

Pulmonary HTN

Learning Objectives:

1. Know the causes of secondary pulmonary hypertension, and how to approach the evaluation of these potential underlying causes. (What should be done to “rule out” secondary causes prior to a diagnosis of primary pulmonary hypertension (PPH)?)
2. Understand the incidence, pathogenesis, and natural history of disease for PPH.
3. Be familiar with the evaluation approach and therapeutic options for patients with PPH.

Required Reading:

Rubin LJ. Primary Pulmonary Hypertension NEJM 1997;336:111-117

For Additional Study:

Hoeper MM, Galie N, Simonneau G, Rubin L. New treatments for pulmonary arterial hypertension. Am J Respir Crit Care Med 2002;165:1209-1216.

Fedullo PF, Auger WR, Kerr KM, Rubin LJ. Chronic thromboembolic pulmonary hypertension. NEJM 2001;345:1465-1472.

Rich S, McLaughlin VV eds. Clinics in Chest Medicine. September 2001, Volume 22.

~~Related MKSAP Questions: 40, 66, 78~~



Review Article

Current Concepts

PRIMARY PULMONARY HYPERTENSION

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P RIMARY pulmonary hypertension is a condition characterized by sustained elevations of pulmonary-artery pressure without a demonstrable cause. The diagnostic criteria used in the National Institutes of Health (NIH) registry¹ include a mean pulmonary-artery pressure of more than 25 mm Hg at rest, or more than 30 mm Hg with exercise, and the exclusion of left-sided cardiac valvular disease, myocardial disease, congenital heart disease, and any clinically important respiratory, connective-tissue, or chronic thromboembolic discases. Pulmonary vascular disease with clinical and pathological features similar to those of primary pulmonary hypertension can occur in patients with portal hypertension,² infection with the human immunodeficiency virus (HIV),³ or a history of cocaine inhalation⁴ and in those who take appetite-suppressant drugs.^{5,6}

INCIDENCE

Estimates of the incidence of primary pulmonary hypertension range from 1 to 2 cases per million people in the general population.^{6,7} The incidence of pulmonary vascular disease in patients with other illnesses is not known, but it appears that 0.5 to 2 percent of patients with portal hypertension or HIV infection have pulmonary vascular disease.^{8,9} In a recent case-control study, any use of appetite suppressants was associated with an increased risk of primary pulmonary hypertension (odds ratio, 6.3), and the odds ratio increased to more than 20 if the drugs were used for more than three months.⁶ Fenfluramine and dexfenfluramine, inhibitors of serotonin uptake widely used to treat obesity, were the drugs most commonly associated with pulmonary hypertension, but amphetamines were also implicat-

ed. The effect of appetite suppressants was independent of body-mass index, which suggests that obesity was not responsible for the increased risk. Because pulmonary hypertension develops in only a small percentage of people with other illnesses, it has been proposed that this form of hypertension requires some predisposition, perhaps one genetically determined.

Familial primary pulmonary hypertension accounted for 6 percent of the 187 cases in the NIH registry.¹ The histopathological and clinical features of the familial form of the disease are identical to those of the sporadic form,¹⁰ although, not unexpectedly, the diagnosis is made earlier in the familial form. The familial form is inherited as an autosomal dominant trait and is associated with a pattern of "genetic anticipation," a worsening of disease in subsequent generations, manifested by greater severity or earlier onset.¹¹ Genetic anticipation is a feature of other conditions in which a trinucleotide-repeat pattern has been implicated, such as the fragile X syndrome.

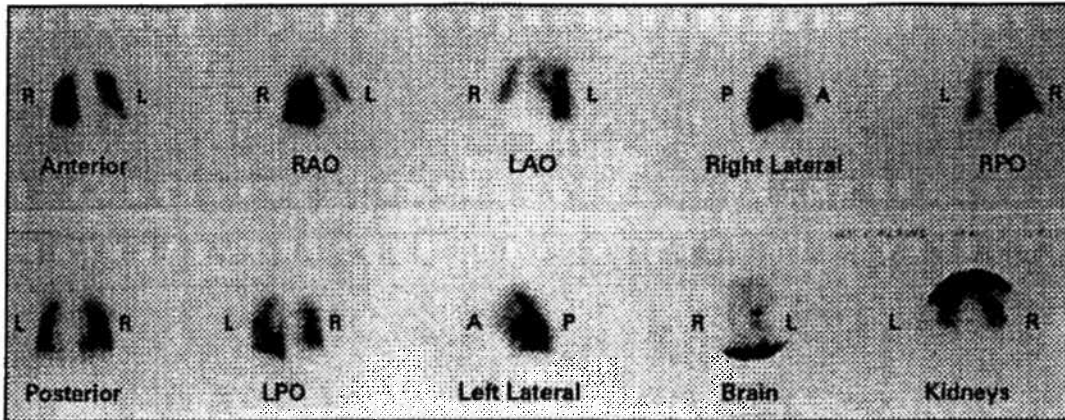
PATHOGENESIS AND PATHOPHYSIOLOGY

Three elements combine to produce increased vascular resistance in patients with primary pulmonary hypertension: vasoconstriction, vascular-wall remodeling, and thrombosis in situ. The pathogenetic importance of vasoconstriction was first suggested by Wood,¹² who noted vasodilation in response to the infusion of acetylcholine. Subsequently, Wagenvoort¹³ stressed that the earliest pathologic feature of primary pulmonary hypertension was medial hypertrophy, which indicated the presence of a stimulus for vasoconstriction and the proliferation of smooth muscle. More recently, Palevsky et al.¹⁴ found a correlation between the hemodynamic response to vasodilators and the area of the vascular-wall media, as measured in pathological specimens.

Altered function of the pulmonary vascular endothelium may also be important. An imbalance in the ratio of the metabolites of prostacyclin to those of thromboxane (both substances are circulating eicosanoids with divergent effects on platelet aggregation and vascular smooth-muscle tone)¹⁵ suggests that either enhanced activity of thromboxane or diminished activity of prostacyclin may contribute to pathogenesis. Impaired synthesis of the endothelium-derived vasorelaxant nitric oxide and enhanced production of the endothelium-derived vasoconstrictor endothelin have also been associated with pulmonary hypertension.^{16,17} Whether these abnormalities are the cause or the result of the disease, however, remains un-

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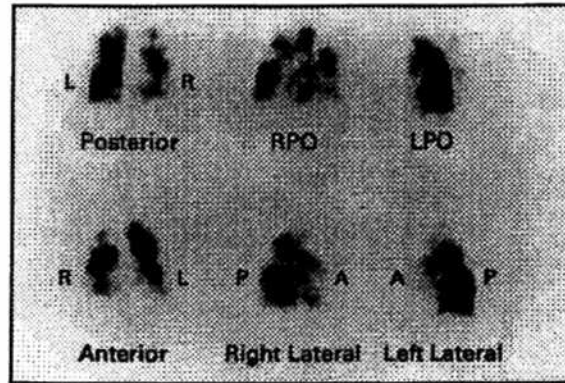
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A

Figure 1. Ventilation-Perfusion Scans and Pulmonary Arteriograms of Patients with Primary Pulmonary Hypertension and Chronic Thromboembolic Pulmonary Hypertension.

Panel A shows ventilation-perfusion scans of the lungs (from a variety of angles), brain, and kidneys of a patient with primary pulmonary hypertension. The tracer uptake in the brain and kidneys is indicative of the presence of a right-to-left shunt. Panel B shows similar lung scans of a patient with chronic thromboembolic pulmonary hypertension. Panels C and D (facing page) show pulmonary arteriograms of a patient with primary pulmonary hypertension and a patient with chronic thromboembolic pulmonary hypertension, respectively. The arrows in Panel D indicate intravascular bands and abrupt cutoffs, which are typical of chronic thrombotic disease. R denotes right, L left, P posterior, A anterior, RAO right anterior oblique, LAO left anterior oblique, RPO right posterior oblique, and LPO left posterior oblique.



B

certain. The proliferation of intimal and adventitial tissue succeeds vasoconstriction as the disease progresses. Thrombosis may result from injury to the endothelium, abnormal fibrinolysis, enhanced procoagulant activity, and platelet abnormalities.¹⁸

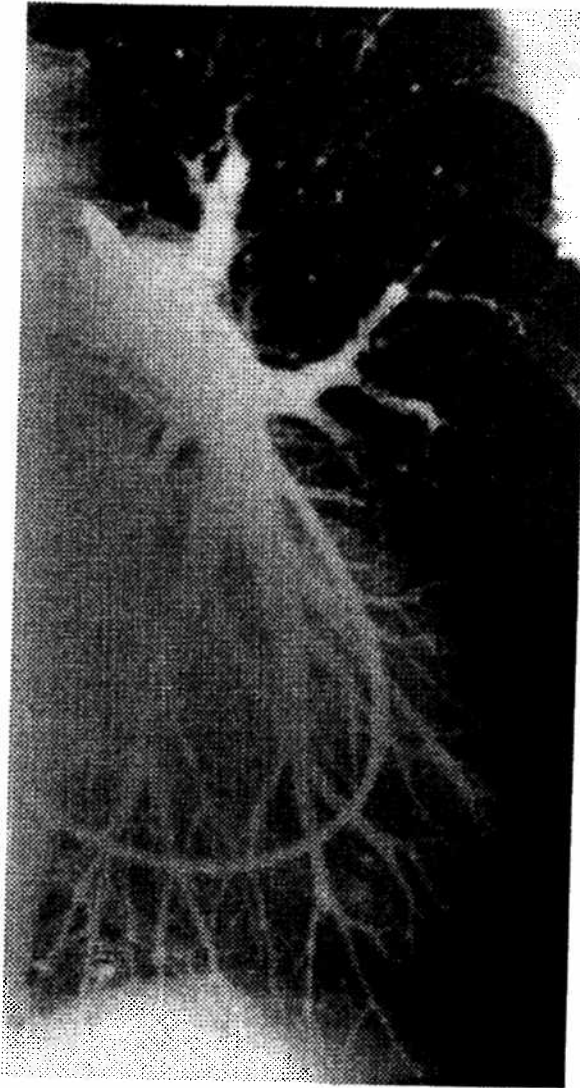
DIAGNOSIS

The major obstacles to establishing a clinical diagnosis early in the course of the disease are the nonspecific nature of the symptoms and the subtlety of the signs of less advanced disease. The mean length of time from the onset of symptoms to the establishment of the diagnosis is about two years, and in about 10 percent of patients, the diagnosis is not established until after three years of symptoms.¹ Dyspnea, the most common reason for seeking medical help, occurs in 60 percent of patients, but is reported by nearly all patients as the disease progresses. Fatigability is a common early symptom; angina and syncope, particularly with exertion, are indicative of more severe limitations in cardiac output. Approximately 10 percent of patients, usually women, report symptoms of Raynaud's phenomenon.

Echocardiography can rule out congenital, valv-

lar, and myocardial disease and may provide a means of estimating pulmonary-artery systolic pressure.¹⁹ The results of ventilation-perfusion scanning are normal or reveal a patchy distribution of tracer, particularly in pulmonary veno-occlusive disease,²⁰ in contrast to the multiple, larger perfusion defects typical of chronic major-vessel thromboembolic pulmonary hypertension (Fig. 1A and 1B). Pulmonary arteriography is useful when the perfusion lung scan is inconclusive and can generally be performed safely even in patients with severe pulmonary hypertension (Fig. 1C and 1D).²¹

Abnormalities in lung function are usually mild, and arterial hypoxemia is almost always found.¹ Cardiopulmonary exercise tests disclose a pattern of altered cardiac function, with reduced maximal oxygen consumption, high minute ventilation, a low anaerobic threshold, reduced maximal oxygen pulse, and an increased alveolar-arterial oxygen gradient. There is a correlation between the distance walked during a six-minute walk test and the severity of pulmonary hypertension, so this noninvasive study of less than maximal exertion may be useful for monitoring the response to therapy.²²



C



D

Serologic studies are often performed in patients with unexplained pulmonary hypertension to screen for connective-tissue diseases. Positive results of antinuclear-antibody tests are common,¹ usually with a low titer, although high titers without a specific pattern have been reported.

Pulmonary hemodynamics are markedly deranged, with increases in pulmonary-artery pressure to levels three or more times normal, elevated right atrial

pressure, and depressed cardiac output.¹ Pressures on the left side of the heart are usually normal, although extreme dilation of the right heart chambers can compress the left chambers to a degree that limits filling and produces small increases in diastolic pressures. The pulmonary-capillary wedge pressure is usually normal, even in veno-occlusive disease, owing to the patency of the larger pulmonary veins and the patchy nature of the disease process in the

veins.²³ However, in veno-occlusive disease, measurements of capillary wedge pressure at several sites may disclose abnormally elevated pressures in some vascular segments.

THERAPY

Primary pulmonary hypertension is a progressive disease for which there is no cure. Spontaneous remission has been reported²⁴ but is rare,²⁵ although patients with the disease who were taking an anorectic drug may have a substantial improvement in their condition or even a remission after the discontinuation of the drug.²⁶ Considerable progress in therapy has been made over the past 15 years, however, and there are both pharmacologic and surgical strategies for treatment.

Vasodilators

The rationale for therapy with vasodilators is based on the observation that vasoconstriction is a prominent feature of this disease. Unfortunately, there is no way to predict from patients' demographic or hemodynamic characteristics who is likely to respond to vasodilators and who is not.²⁷ The initial response to vasodilator challenge, however, accurately identifies patients who are likely to respond to long-term oral therapy.^{28,29} Hence, it is imperative to evaluate pulmonary vasoreactivity during the initial hemodynamic study before embarking on a course of long-term therapy. The most suitable drugs for testing acute response are potent, short-acting, and titratable vasodilators such as nitric oxide,³⁰ epoprostenol (prostacyclin),³¹ and adenosine.³² The action of nitric oxide is most specific to the pulmonary vascular bed, since the binding of the agent to hemoglobin in the pulmonary capillary blood markedly reduces its systemic vasodilator activity. The pulmonary vascular responses to intravenous epoprostenol or adenosine are usually similar to those of inhaled nitric oxide.³³ Aerosolized epoprostenol produces selective effects similar to those of inhaled nitric oxide.³⁴

There are no uniformly accepted criteria for a beneficial response to acute vasodilator challenge. Patients who have a reduction in pulmonary-artery pressure, accompanied by an increase in cardiac output and little change in systemic pressure or arterial-oxygen saturation, are likely to have sustained hemodynamic and symptomatic improvement³⁵ as well as prolonged survival.³⁶ In contrast, a patient's condition is more likely to deteriorate if the pulmonary-artery pressure increases or remains unchanged, the systemic blood pressure falls excessively, the cardiac output or oxygen saturation declines, or the right atrial pressure increases. The usefulness of oral vasodilator therapy is controversial in patients who (during vasodilator challenge) have an acute reduction in pulmonary vascular resistance resulting from an increased cardiac output without a fall in pulmonary-

TABLE 1. DOSE RANGES, ROUTES OF ADMINISTRATION, AND HALF-LIVES OF THE MOST FREQUENTLY USED VASODILATORS IN PATIENTS WITH PRIMARY PULMONARY HYPERTENSION.

DRUG	ROUTE	DOSE RANGE	HALF-LIFE
Epoprostenol*	Intravenous	2-20 ng/kg of body weight/min	3-5 min
Adenosine	Intravenous	50-200 µg/kg of body weight/min	5-10 sec
Nitric oxide	Inhaled	5-80 ppm	15-30 sec
Nifedipine†	Oral	30-240 mg/day	2-5 hr
Diltiazem†	Oral	120-900 mg/day	2-4.5 hr

*The dose range shown is for a short-term infusion; the dose range for long-term infusions often exceeds 100 to 150 ng per kilogram per minute.

†The half-life shown refers to conventional preparations; sustained-release preparations may be administered once daily.

artery pressure. Although exercise tolerance may be improved in such patients, right ventricular function may be adversely affected.³⁷ It is not known whether long-term vasodilator therapy improves survival in this group of patients.

The most widely used drugs for long-term therapy are the calcium-channel blockers nifedipine and diltiazem, which produce sustained improvement in the condition of 25 to 30 percent of patients.^{35,36} Doses of these drugs that are larger than those used to treat systemic hypertension or coronary artery disease may be necessary to produce beneficial effects in primary pulmonary hypertension,^{35,36} although dosage requirements and tolerance vary considerably. Experience with verapamil has been disappointing, in part because of its negative inotropic effects.³⁷ In contrast to their important benefits in patients with systemic vascular disease, the effects of angiotensin-converting-enzyme inhibitors appear to be small in primary pulmonary hypertension, at least acutely.³⁸ The most commonly used vasodilators are listed in Table 1.

Oral vasodilator therapy should be adjusted on the basis of symptoms and objective findings, including blood pressure, oxygen saturation, and the results of physical examination. Echocardiography may be a useful, noninvasive way to monitor the effects of therapy: reductions in right-chamber size and estimated pulmonary-artery systolic pressure may be observed in patients given long-term therapy with calcium-channel blockers.³⁵ Assessment of hemodynamic measures by catheterization remains, however, the best test for evaluating the response to therapy. The side effects of long-term vasodilator therapy include systemic hypotension, edema, and hypoxemia. Hypoxemia may be caused by three sets of circumstances: a worsening ventilation-perfusion ratio caused by increased perfusion of poorly ventilated portions of the lung; mixed venous hypoxemia

due to drug-induced depression of cardiac output; and shunting through a patent foramen ovale if systemic vasodilation is present.³⁹

The observation that epoprostenol produces acute hemodynamic effects in a substantial proportion of patients³¹ led to its use in long-term therapy. Epoprostenol must be given by continuous intravenous infusion, since it has a short half-life in the circulation and is inactivated by the low pH of the stomach. The drug is delivered with a portable infusion pump attached to a permanent indwelling central venous catheter. In a three-month randomized, prospective trial, the infusion of epoprostenol improved hemodynamic characteristics, exercise tolerance, quality of life, and survival in patients in New York Heart Association functional classes III and IV, as compared with a group of similar patients receiving conventional therapy.²² Beneficial long-term hemodynamic responses have also been reported, although the dosage required to sustain these effects increases with time.⁴⁰ The major adverse effects of long-term therapy with epoprostenol are attributable to the complex delivery system involved; they include pump malfunction, catheter-related infections, and thrombosis.^{22,40,41} Interruption of the infusion may lead to a prompt return of symptoms, which may be life-threatening. Drug-induced side effects are common and include jaw pain, cutaneous erythema, diarrhea, and arthralgias. Short-term infusion of epoprostenol can also produce pulmonary edema in veno-occlusive disease, because of increased pulmonary perfusion in the presence of downstream vascular obstruction.⁴¹ Intermittent therapy with nebulized iloprost, a stable analogue of prostacyclin, may be feasible,⁴² although the long-term effects of this approach have not been evaluated.

Long-term therapy with epoprostenol produces sustained hemodynamic responses even in patients who have little or no response to acute infusion.²² Properties of the drug other than its vasodilator activity, including the inhibition of platelet aggregation and effects on vascular remodeling, may be responsible for these long-term effects. Thus, in contrast to oral vasodilators, which should not be used without evidence of a patient's vasoreactivity to acute challenge, therapy with epoprostenol may be initiated without an acute challenge. Epoprostenol has been used as a primary mode of therapy or as a bridge to transplantation. Several patients have been receiving epoprostenol by continuous infusion for almost 10 years with sustained clinical and hemodynamic benefits.

Transplantation

Lung transplantation and combined heart-lung transplantation have been performed for primary pulmonary hypertension^{43,44}; survival rates after the two procedures are similar.⁴⁵ The limited availability

of hearts for transplantation makes lung transplantation particularly appealing, since the waiting time for a lung transplant is approximately half that for the combined transplant. Even markedly depressed right ventricular function improves considerably with single- or double-lung transplantation.⁴³ One-year survival rates after lung transplantation for primary pulmonary hypertension range from 65 to 70 percent.⁴⁵ Mortality rates after lung transplantation are significantly higher among patients with primary pulmonary hypertension than among those who had other indications for the surgery.⁴⁶ Obliterative bronchiolitis, the major long-term complication of transplantation, also occurs more frequently in patients who are operated on for primary pulmonary hypertension.⁴⁶ Recurrence of primary pulmonary hypertension after transplantation has not been reported.

The timing of transplantation is a difficult challenge. Patients must be sufficiently ill to warrant transplantation, yet not be so ill that surviving surgery seems unlikely. The approach followed at many centers is to initiate epoprostenol therapy and put the patients on the list for transplantation, with periodic assessment of clinical status. Patients whose condition improves substantially with epoprostenol may wish to defer transplantation; those with little or no response to the drug are more likely to require transplantation. Although most patients who have sustained improvement of their condition with epoprostenol maintain this response, sudden deterioration or life-threatening complications can occur. An algorithm for the treatment of patients with primary pulmonary hypertension is shown in Figure 2.

Anticoagulation

Anticoagulation has been recommended as therapy because there is an increased risk of thrombosis and thromboembolism in situ due to sluggish pulmonary blood flow, dilation of the right heart chambers, venous stasis, and the limitations in physical activity imposed by the disease. Both a retrospective analysis⁴⁷ and a small, nonrandomized, prospective study³⁶ suggest that anticoagulation prolongs life. Warfarin is the anticoagulant of choice, in doses adjusted to achieve an international normalized ratio of approximately 2.0.

Other Supportive Measures

Diuretics are useful in reducing excessive preload in patients with right heart failure, particularly when hepatic congestion and ascites are present. Patients with hypoxemia, at rest or exercise-induced, may have symptomatic improvement with supplemental oxygen. Some researchers advocate the use of cardiac glycosides when calcium-channel blockers are given,³⁶ in order to counteract the negative inotropic properties of the calcium-channel blockers.

Mechanical compression of the left side of the

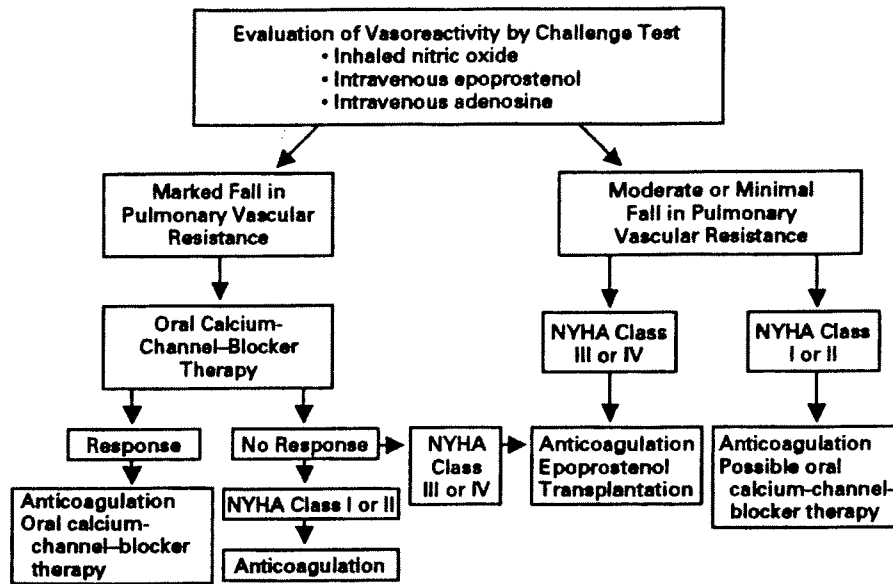


Figure 2. Algorithm for the Management of Primary Pulmonary Hypertension. NYHA denotes New York Heart Association.

heart can result from massive dilation of the right side, leading to underfilling of the left ventricle. The creation of a right-to-left shunt by blade-balloon atrial septostomy has been reported to improve forward output and alleviate refractory right-sided heart failure by providing blood with a low-resistance channel, thereby decompressing the right atrium and improving filling of the left side of the heart.⁴⁸ The objective of this approach is to improve systemic oxygen transport by increasing cardiac output sufficiently to offset the decline in oxygen content that results from the increased admixture of venous blood due to the shunt.

The hemodynamic stresses of pregnancy are poorly tolerated by women with primary pulmonary hypertension, and sudden deterioration, particularly in the immediate postpartum period, can be fatal.⁴⁹ Oral contraceptives are not recommended for birth control, since their use may exacerbate pulmonary hypertension.⁵⁰

SURVIVAL AND NATURAL HISTORY

The median period of survival after diagnosis, as recorded in the NIH registry, is 2.5 years,⁵¹ but patients may survive for lengthy periods, particularly with the use of newer means of treatment. Anticoagulants nearly double the three-year survival rate,⁴⁷ and patients who respond to calcium-channel blockers have a five-year survival rate of 95 percent.³⁶ The five-year survival rate among patients in New York Heart Association classes III and IV who were treated with

epoprostenol (54 percent) was twice that of matched historical control patients (27 percent).⁴¹ Predictors of survival in primary pulmonary hypertension include indicators of the severity of disease as assessed by measurement of hemodynamic characteristics (mean pulmonary-artery pressure, right atrial pressure, cardiac index, and mixed venous oxygen saturation), functional class, exercise tolerance (six-minute walk test), anticoagulant therapy, and the response to vasodilators.^{22,36,51} Most patients succumb to progressive right-sided heart failure, but sudden death accounts for approximately 7 percent of deaths.

FUTURE DIRECTIONS

The study of explanted tissue from patients who undergo transplantation and of genetic material from patients with familial disease may help clarify the molecular mechanisms responsible for primary pulmonary hypertension. Surveillance studies are needed to assess the long-term risks of the use of anorectic drugs and to provide additional insight into risk factors for pulmonary hypertension. Long-term therapy with stable prostacyclin analogues (in inhaled, transdermal, or oral form)⁵² or with inhaled nitric oxide⁵³ could replace therapy dependent on the cumbersome delivery system for epoprostenol currently in use.

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