoing a total of 28 surgical procedures, found that although perioperative risk was increased, it was mostly related to complications arising from the disease for which surgery was performed. In another study,[19] factors predictive of short-term illness after noncardiac surgery included symptoms consistent with NYHA class II or higher, intermediate- or high-risk surgery, history of pulmonary embolism, and anesthesia lasting longer than 3 hours.

Experts recommend using the least invasive surgical approach and avoiding general anesthesia if possible.[3,17,18] We also advise that surgery be performed at a center with expertise in treating patients with pulmonary arterial hypertension, where worsening right ventricular function can be addressed should it occur.[17–19]

High-altitude travel. Travel to high altitudes may induce hypobaric hypoxemia, leading to pulmonary vasoconstriction.[20] Airline travel may also induce hypoxia and precipitate acute hemodynamic changes. Most commercial aircraft cabins are pressurized to 2,400 meters (7,874 feet); patients with borderline oxygen saturation at sea level may require supplemental oxygen, and those already on supplemental oxygen may need to increase their flow rate. Patients should either undergo altitude simulation testing or use supplemental oxygen during commercial flights.[21,22]

Pregnancy. Women with pulmonary arterial hypertension have a 30% to 50% risk of death during pregnancy due to associated severe hemodynamic changes. In addition, endothelin receptor antagonists such as bosentan (Tracleer) can be teratogenic.[23] Although successful pregnancies have been reported in patients treated with inhaled nitric oxide or intravenous epoprostenol (Flolan), most experts recommend that all pregnancies be terminated early.[3]

WHO NEEDS RIGHT HEART CATHETERIZATION, AND WHY?

The American College of Chest Physicians recommends that all patients with suspected pulmonary arterial hypertension undergo right-sided heart catheterization so that an accurate diagnosis can be made.

It is important to diagnose the disease accurately because pulmonary arterial hypertension is progressive and deadly and requires significant lifestyle changes, requiring lifelong therapy with expensive medications that do not cure the disease.[24,25] The diagnosis should be based on direct measurement of mean pulmonary arterial pressure and not on echocardiography, which has technical limitations even under optimal conditions.[26]

Right-sided heart catheterization also allows one to measure right atrial pressure, pulmonary vascular resistance, and right ventricular performance (via the cardiac index and mixed venous oxygen saturation), from which one can assess the prognosis (see below).[24] The procedure can also help detect congenital heart diseases.

Hemodynamics predict survival

Hemodynamic measurements obtained during right-sided heart catheterization can be used to predict survival, using an equation based on data from a National Institutes of Health (NIH) registry[24]:

$$P(t) = [H(t)]^{A(x,y,z)};$$
$$H(t) = [0.88 - 0.14t + 0.01t^2];$$
$$A(x,y,z) = e^{(0.007325x + 0.0526y - .3275z)}$$

where $P(t)$ = a patient's chances of survival at t years; t = 1, 2, or 3 years; x = mean pulmonary artery pressure; y = mean right atrial pressure; and z = cardiac index.

Vasoreactivity predicts success of calcium channel blocker therapy

Yet another reason to do right-sided heart catheterization is to perform a vasoreactivity challenge. The test helps determine long-term prognosis as well as appropriate therapy. Patients with pulmonary hypertension related to connective tissue disease are less likely to demonstrate vasoreactivity, so testing is not as strongly recommended for them.[3,4]

All patients should undergo right heart catheterization prior to initiation of therapy

Vasoreactivity testing is usually performed with a short-acting pulmonary vasodilator such as inhaled nitric oxide, intravenous adenosine, or intravenous epoprostenol. A positive test is defined as a drop in mean pulmonary artery pressure of more than 10 mm Hg, to 40 mm Hg or less, with unchanged or increased cardiac output.

Only about 10% to 15% of patients have a positive response. These patients are more likely to benefit from monotherapy with calcium channel blockers,[16] although about half of this group deteriorates over time if treated with these drugs alone. Patients treated with only calcium channel blockers should be followed closely and given additional therapy if the disease progresses.[27] Calcium channel blockers should never be used empirically to treat pulmonary arterial hypertension and

TABLE 3

Vasoactive drugs for treating pulmonary arterial hypertension

DRUG NAME	CLASS	ROUTE AND FREQUENCY OF DOSING
APPROVED AGENTS		
Epoprostenol (Flolan)	Prostacyclin analogue	Continuous intravenous infusion
Treprostinil (Remodulin)	Prostacyclin analogue	Continuous intravenous infusion Subcutaneous infusion
Iloprost (Ventavis)	Prostacyclin analogue	Inhaled six to nine times daily
Bosentan (Tracleer)	Nonselective endothelin receptor antagonist	Oral twice daily
Ambrisentan (Letairis)	ET(A) selective endothelin receptor antagonist	Oral once daily
Sildenafil (Revatio)	Phosphodiesterase type 5 inhibitor	Oral three times daily
INVESTIGATIONAL AGENTS		
Sitaxsentan (Thelin)	ET(A) selective endothelin receptor antagonist	Oral once daily
Treprostinil	Prostacyclin analogue	Oral once daily Inhaled four times daily
Tadalafil (Cialis)	Phosphodiesterase type 5 inhibitor	Oral once daily

should not be used without demonstrated vasoreactivity.[3,4]

WHAT TREATMENTS ARE AVAILABLE?

Vasoactive agents approved by the US Food and Drug Administration (FDA) for treating pulmonary arterial hypertension are listed in TABLE 3. New therapies targeting the different pathways believed to be central to disease development (FIGURE 1) have led to improved outcomes and have dramatically reduced the use of calcium channel blockers.

Parenteral agents for severe disease

Intravenous or subcutaneous agents should be used for most patients in functional class IV (ie, unable to perform any physical activity without symptoms) and for all patients with overt right-sided heart failure or those with worsening symptoms despite treatment with oral vasoactive agents.

Parenteral agents used to treat pulmonary arterial hypertension are analogues of prostacyclin, a potent vasodilator with antiplatelet activity. Endogenous prostacyclin is produced by the vascular endothelium and is a metabolite of arachidonic acid; decreased levels may have a role in causing pulmonary arterial hypertension.[28]

Though newer oral agents provide hope, parenteral agents remain the most effective

Epoprostenol. The development of epoprostenol in the early 1980s was a major milestone in the treatment of pulmonary arterial hypertension.[29] Prospective studies demonstrated that continuous infusion of this drug—which has a half-life of only 5 to 7 minutes—improved exercise capacity, hemodynamic variables, quality of life, and survival rates compared with conventional therapy in patients with functional class III or IV symptoms (marked-to-severe limitation of activity).[30,31]

Long-term retrospective studies found that 1-, 2-, and 3-year survival rates were better in treated patients with class III or IV idiopathic disease than in historical controls[32] and better than the rates predicted by the NIH equation (see above).[29] One study demonstrated that a lack of a favorable response to

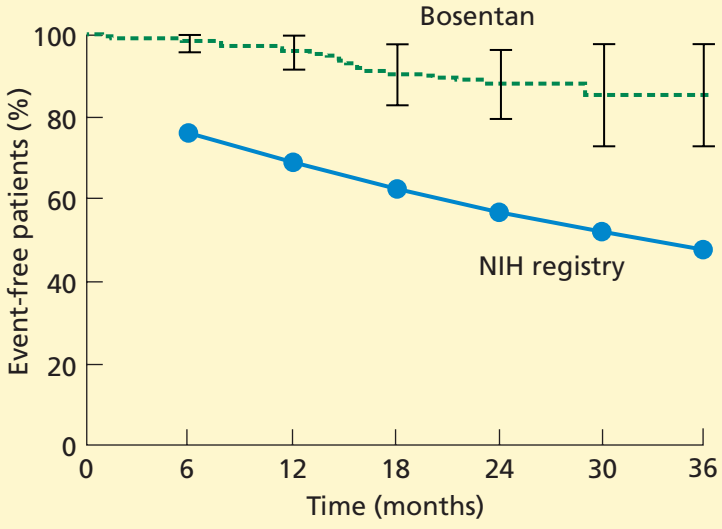

FIGURE 2. Kaplan-Meier estimates of observed survival in patients with idiopathic pulmonary arterial hypertension using first-line bosentan therapy (dashed line) with 99.9% confidence intervals and predicted survival using the National Institutes of Health (NIH) registry equation (solid line). The 99.9% confidence intervals of the Kaplan-Meier estimates do not approach the predicted survival, demonstrating a significant difference between the two curves.

WITH PERMISSION FROM MCLAUGHLIN VV, SITBON O, BADESCH DB, ET AL. SURVIVAL WITH FIRST-LINE BOSENTAN IN PATIENTS WITH PRIMARY PULMONARY HYPERTENSION. EUR RESPIR J 2005; 25:244–249.

epoprostenol within the first 3 months of therapy indicates a poor prognosis,[32] and that such patients should be evaluated for lung transplantation.

Once epoprostenol therapy is started, it is typically continued for life. Occasional reports have been published about adding oral agents and tapering off epoprostenol, but because no clear criteria exist for stopping epoprostenol, it should be attempted only in experienced pulmonary hypertension centers in carefully selected patients who can be closely monitored.[33–35]

Treprostinil (Remodulin) is a prostacyclin analogue that is stable at room temperature and has a half-life of 4.5 hours, allowing it to be given subcutaneously in a continuous infusion, using a small pump similar to an insulin pump.[36] The drug comes in a medication cartridge that the patient can change every 2 days. However, persistent injection-site pain limits its use, despite rotating the injection sites or using ice packs, topical analgesics, anti-inflammatory drugs, and tricyclic antidepressants.

Treprostinil was recently approved for continuous intravenous administration, a route that has the advantages of causing less local pain and allowing higher doses to be given, as with epoprostenol.[37] Its stability at room temperature and longer half-life compared with epoprostenol have potential advantages in terms of patient comfort and safety.

A recent, multicenter, retrospective analysis has demonstrated that, similar to epoprostenol, parenteral treprostinil can produce sustained clinical improvement long-term.[38]

Intravenous medications are preferred for patients with functional class IV symptoms, but because these drugs are costly, pose risks of infection and thrombosis, and can be inconvenient to use, they may not be the first choice for patients with class III disease.

Oral and inhaled vasoactive agents for moderate disease

Patients in functional class II or III and those who have no evidence of overt right-sided heart failure, presyncope, or chest pain can be considered for oral vasoactive therapy.

Endothelin-1—a potent vasoconstrictor that induces proliferation of vascular smooth muscle cells—is overexpressed in patients with pulmonary arterial hypertension, and the more endothelin, the more severe the disease[39] and the lower the survival rate. Two receptors for endothelin-1 have been identified: ET(A), which is mainly responsible for vasoconstriction, and ET(B), which clears endothelin from the circulation and may promote vasodilation (FIGURE 1). Endothelin receptor antagonists that target either the ET(A) receptor alone or both receptors have been developed.

Bosentan, a dual ET(A) and ET(B) receptor antagonist, was the first endothelin receptor antagonist approved by the FDA for treating patients with pulmonary arterial hypertension. Approval is restricted to patients with functional class III or IV symptoms.

After an initial pilot study,[40] the larger, multicenter Bosentan Randomized Trial of

Endothelin Receptor Antagonist Therapy for Pulmonary Arterial Hypertension (BREATHE-1)[41] was conducted. This double-blind trial randomized 213 patients with functional class III or IV pulmonary arterial hypertension (idiopathic or associated with connective-tissue disease) to receive either bosentan or placebo. After 16 weeks, patients taking bosentan had improved in their 6-minute walking distance, functional class, and right ventricular function as assessed by echocardiography, and time to clinical worsening was improved.

McLaughlin et al[42] conducted a 2-year analysis of 169 patients with functional class III or IV idiopathic pulmonary arterial hypertension using open-label bosentan and found their survival rate was higher than predicted by the NIH equation (FIGURE 2). However, only 85% of the patients were still on bosentan monotherapy at 1 year and 70% at 2 years.

Bosentan is associated with abnormal hepatic function and should not be given to patients with moderate to severe liver impairment. The FDA requires that liver function be checked monthly. Pregnancy must be excluded before beginning therapy, and women of childbearing age should be counseled regarding contraception. Bosentan is associated with testicular atrophy, worsening of peripheral edema, mild anemia, and many drug interactions.[23]

Ambrisentan (Letairis) was recently approved and is the only ET(A) endothelin receptor blocker approved by the FDA for the treatment of NYHA class II and III patients with pulmonary arterial hypertension.

Galie et al[43] conducted a randomized dose-ranging trial in 64 patients with pulmonary arterial hypertension and found that 3 months of therapy with ambrisentan improved exercise capacity, functional class, and hemodynamics.

Preliminary results from two phase III randomized, placebo-controlled studies with ambrisentan in patients with pulmonary arterial hypertension have recently been reported. In a European study,[44] 2.5 mg and 5 mg of ambrisentan taken once daily for 12 weeks improved the placebo-adjusted 6-minute walking distance by 32 meters and 59 meters, respectively. In a North American study,[45] 5 mg and 10 mg of ambrisentan taken once daily for 12 weeks improved the placebo-adjusted 6-minute walking distance by 31 meters and 51 meters, respectively (FIGURE 3). Time to clinical worsening was also improved.

Ambrisentan increases walking distance in pulmonary arterial hypertension

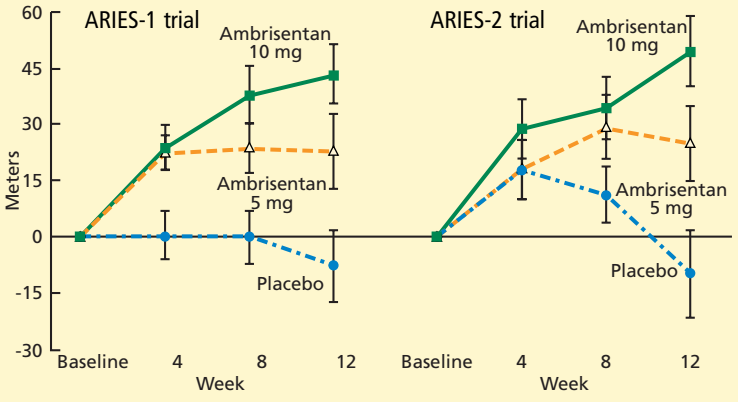

FIGURE 3. Mean change in 6-minute walking distance in two clinical trials of ambrisentan (Letairis).

WITH PERMISSION FROM: GILEAD SCIENCES, INC.

Ambrisentan can cause pedal edema and elevation in liver enzymes (in < 3% of patients) and may have teratogenic effects. As such, as with bosentan, patients on ambrisentan require monthly liver function testing, monitoring for peripheral edema, and termination of pregnancy should it occur.

Phosphodiesterase type 5 inhibitors. Phosphodiesterases are enzymes that inactivate cyclic guanosine monophosphate (cGMP), which serves as a second messenger for nitric oxide. Selective phosphodiesterase type 5 inhibitors increase cGMP levels and promote nitric-oxide-mediated vasodilation (FIGURE 1). Best studied is sildenafil, sold as Viagra for the treatment of erectile dysfunction and approved and sold as Revatio for the treatment of pulmonary arterial hypertension. Tadalafil (Cialis), another drug of this class, has the potential advantage of once-a-day administration, but its use in treating pulmonary arterial hypertension is still under investigation.

Sildenafil, used in erectile dysfunction, is also approved for treating pulmonary arterial hypertension

The double-blind Sildenafil Use in Pulmonary Arerial Hypertension (SUPER-1) study[46] randomized 278 patients with sympto-

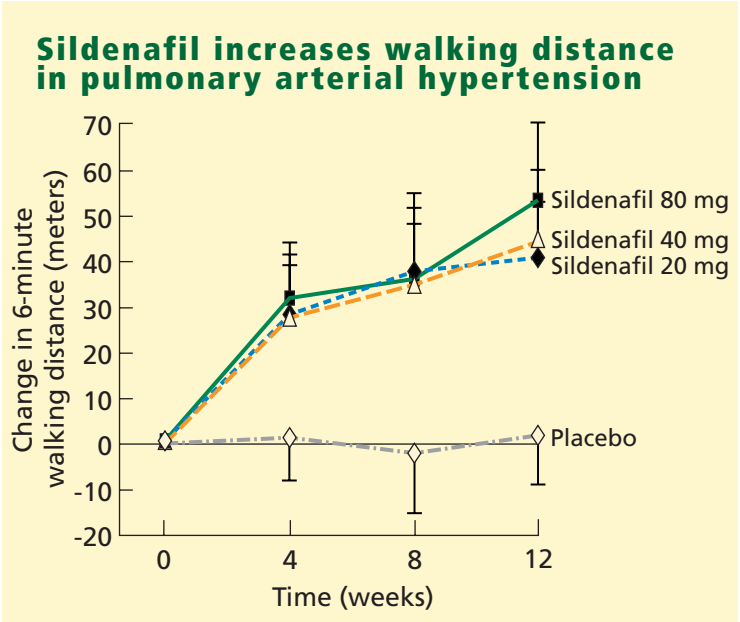

FIGURE 4. Improvement in 6-minute walking distance in a study of patients with pulmonary arterial hypertension treated with sildenafil.

WITH PERMISSION FROM GALIE N, GHOFRANI HA, TORBICKI A, ET AL. SILDENAFIL USE IN PULMONARY ARTERIAL HYPERTENSION (SUPER) STUDY GROUP. SILDENAFIL CITRATE THERAPY FOR PULMONARY ARTERIAL HYPERTENSION. N ENGL J MED 2005; 353:2148–2157.

matic pulmonary arterial hypertension to receive placebo or sildenafil 20, 40, or 80 mg orally three times daily. At 12 weeks, distances on the 6-minute walking test had improved by a mean of 36 meters in patients taking sildenafil 20 mg, 46 meters with 40 mg, and 50 meters with 80 mg, but remained unchanged in the placebo group ($P < .001$ for all comparisons with the placebo group; FIGURE 4). In addition, significantly more patients taking sildenafil than placebo improved in their functional class, and the sildenafil groups improved more in their hemodynamic variables.

On the basis of the data from this trial, the FDA approved sildenafil 20 mg three times per day for patients with pulmonary arterial hypertension (with no functional class restriction).

Preliminary results from the open-label SUPER-2 study[47,48] suggest that patients continue to benefit in terms of improved 6-minute walking distance and functional class at 12 months of therapy with sildenafil 80 mg three times a day. Only 6% of patients required an escalation of therapy. Ninety-six percent of the patients were still alive at 1 year, whereas the survival rate predicted by the NIH equation was 71%.

Sildenafil is well tolerated. Its most common side effect is headache; other side effects include hypotension, which is serious in some cases, and changes in vision and color perception at high doses. Treatment requires no monitoring with specific laboratory tests. Patients taking nitrates should not use sildenafil because it may increase hypotension.

Iloprost (Ventavis) is a prostacyclin analogue that is approved for use in the United States via inhalation. Inhaled iloprost is a potent vasodilator but is short-acting: acute hemodynamic effects disappear within 45 to 60 minutes. Owing to its short half-life, it typically must be used six to nine times per day.

Olschewski et al[49] randomized patients with pulmonary arterial hypertension with functional class III and IV symptoms to receive either inhaled iloprost or placebo. At 3 months, the 6-minute walking distance, functional class, and hemodynamic variables were better with iloprost than with placebo. On the basis of this trial, inhaled iloprost was recently approved in Europe and the United States for treating patients with pulmonary arterial hypertension functional class III.

WHAT AGENTS ARE UNDER STUDY?

Selective ET(A) antagonists

Sitaxsentan is a drug that is about 6,000 times more selective for ET(A) than for ET(B) receptors. As of this writing, it has not yet been approved by the FDA, but is approved in Europe and Canada for use in patients with pulmonary arterial hypertension.

The Sitaxsentan to Relieve Impaired Exercise (STRIDE-1) study[50] randomized 178 patients to receive either placebo or sitaxsentan 100 mg or 300 mg orally. After 12 weeks, patients taking the smaller dosage had increased their 6-minute walking distance by 35 meters, and those taking the higher dosage improved by 33 meters ($P < .01$ vs placebo for both dosages).

The STRIDE-2 study[51] randomized 247 patients to receive placebo, sitaxsentan 50 mg

or 100 mg, or open-label bosentan 125 mg twice daily. At 18 weeks, the group receiving sitaxsentan 100 mg could walk 24.9 meters farther in 6 minutes than they could at baseline, whereas the distance in the placebo group had declined by 6.5 meters ($P = .03$).

Other investigational drugs include inhaled and oral treprostinil and vasoactive intestinal peptide, a systemic and pulmonary vasodilator and inhibitor of proliferation of vascular smooth muscle cells. These drugs are currently undergoing clinical trials or will be soon. Inhaled treprostinil's longer half-life will make it particularly attractive if it is proven effective.

Combination therapy

Because different classes of medications used to treat pulmonary arterial hypertension target different pathways, it is hoped that their combined actions will achieve a greater therapeutic effect.

Two recent reports[52,53] suggest that adding sildenafil produces a sustained improvement in 6-minute walking distance and functional class in patients whose condition has deteriorated while on bosentan therapy alone.

Combination therapy may be effective where monotherapy is failing

Hoeper et al[54] treated 123 patients with pulmonary arterial hypertension according to a predefined, goal-oriented therapeutic strategy using bosentan, sildenafil, iloprost, and parenteral prostenoids. The survival rate was 93% at 1 year, 83% at 2 years, and 79.9% at 3 years, which was better than in a historical control group.

Evidence from a recently completed trial[55] found that patients with functional class III or IV disease on stable doses of bosentan who were treated with inhaled iloprost had improved 6-minute walking distances by a mean of 26 meters ($P = .051$). Another preliminary study[56] found that patients already on epoprostenol had significantly improved 6-minute walking distances after the addition of sildenafil to therapy.

Although these studies are promising, many of these medicines have only recently been approved, and questions regarding the best drug combinations, timing strategies, acceptable levels of benefit, and appropriate patient candidates must be answered through well-designed, prospective trials.

WHAT SURGICAL OPTIONS ARE AVAILABLE?

Atrial septostomy for select patients awaiting lung transplantation

A patent foramen ovale confers a survival advantage in patients with severe idiopathic pulmonary arterial hypertension who are awaiting lung transplantation.[57] Creating a right-to-left intra-atrial shunt with an atrial septostomy may decompress the right ventricle and increase right ventricular function and exercise capacity. The procedure has a mortality rate of up to 50%, so it should only be considered in patients with severe symptoms that are refractory to medical management.[58,59]

Pulmonary thromboendarterectomy for chronic thromboembolic disease

For patients with chronic thromboembolic pulmonary hypertension, pulmonary thromboendarterectomy improves hemodynamics, functional status, and survival and is the preferred treatment for patients with operable disease. Patients with disease not amenable to surgery or those with residual pulmonary hypertension after surgery should receive medical therapy.[60,61]

Lung transplantation for severe cases

Lung transplantation is an option for patients whose disease is refractory to medical therapy. Patients who present with functional class IV symptoms or have progressive symptoms despite medical therapy should be evaluated at a transplant center so the listing process may be expedited if the disease worsens.[62] Survival rates following lung transplantation for pulmonary hypertension are 73% after 1 year and 56% after 3 years.[63]

REFERENCES

1. **Rubin LJ; American College of Chest Physicians.** Diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004; 126:7S–10S.
2. **Galie N, Torbicki A, Barst R, et al; Task Force.** Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Eur Heart J 2004; 25:2243–2278.
3. **Badesch DB, Abman SH, Ahearn GS, et al; American College of Chest Physicians.** Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004; 126:35S–62S.

4. **Badesch DB, Abman SH, R, Simonneau G, Rubin LJ McLaughlin VV;** Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. Chest 2007; 131:1917–1928.
5. **Galie N, Seeger W, Naeije R, Simonneau G, Rubin LJ.** Comparative analysis of clinical trials and evidence-based treatment algorithm in pulmonary arterial hypertension. J Am Coll Cardiol 2004; 43:81S–88S.
6. **Minai O, Budev MM.** Diagnostic strategies for suspected pulmonary arterial hypertension: a primer for the internist. Cleve Clin J Med 2007; 74:737–747.
7. **Mughal MM, Mandell B, James K, Stelmach K, Minai OA.** Implementing a shared-care approach to improve the management of patients with pulmonary arterial hypertension. Cleve Clin J Med 2003; 70:S28–S33.
8. **Rubin LJ, Badesch DB.** Evaluation and management of the patient with pulmonary arterial hypertension. Ann Intern Med 2005; 143:282–292.
9. **McLaughlin VV, Rich S.** Pulmonary hypertension. Curr Prob Cardiol 2004; 29:575–634.
10. **Dajani AS, Taubert KA, Wilson W, et al.** Prevention of bacterial endocarditis. Recommendations by the American Heart Association. JAMA 1997; 277:1794–1801.
11. **Mehta AC, Minai OA.** Infection control in the bronchoscopy suite. A review. Clin Chest Med 1999; 20:19–32, ix.
12. **Minai OA, Pandya CM, Golish JA, et al.** Predictors and significance of nocturnal oxygen desaturation in pulmonary arterial hypertension. Chest 2007; 131:109–117.
13. **Carro-Jimenez EJ, Lopez JE.** Primary pulmonary hypertension and pregnancy. Bol Asoc Med P R 2005; 97:328–333.
14. **Rich S, Seidlitz M, Dodin E, et al.** The short-term effects of digoxin in patients with right ventricular dysfunction from pulmonary hypertension. Chest 1998; 114:787–792.
15. **Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL.** Primary pulmonary hypertension: natural history and the importance of thrombosis. Circulation 1984; 70:580–587.
16. **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.
17. **Kaw R, Sharma P, Minai OA.** What risks does a history of pulmonary hypertension present for patients undergoing noncardiac surgery? Cleve Clin J Med 2007; 74 (e-suppl). www.ccjm.org/PDFFILES/Periopimpactconsults_07.pdf#Kaw2. Accessed October 4, 2007.
18. **Minai OA, Venkateshiah SB, Arroliga AC.** Surgical intervention in patients with moderate to severe pulmonary arterial hypertension. Conn Med 2006; 70:239–244.
19. **Ramakrishna G, Sprung J, Ravi BS, Chandrasekaran K, McGoon MD.** Impact of pulmonary hypertension on the outcomes of noncardiac surgery. J Am Coll Cardiol 2005; 45:1691–1699.
20. **Naeije R, Vachiery JL.** Medical therapy of pulmonary hypertension. Conventional therapies. Clin Chest Med 2001; 22:517–527.
21. **Minai OA, Gildea TR, McCarthy K.** Altitude simulation test in pulmonary arterial hypertension: a valuable tool [abstract]. Proc Am Thorac Soc 2005; 2:A202.
22. **Naeije R.** Preflight medical screening of patients. Eur Respir J 2000; 16:197–199.
23. **Channick RN, Sitbon O, Barst RJ, Manes A, Rubin LJ.** Endothelin receptor antagonists in pulmonary arterial hypertension. J Am Coll Cardiol 2004; 43:62S–67S.
24. **D'Alonzo GE, Barst RJ, Ayres SM, et al.** Survival in patients with primary pulmonary hypertenson. Results from a national prospective registry. Ann Intern Med 1991; 115:343–349.
25. **Heresi GA, Minai OA.** Lupus-associated pulmonary hypertension: long-term response to vasoactive therapy. Respir Med 2007; 101:2009–2107.
26. **McGoon M, Gutterman D, Steen V, et al; American College of Chest Physicians.** Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004; 126:14S–34S.
27. **Sitbon O, Humbert M, Jais X, et al.** Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005; 111:3105–3111.
28. **Badesch DB, McLaughlin VV, Delcroix M, et al.** Prostanoid therapy for pulmonary arterial hypertension. J Am Coll Cardiol 2004; 43:56S–61S.
29. **McLaughlin VV, Shillington A, Rich S.** Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002; 106:1477–1482.
30. **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.
31. **Badesch DB, Tapson VF, McGoon MD, et al.** Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. Ann Intern Med 2000; 132:425–434.
32. **Sitbon O, Humbert M, Nunes H, et al.** Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002; 40:780–788.
33. **Diaz EGZ, Minai OA, Bair N, Banjac S, Arroliga AC.** Long-term follow-up after successful discontinuation of prostacyclin analogues in patients with pulmonary arterial hypertension [abstract]. Chest 2005; 128(suppl):161S.
34. **Johnson RF, Loyd JE, Mullican AL, Fink CA, Robbins IM.** Long-term follow-up after conversion from intravenous epoprostenol to oral therapy with bosentan or sildenafil in 13 patients with pulmonary arterial hypertension. J Heart Lung Transplant 2007; 26:363–369.
35. **Steiner MK, Preston IR, Klinger JR, et al.** Conversion to bosentan from prostacyclin infusion therapy in pulmonary arterial hypertension. Chest 2006; 130:1471–1480.
36. **Simonneau G, Barst RJ, Galie N, et al; Treprostinil Study Group.** Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 2002; 165:800–804.
37. **Tapson VF, Gomberg-Maitland M, McLaughlin VV, et al.** Safety and efficacy of IV treprostinil for pulmonary arterial hypertension: a prospective, multicenter, open-label, 12-week trial. Chest 2006; 129:683–688.
38. **Barst RJ, Galie N, Naeije R, et al.** Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. Eur Respir J 2006; 28:1195–1203.
39. **Giaid A, Yanagisawa M, Langleben D, et al.** Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med 1993; 328:1732–1739.
40. **Channick RN, Simonneau G, Sitbon O, et al.** Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomized placebo-controlled study. Lancet 2001; 358:1119–1123.
41. **Rubin LJ, Badesch DB, Barst RJ, et al.** Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002; 346:896–903. Erratum in: N Engl J Med 2002; 346:1258.
42. **McLaughlin VV, Sitbon O, Badesch DB, et al.** Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J 2005; 25:244–249. Erratum in: Eur Respir J 2005; 25:942.
43. **Galie N, Badesch D, Oudiz R, et al.** Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol 2005; 46:529–535.
44. **Olschewski H, Galie N, Ghofrani HA, et al.** Ambrisentan improves exercise capacity and time to clinical worsening in patients with pulmonary arterial hypertension: results of the ARIES-2 study [abstract]. Proc Am Thorac Soc 2006; 3:A728.
45. **Oudiz RJ, Badesch DB, Rubin LJ, et al.** ARIES-E: long-term safety and efficacy of ambrisentan in pulmonary arterial hypertension [abstract]. Am J Respir Crit Care Med 2007; 175:A300.
46. **Galie N, Ghofrani HA, Torbicki A, et al; Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group.** Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005; 353:2148–2157. Erratum in: N Engl J Med 2006; 354:2400–2401.
47. **Rubin L, Burgess G, Parpia T, et al.** Effects of sildenafil on 6 minute

walk distance and WHO functional class after 1 year of treatment [abstract]. Proc Am Thorac Soc 2005; 2:A299.
48. **Galie N, Burgess G, Parpia T, et al.** Effects of sildenafil on 1-year survival of patients with idiopathic pulmonary arterial hypertension [abstract]. Proc Am Thorac Soc 2005; 2:A802.
49. **Olschewski H, Simonneau G, Galie N, et al; Aerosolized Iloprost Randomized Study Group.** Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 2002; 347:322–329.
50. **Barst RJ, Langleben D, Frost A, et al; STRIDE-1 Study Group.** Sitaxsentan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med 2004; 169:441–447.
51. **Barst RJ, Langleben D, Badesch D, et al; STRIDE-2 Study Group.** Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. J Am Coll Cardiol 2006; 47:2049–2056.
52. **Minai OA, Arroliga AC.** Long-term results after addition of sildenafil in idiopathic PAH patients on bosentan. South Med J 2006; 99:880–883.
53. **Hoeper MM, Faulenbach C, Golpon H, Winkler J, Welte T, Niedermeyer J.** Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. Eur Respir J 2004; 24:1007–1010.
54. **Hoeper MM, Markevych I, Spiekerkoetter E, Welte T, Niedermeyer J.** Goal-oriented treatment and combination therapy for pulmonary artery hypertension. Eur Respir J 2005; 26:858–863.
55. **McLaughlin VV, Oudiz RJ, Frost A, et al.** Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. Am J Respir Crit Care Med 2006; 174:1257–1263.
56. **Simonneau G, Burgess G, Collings L, et al.** Safety and efficacy of combination therapy with sildenafil and epoprostenol in patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 2006; 3:A58.
57. **Glanville AR, Burke CM, Theodore J, Robin ED.** Primary pulmonary hypertension. Length of survival in patients referred for heart-lung transplantation. Chest 1987; 91:675–681.
58. **Klepetko W, Mayer E, Sandoval J, et al.** Interventional and surgical modalities of treatment for pulmonary arterial hypertension. J Am Coll Cardiol 2004; 43:73S–80S.
59. **Sandoval J, Gaspar J, Pulido T, et al.** Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension. A therapeutic alternative for patients nonresponsive to vasodilator treatment. J Am Coll Cardiol 1998; 32:297–304.
60. **Moser KM, Auger WR, Fedullo PF, Jamieson SW.** Chronic thromboembolic pulmonary hypertension: clinical picture and surgical treatment. Eur Respir J 1992; 5:334–342.
61. **Doyle RL, McCrory D, Channick RN, Simonneau G, Conte J; American College of Chest Physicians.** Surgical treatments/interventions for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004; 126:63S–71S.
62. **Minai OA, Budev MM.** Referral for lung transplantation: a moving target. Chest 2005; 127:705–707.
63. **United Network for Organ Sharing.** Available at www.unos.org. Accessed October 5, 2007.

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