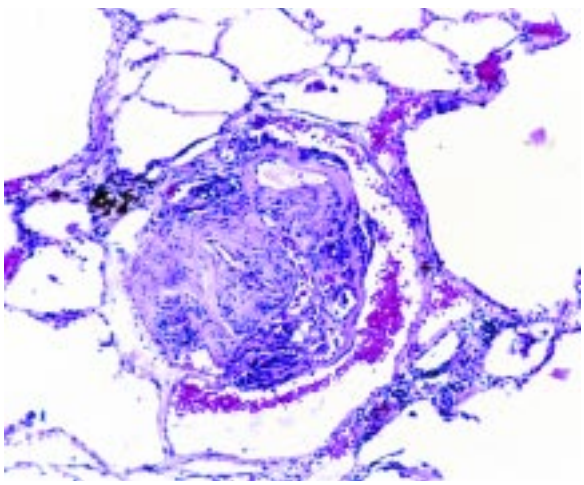
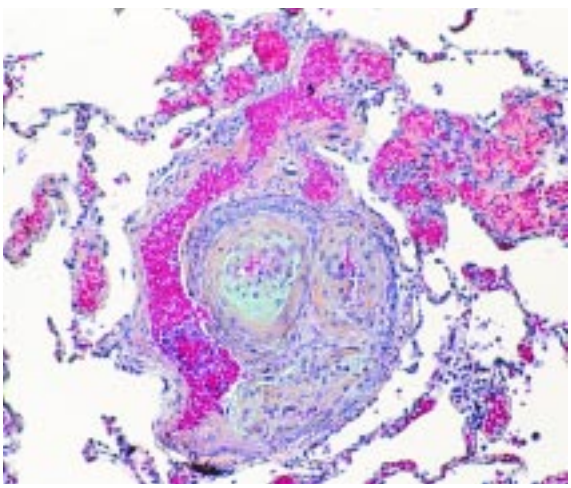
THE CLEVELAND CLINIC FOUNDATION

CLEVELAND CLINIC JOURNAL OF MEDICINE

THE MANAGEMENT OF PULMONARY ARTERIAL HYPERTENSION





SUPPLEMENT EDITOR:
ALEJANDRO C. ARROLIGA, MD
THE CLEVELAND CLINIC

SUPPLEMENT 1 TO VOLUME 70
APRIL 2003

SPECIAL ISSUE

Foreword

ALEJANDRO C. ARROLIGA, MD, EDITOR

A few months ago, we decided, together with the editorial staff of the *Cleveland Clinic Journal of Medicine*, to create a supplement that would summarize recent advances in the diagnosis and management of patients with pulmonary arterial hypertension (PAH), with an emphasis on primary pulmonary hypertension (PPH). Our aim has been to present the latest information in an accessible form that will serve as a useful reference to the physicians who are the first to evaluate patients with PAH—namely, internists, family practitioners, cardiologists, and pulmonologists.

In the supplement's first article, Ghamra and Dweik provide an elegant and state-of-the-art overview of the pathogenesis and epidemiology of PPH. Next, Budev et al profile in the second article the diagnostic workup for the patient who presents with symptoms suggestive of pulmonary hypertension. In the third paper, Gildea et al share an exhaustive review of the current management of patients with PAH. Finally, Mughal et al conclude the supplement with an article summarizing the roles of the various health care providers involved in the complicated care of patients with PAH.

The information presented by this team is of the highest quality; every suggestion presented in these papers is backed up by the best evidence available in the published literature as of the end of 2002.

I want to thank all the members of the Cleveland Clinic's Departments of Pulmonary and Critical Care Medicine, Cardiovascular Medicine, and Rheumatic and Immunologic Disease who participated in the creation of this supplement. I wish to thank as well my friend Julio Sandoval, MD, for critically reviewing, on short notice, the four manuscripts that became this supplement. Finally, Glenn Campbell of the *Cleveland Clinic Journal of Medicine* staff was of very much help during the development of this publication.

This supplement would not have been possible without the economic support of an unrestricted grant from Actelion Pharmaceuticals. The professional staff of Actelion did not participate in the planning of the supplement and were not involved in the writing of any part of it.

I hope that our effort will translate into the earlier diagnosis and better management of patients with PAH.

ALEJANDRO C. ARROLIGA, MD
Section Head, Critical Care Medicine,
Department of Pulmonary
and Critical Care Medicine,
The Cleveland Clinic

On the cover: Two histopathologic photographs of a single plexogenic pulmonary arteriopathy lesion. Photos courtesy of Carol F. Farver, MD.

CLEVELAND CLINIC JOURNAL OF MEDICINE

Supplement 1 to Volume 70, April 2003

THE MANAGEMENT OF PULMONARY ARTERIAL HYPERTENSION

SUPPLEMENT EDITOR:
ALEJANDRO C. ARROLIGA, MD
THE CLEVELAND CLINIC

This publication is supported by an unrestricted educational grant from Actelion Pharmaceuticals US, Inc.

Topics and editors for supplements to the *Cleveland Clinic Journal of Medicine* are determined by the *Journal's* editor-in-chief and staff. Supplement editors are chosen for their expertise in the topics discussed and are responsible for the scientific quality of supplements, including the review process. The *Journal* ensures that supplement editors and authors fully disclose any relationships with industry, including the supplement underwriter. For full guidelines on grant-supported supplements to the *Journal*, go to **www.ccjm.org/pdffiles/guidelines.pdf.**

The *Cleveland Clinic Journal of Medicine* (ISSN 0891-1150) is published 12 times yearly by The Cleveland Clinic Foundation.

Subscription rates: U.S. and possessions: personal $98; institutional $124; single copy/back issue $16. Foreign: $124; single copy/back issue $16. Institutional (multiple-reader rate) applies to libraries, schools, hospitals, and federal, commercial, and private institutions and organizations. Individual subscriptions must be in the names of, billed to, and paid by individuals.

Postmaster address changes: Cleveland Clinic Journal of Medicine, NA32, 9500 Euclid Avenue, Cleveland, OH 44195. Subscription orders, editorial, reprint, and production offices (same address): Phone (216) 444-2661; Fax (216) 444-9385; E-mail, ccjm@ccf.org World Wide Web address: http://www.ccjm.org

Printed in USA.

Primary pulmonary hypertension: An overview of epidemiology and pathogenesis

ZIAD W. GHAMRA, MD, AND RAED A. DWEIK, MD

ABSTRACT

Pulmonary arterial hypertension (PAH) refers to a group of diseases characterized by high pulmonary artery pressure of unknown mechanism. Primary pulmonary hypertension (PPH) is the idiopathic subset of PAH that affects a mostly young population and is more common in females than in males. A familial form of PPH accounts for about 6% of cases, and its autosomal dominant gene was recently identified. Pulmonary arterial hypertension is histologically characterized by endothelial and smooth muscle cell proliferation, medial hypertrophy, and thrombosis in situ. The pathogenesis of PAH remains unclear. Elevated pulmonary vascular resistance seems to result from an imbalance between locally produced vasodilators and vasoconstrictors, in addition to vascular wall remodeling. Nitric oxide, a locally produced selective pulmonary vasodilator, appears to play a central role in the pathobiology of PAH.

From the Department of Pulmonary and Critical Care Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio.

Address: Raed A. Dweik, MD, Department of Pulmonary and Critical Care Medicine, A90, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail: dweikr@ccf.org.

Disclosure: Both authors have indicated that they have no commercial affiliations or interests that pose a potential conflict of interest with this article.

Better understanding of the pathogenesis of primary pulmonary hypertension (PPH) over the last decade has led to new treatments that have changed the course of this once uniformly fatal condition. This progress is especially welcome because PPH affects a predominantly young and productive population. This article reviews recent advances in our understanding of the pathogenesis, epidemiology, and genetics of PPH.

DEFINITION AND CLASSIFICATION

Primary pulmonary hypertension is defined by an elevation in mean pulmonary artery pressure to greater than 25 mm Hg at rest or greater than 30 mm Hg during exercise in the absence of an identifiable etiology. In 1998 the second World Health Organization (WHO) conference on pulmonary hypertension[1] classified PPH with other pulmonary hypertensive conditions under the grouping of *pulmonary arterial hypertension* (PAH). Under this so-called Evian classification (the WHO conference was held in Evian, France), which was based on similarities in clinical features, PAH refers to a vasculopathy of unknown mechanism that involves the small muscular arteries and arterioles. Pulmonary arterial hypertension can be associated with known diseases, such as connective tissue diseases and human immunodeficiency virus (HIV) infection, in addition to classic idiopathic PPH **(Table 1)**.

HISTOPATHOLOGY

The hypertensive pulmonary arteriopathy seen in patients with PPH affects the muscular arteries and

arterioles and probably represents a combination of injury and repair. Several histopathologic patterns can be seen, although none is pathognomonic, since the diagnosis of PPH still relies on the exclusion of secondary causes.[2,3]

Plexogenic pulmonary arteriopathy (Figure 1) is the most common lesion seen in PPH. It is characterized by medial hypertrophy, fibrotic intimal lesions that may comprise organized thrombi, and destructive lesions involving the entire arterial wall. **Thrombotic pulmonary arteriopathy** is defined by the presence of organized mural thrombi resulting from thrombosis in situ in the setting of an intact arterial wall and a nondilated vessel. These two lesion types, though distinct histologically, appear to be the product of the same disease process, since different members of kindreds with familial PPH had evidence of both lesions.[4]

Isolated medial hypertrophy, the third type of histopathologic lesion in PPH, consists of a pattern of increased thickness of the medial smooth muscle wall, duplication of the elastic laminae in muscular arteries, and muscularization of the arterioles. This rare pattern may actually precede the formation of the plexogenic lesions and is thought to be reversible with treatment.[5]

TABLE 1
The 1998 WHO Evian classification of pulmonary hypertension

1. Pulmonary arterial hypertension
- 1.1 Primary pulmonary hypertension
  - a. Sporadic
  - b. Familial
- 1.2 Related to:
  - a. Collagen vascular disease
  - b. Congenital systemic to pulmonary shunts
  - c. Portal hypertension
  - d. HIV infection
  - e. Drugs/toxins (anorexigens or others)
  - f. Persistent pulmonary hypertension of the newborn
  - g. Other

2. Pulmonary venous hypertension
- 2.1 Left-sided atrial or ventricular heart disease
- 2.2 Left-sided valvular heart disease
- 2.3 Extrinsic compression of central pulmonary veins
  - a. Fibrosing mediastinitis
  - b. Adenopathy/tumors
- 2.4 Pulmonary veno-occlusive disease
- 2.5 Other

3. Pulmonary hypertension associated with disorders of the respiratory system or hypoxemia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Sleep-disordered breathing
- 3.4 Alveolar hypoventilation disorders
- 3.5 Chronic exposure to high altitude
- 3.6 Neonatal lung disease
- 3.7 Alveolar-capillary dysplasia
- 3.8 Other

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
- 4.1 Thromboembolic obstruction of proximal pulmonary arteries
- 4.2 Obstruction of distal pulmonary arteries
  - a. Pulmonary embolism (thrombus, tumor, ova, parasites, foreign matter)
  - b. In situ thrombosis
  - c. Sickle cell disease

5. Pulmonary hypertension due to disorders directly affecting the pulmonary vasculature
- 5.1 Inflammatory
  - a. Schistosomiasis
  - b. Sarcoidosis
  - c. Other
- 5.2 Pulmonary capillary hemangiomatosis

Adapted from reference 1 with permission of the World Health Organization.

■ EPIDEMIOLOGY

A few case series of elevated pulmonary artery pressures in otherwise healthy young people in the 1950s and 1960s,[6,7] along with the epidemic of anorexigenic-associated PPH in Europe, led to the first WHO conference on PPH in 1973. As part of an ensuing international effort to better understand this rare condition, the National Heart, Lung, and Blood Institute's Division of Lung Disease in 1981 initiated the national Primary Pulmonary Hypertension Patient Registry. The registry prospectively enrolled 187 patients from 32 referral centers nationwide through 1985.[8] These patients' demographic characteristics constitute the best available data to date on the epidemiology of PPH.

The mean age of this population was 36.4 years (± 15 SD; range 1–81). A 1.7:1.0 female-to-male preponderance was noted. Nearly one tenth of patients were older than 60 years of age. No racial predilection was found.

Subsequent retrospective reports from France,[9] Israel,[10] and Japan[11] found comparable mean ages among samples of patients with PPH (39.0, 42.8, and 41.8 years, respectively) and similar female-to-male ratios, indicating an apparent worldwide female preponderance.

No studies on the incidence of PPH have yet been performed, but the incidence has been estimated at 1 to 2 cases per 1 million inhabitants per

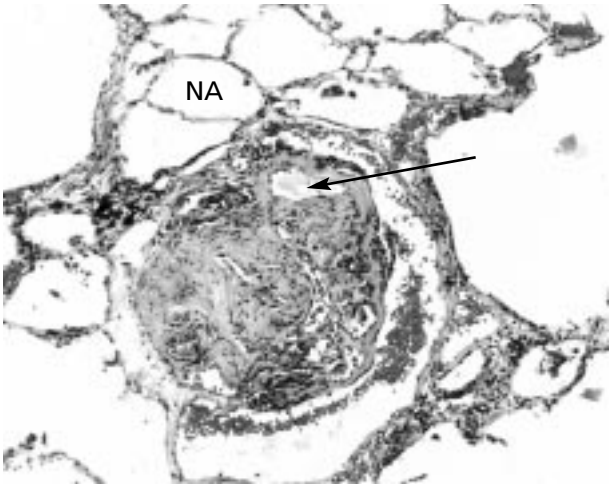


Figure 1. Histopathologic photograph of a plexogenic pulmonary arteriopathy lesion surrounded by normal alveoli (NA). The arrow points to a newly formed vascular lumen. Color versions of this photograph and another photograph of this lesion taken with a different stain appear on the cover of this supplement. Photo courtesy of Carol F. Farver, MD.

year.[8] Considering the rarity and subtle presentation of this disease, underdiagnosis and underreporting are likely widespread, making calculation of a true incidence difficult.

Familial PPH

In the national registry for PPH,[8] 12 (6%) of the 187 enrolled patients had a first-degree relative affected by the same disease process. Familial PPH appears to be inherited as an autosomal dominant trait with a variable but low gene penetrance, with some individuals inheriting the trait without exhibiting the phenotype.[12] Genetic anticipation further affects the gene penetrance, with subsequent generations developing PPH at an earlier age.[13] Interestingly, 160 (57%) of 282 children born to parents who were carriers of the gene for familial PPH were female, suggesting either a selective wastage of male fetuses or a preferential fertilization by an X over a Y male gamete.[13]

In 1997, the gene for familial PPH was mapped to chromosome 2q31–32.[14,15] In 2000, the bone morphogenetic protein receptor type II gene (*BMPR2*) was identified as the actual gene for familial PPH and its product was recognized as a transforming growth factor beta receptor, suggesting a role for this receptor in maintaining pulmonary vascular integrity.[16,17] In fact, mutations in *BMPR2* were also found in 13 (26%) of 50 patients with sporadic or nonfamilial PPH in one series,[18] which suggests that it may soon be possible to identify individuals at risk for PPH.

These landmark discoveries in the genetics of familial PPH have opened the way to a better understanding of the pathogenesis of PPH and may have important therapeutic implications as more of the molecular pathways are revealed.

■ PATHOGENESIS

Pulmonary arterial hypertension, although associated with some disease entities, has a still-unknown mechanism that probably results from multiple noxious stimuli targeting a predisposed pulmonary vasculature. The most obvious predisposing factors are the mutations in the *BMPR2* gene[16,17] that result in familial PPH and in some cases of sporadic PPH, as discussed above.[18]

The epidemic of PAH that developed in users of appetite-suppressant drugs,[19,20] probably through these drugs' serotonergic effects,[20,21] is an example of a noxious stimulus causing PAH. However, because only 0.1% of aminorex users were affected, possible polymorphism at the level of the vascular smooth muscle serotonin transporter was recently hypothesized as a predisposing factor for PPH in these individuals.[21] The mechanism of injury leading to PAH associated with HIV infection is less clear,[22] although some evidence points to stimulation of endothelial cell growth by infected T lymphocytes.[23] Pulmonary arterial hypertension is also associated with connective tissue diseases without any obvious pathophysiologic link.[24] Some have proposed the possibility of an autoimmune injury leading to the vasculopathy.[25,26] Deficiency of thyroid hormone, either through a shared autoimmune insult to the thyroid gland and the pulmonary vasculature, or through loss of the thyroid hormone's vasomotor role, has also been associated with PPH.[27] Moreover, the paracrine actions of the vascular endothelium appear dysfunctional in PAH, resulting in abnormal proliferation of vascular smooth muscle and endothelial cells, which may contribute to the increased pulmonary vascular resistance observed in this disease.

Many advances have been made in unraveling the pathogenesis of PAH. In many instances, however, any cause-and-effect explanation for the observed abnormalities remains blurred, as most abnormalities are found in advanced stages of pulmonary hypertension.

Endothelial dysfunction/vasoconstriction

An injured endothelium probably represents the response to a variety of stimuli that lead to secondary pulmonary hypertension, but the endothelial dysfunction seen in PPH seems to be idiopathic, or of yet unknown etiology. It remains uncertain whether this constitutes one of the triggers for the vasculopathy of PPH or whether it is in response to a variety of noxious mechanical and chemical stimuli. The endothelial malfunction is manifested by an imbalance between locally produced vasoconstrictors and vasodilators, resulting in abnormal vascular tone. Of those local mediators, nitric oxide, prostacyclin, and endothelin-1 are among the best studied and carry several therapeutic implications.

Nitric oxide. The endothelium-derived relaxing factor nitric oxide (NO) has been shown to play a pivotal role in the pathobiology of PPH.[28–33] Nitric oxide is a potent pulmonary vasodilator that is produced locally in the lung and has profound effects on smooth muscle relaxation and proliferation. Normal pulmonary vascular tone is maintained in part by local production of the vasodilator NO, and NO exerts an inhibitory effect on vascular smooth muscle cell proliferation and migration.[34] Anatomic sources of NO in the lung include the pulmonary circulation, the lower airways, and the upper airways and paranasal sinuses.[35]

Nitric oxide is endogenously synthesized by NO synthases, which convert L-arginine to L-citrulline and NO in the presence of oxygen and several cofactors.[36,37] Three NO synthases (types I, II, and III) have been identified and are widely expressed in various tissues, including the lungs.[38] Nitric oxide also can be detected in the exhaled breath of humans.[35,39]

Once produced, NO is freely diffusible and enters pulmonary smooth muscle cells to activate soluble guanylate cyclase and produce guanosine 3′,5′-cyclic monophosphate (cGMP).[36] Increased cGMP activates a kinase that phosphorylates a calcium-dependent potassium channel, leading to hyperpolarization and pulmonary vascular smooth muscle relaxation. The close proximity of the airways to the blood vessels allows the NO produced in high levels in the upper[40] and lower airways by NO synthase II[35] to affect the pulmonary vascular tone in concert with the low NO levels produced by NO synthase III in the vascular endothelium. As soon as this potent vasodilator's job is done in the lung, it binds to hemoglobin and has virtually no effect on systemic hemodynamics, making it a truly selective pulmonary vasodilator.

Interestingly, patients with PPH have low levels of NO in their exhaled breath.[30] In fact, the severity of pulmonary hypertension correlates inversely with NO levels estimated by measurement of NO reaction products in bronchoalveolar lavage fluid **(Figure 2)**.[30] Although this is a more complex issue than simple lack of a vasodilator, replacement of NO seems to work well in treating the problem.[41] Exogenous administration of NO gas by inhalation is a highly effective and specific therapy for PPH.[33,41,42] Although cost and unresolved technical difficulties in the delivery of inhaled NO have prevented its widespread use to date,[41] recent evidence suggests that other therapies for PPH may exert their benefits at least partially through endogenous NO.[28,31] Nitric oxide levels were found to be increased in the exhaled breath of patients with PPH after therapeutic infusion of epoprostenol, a prostacyclin analogue.[31]

Endothelin-1 is a peptide produced by the vascular endothelium that has potent vasoconstrictive and proliferative paracrine actions on vascular smooth muscle cells.[43] The pulmonary circulation plays an important role in the production and clearance of endothelin-1, and this physiologic balance is reflected in circulating levels of endothelin-1.[44] Patients with pulmonary hypertension, PPH in particular, have an increased expression of endothelin-1 in pulmonary vascular endothelial cells.[45] Similarly, serum endothelin-1 levels are increased in patients with pulmonary hypertension.[46]

Prostacyclin. The endothelium also produces prostacyclin (PGI_2) by cyclooxygenase metabolism of arachidonic acid. Prostacyclin causes vasodilation throughout the human circulation[47] and is an inhibitor of platelet aggregation by its action on platelet adenylate cyclase.[48]

The final enzyme in the production of PGI_2 is prostacyclin synthase. Transgenic mice overexpressing this enzyme in their respiratory epithelial cells are protected against the development of hypoxic pulmonary hypertension,[49] and the remodeled pulmonary vasculature in lung tissue obtained from patients with severe PPH expresses low levels of prostacyclin synthase when compared with normal lung tissue.[50] In addition, a PGI_2 metabolite, 2,3-dinor-6-keto-PGF, is diminished in the urine of patients with pulmonary hypertension, further underscoring the role of endothelial dysfunction in the pathobiology of PPH.[51]

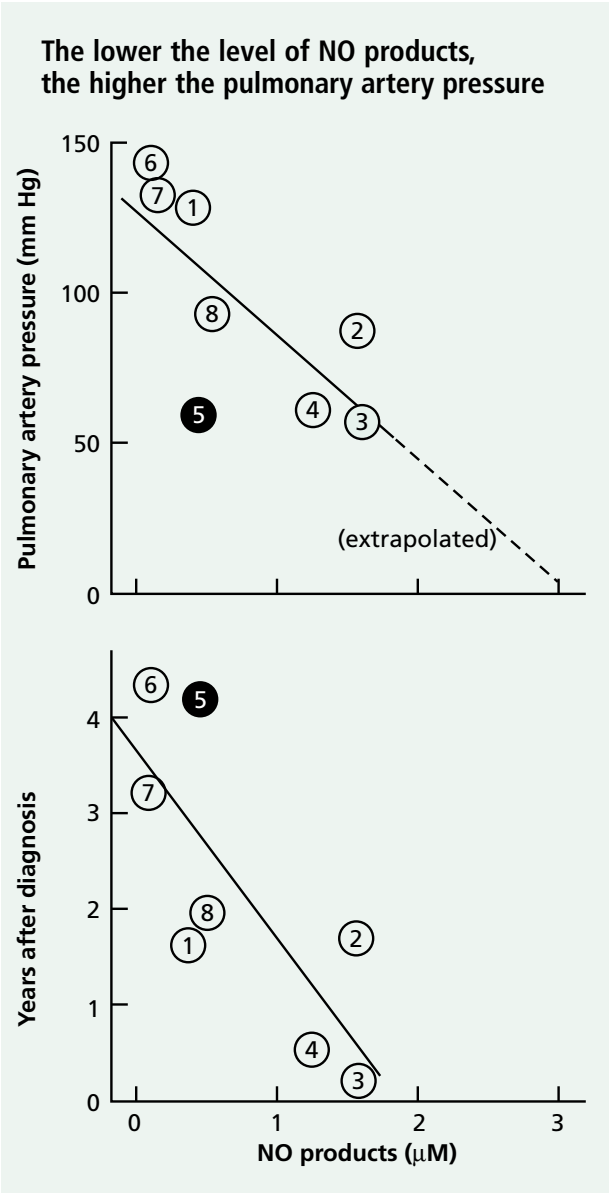


Figure 2. Relationship of reaction products of nitric oxide (NO) in bronchoalveolar lavage fluid to pulmonary artery pressures (top) and years after diagnosis of PPH (bottom). The circles represent individual patients. The filled circle represents a patient with familial PPH who died during the study. Reprinted, with permission, from reference 30. © American Lung Association

Remodeling

In addition to the pulmonary vasoconstriction that results from dysregulation of the local endothelial mediators as discussed above, pulmonary vascular remodeling seems to play a major role in the increased vascular resistance seen in PPH. An abnormal proliferation of endothelial cells occurs in the irreversible plexogenic lesion.[52] These proliferating endothelial cells are monoclonal in origin, raising the possibility that a random somatic mutation may be one of the initial steps leading to sporadic PPH.[53] The endothelial cells express angiogenic factors (eg, vascular endothelial growth factor), which suggests a role for them in the disordered angiogenesis that may be part of the plexiform lesion formation.[54] In addition, pulmonary vascular smooth muscle cells that normally have a low rate of multiplication undergo proliferation and hypertrophy. Those smooth cell changes arise from the loss of the antimitogenic endothelial substances (eg, PGI_2 and NO)[55,56] and an increase in mitogenic substances (eg, endothelin-1).[57] At the same level, the growth-inhibitory effect of transforming growth factor beta on vascular smooth cells is lost, which may explain the molecular mechanism of the mutation in familial PPH.[18,58]

Other stimuli arise from locally activated platelets that release thromboxane A_2 and serotonin, which act as growth-promoting substances on the vascular smooth muscle cells.[52,59,60] In fact, elevated blood levels of serotonin are found in patients with PPH,[61] perhaps because of an abnormality in the platelet storage pool that is the main source of serotonin in the human circulation.[62] Pulmonary vascular smooth cell hyperplasia also correlates with polymorphism and overexpression of the serotonin transporter, which may constitute an additional factor in an individual's genetic susceptibility to developing PPH.[21,63] On the other hand, the pulmonary artery smooth muscle cells in PPH appear to be in an abnormally depolarized state.[64] This abnormal resting potential results in a heightened state of vasoconstriction secondary to increased levels of cytosolic Ca2+ and seems to relate to a primary dysfunction or downregulation of the voltage-gated K+ channels.[64,65]

In addition to smooth muscle cell proliferation, an increase in extracellular matrix deposition contributes to the medial hypertrophy in PAH.[66] The extracellular matrix is remodeled through a dynamic process of matrix protein degradation and synthesis triggered by the high flow and pressure in the pulmonary vasculature, resulting in the obliterative changes seen in the pulmonary arteries.[66] A perivascular inflammatory cell infiltrate observed in the plexogenic lesion indicates that cytokines may also play a role in its development.[52]

Thrombosis

In a large retrospective series that looked at lung tissue obtained from autopsy specimens of patients with PPH,[67] 22 of 56 pathologic specimens showed evidence of thrombi confined to the small muscular arteries. This was atypical for the classic appearance of venous thromboembolism, and the concept of thrombosis in situ in PPH emerged.

Pulmonary arterial hypertension seems to be associated with a prothrombotic milieu that is a consequence rather than a cause of the vasculopathy, although this remains debatable. The determinants of this increased propensity for thrombosis arise at the level of the microvasculature, where the dysfunctional endothelium loses the anticoagulant properties that usually prevent intravascular clotting of blood material.[68] Instead, the procoagulation mediators that are usually inhibited under physiologic conditions seem to be activated. In fact, blood thrombin activity is increased in patients with pulmonary hypertension, indicating activation of intravascular coagulation,[69] whereas soluble thrombomodulin, a cell membrane protein that acts as an important site of thrombin binding and coagulation inactivation, is decreased.[70] In addition, PGI_2 and NO, both inhibitors of platelet aggregation, are decreased at the level of the injured endothelial cell, as discussed above. Circulating platelets in patients with PAH seem to be in a continuous state of activation[51] and contribute to the prothrombotic milieu by aggregating at the level of the injured endothelial cells.[71]

■ REFERENCES

1. **Rich S, ed.** Primary pulmonary hypertension: executive summary from the World Symposium on Primary Pulmonary Hypertension. Geneva: World Health Organization, 1998.
2. **Pietra GG, Edwards WD, Kay M, et al.** Histopathology of primary pulmonary hypertension. A qualitative and quantitative study of pulmonary blood vessels from 58 patients in the National Heart, Lung, and Blood Institute Primary Pulmonary Hypertension Registry. Circulation 1989; 80:1198–1206.
3. **Pietra GG.** Histopathology of primary pulmonary hypertension. Chest 1994; 105(2 suppl):2S–6S.
4. **Loyd JE, Atkinson JB, Pietra GG, et al.** Heterogeneity of pathologic lesions in familial primary pulmonary hypertension. Am Rev Respir Dis 1988; 138:952–957.
5. **Bjornsson J, Edwards WD, Kay JM, et al.** Primary pulmonary hypertension: a histopathologic study of 80 cases. Mayo Clin Proc 1985; 60:16–25.
6. **Dresdale DT, Schultz M, Michtom RJ.** Primary pulmonary hypertension: clinical and hemodynamic study. Am J Med 1951; 11:686–694.
7. **Wood P.** Pulmonary hypertension with special reference to the vasoconstrictive factor. Br Heart J 1959; 21:557–570.
8. **Rich S, Dantzker DR, Ayres SM, et al.** Primary pulmonary hypertension: a national prospective study. Ann Intern Med 1987; 107:216–223.
9. **Brenot F.** Primary pulmonary hypertension. Case series from France. Chest 1994; 105(suppl):33S–36S.
10. **Appelbaum L, Yigla M, Bendayan D, et al.** Primary pulmonary hypertension in Israel: a national survey. Chest 2001; 119:1801–1806.
11. **Kuriyama T.** Epidemiology of primary pulmonary hypertension in Japan. Nippon Rinsho 2001; 59:1047–1052.
12. **Loyd JE, Primm RK, Newman JH.** Familial primary pulmonary hypertension: clinical patterns. Am Rev Respir Dis 1984; 129:194–197.
13. **Loyd JE, Butler MG, Foroud TM, et al.** Genetic anticipation and abnormal gender ratio at birth in familial primary pulmonary hypertension. Am J Respir Crit Care Med 1995; 152:93–97.
14. **Nichols WC, Koller DL, Slovis B, et al.** Localization of the gene for familial primary pulmonary hypertension to chromosome 2q31-32. Nat Genet 1997; 15:277–280.
15. **Morse JH, Jones AC, Barst RJ, et al.** Mapping of familial primary pulmonary hypertension locus (PPH1) to chromosome 2q31-32. Circulation 1997; 95:2603–2606.
16. **Deng Z, Morse JH, Slager SL, et al.** Familial primary pulmonary hypertension (gene PPH1) is caused by mutations in the bone morphogenetic protein receptor-II gene. Am J Hum Genet 2000; 67:737–744.
17. **Lane KB, Machado RD, Pauciulo MW, et al.** Heterozygous germline mutations in BMPR2, encoding a TGF-β receptor, cause familial primary pulmonary hypertension. The International PPH Consortium. Nat Genet 2000; 26:81–84.
18. **Thomson JR, Machado RD, Pauciulo MW, et al.** Sporadic primary pulmonary hypertension is associated with germline mutations of the gene encoding BMPR-II, a receptor member of the TGF-β family. J Med Genet 2000; 37:741–745.
19. **Gurtner HP.** Pulmonary hypertension, "plexogenic pulmonary arteriopathy" and the appetite depressant drug aminorex: post or propter? Bull Physiopathol Res 1979; 15:897–923.
20. **Rothman RB, Ayestas MA, Dersch CM, Baumann MH.** Aminorex, fenfluramine, and chlorphentermine are serotonin transporter substrates. Implications for primary pulmonary hypertension. Circulation 1999; 100:869–875.
21. **Eddahibi S, Humbert M, Fadel E, et al.** Hyperplasia of pulmonary artery smooth muscle cells is causally related to overexpression of the serotonin transporter in primary pulmonary hypertension. Chest 2002; 121(3 suppl):97S–98S.
22. **Mehta NJ, Khan IA, Mehta RN, Sepkowitz DA.** HIV-related pulmonary hypertension: analytic review of 131 cases. Chest 2000; 118:1133–1141.
23. **Ascheri G, Hohendl C, Schatz O, et al.** Infection with human immunodeficiency virus-1 increases expression of vascular endothelial cell growth factor in T cells: implications for acquired immunodeficiency syndrome–associated vasculopathy. Blood 1999; 93:4232–4241.
24. **Gurubhagavatula I, Palevsky HI.** Pulmonary hypertension in systemic autoimmune disease. Rheum Dis Clin North Am 1997; 23:365–394.
25. **Yanai-Landau H, Amital H, Bar-Dayan Y, et al.** Autoimmune aspects of primary pulmonary hypertension. Pathobiology 1995; 63:71–75.
26. **Barst RJ, Flaster ER, Menon A, et al.** Evidence for the association of unexplained pulmonary hypertension in children with the major histocompatibility complex. Circulation 1992; 85:249–258.
27. **Curnock AL, Dweik RA, Higgins BH, et al.** High prevalence of hypothyroidism in patients with primary pulmonary hypertension. Am J Med Sci 1999; 318:289–292.
28. **Dweik RA.** Pulmonary hypertension and the search for the selective pulmonary vasodilator. Lancet 2002; 360:886.
29. **Dweik RA.** The promise and reality of nitric oxide in the diagnosis

and treatment of lung disease. Cleve Clin J Med 2001; 68:486–493.
30. **Kaneko FT, Arroliga AC, Dweik RA, et al.** Biochemical reaction products of nitric oxide as quantitative markers of primary pulmonary hypertension. Am J Respir Crit Care Med 1998; 158:917–923.
31. **Ozkan M, Dweik RA, Laskowski D, et al.** High levels of nitric oxide in individuals with pulmonary hypertension receiving epoprostenol therapy. Lung 2001; 179:233–243.
32. **Ozkan M, Dweik RA, Ahmad M.** Drug-induced lung disease. Cleve Clin J Med 2001; 68:782–795.
33. **Arroliga AC, Dweik RA, Kaneko FJ, Erzurum SC.** Primary pulmonary hypertension: update on pathogenesis and novel therapies. Cleve Clin J Med 2000; 67:175–190.
34. **Dweik RA, Erzurum SC.** Effects of nitric oxide and cyclic GMP on smooth muscle proliferation. In: Moss J, ed. LAM and Other Diseases Characterized by Smooth Muscle Proliferation (Lung Biology in Health and Disease series). New York: Marcel Dekker, 1999; 131:333–349.
35. **Dweik RA, Laskowski D, Abu-Soud HM, et al.** Nitric oxide synthesis in the lung. Regulation by oxygen through a kinetic mechanism. J Clin Invest 1998; 101:660–666.
36. **Moncada S, Higgs A.** The L-arginine–nitric oxide pathway. N Engl J Med 1993; 329:2002–2012.
37. **Nathan C, Xie QW.** Nitric oxide synthases: roles, tolls, and controls. Cell 1994; 78:915–918.
38. **Kobzik L, Bredt DS, Lowenstein CJ, et al.** Nitric oxide synthase in human and rat lung: immunocytochemical and histochemical localization. Am J Respir Cell Mol Biol 1993; 9:371–377.
39. **Gustafsson LE, Leone AM, Persson MG, et al.** Endogenous nitric oxide is present in the exhaled air of rabbits, guinea pigs and humans. Biochem Biophys Res Commun 1991; 181:852–857.
40. **Lundberg JO, Farkas-Szallasi T, Weitzberg E, et al.** High nitric oxide production in human paranasal sinuses. Nat Med 1995; 1:370–373.
41. **Channick RN, Newhart JW, Johnson FW, et al.** Pulsed delivery of inhaled nitric oxide to patients with primary pulmonary hypertension: an ambulatory delivery system and initial clinical tests. Chest 1996; 109:1545–1549.
42. **Rubin LJ.** Primary pulmonary hypertension. N Engl J Med 1997; 336:111–117.
43. **Yanagisawa M, Kurihara H, Kimura S, et al.** A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 1988; 332:411–415.
44. **Dupuis J, Duncan JS, Cernacek P, Gosselin G.** Human pulmonary circulation is an important site for both clearance and production of endothelin-1. Circulation 1996; 94:1578–1584.
45. **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.
46. **Stewart DJ, Levy RD, Cernacek P, Langleben D.** Increased plasma endothelin-1 in pulmonary hypertension: marker or mediator of disease? Ann Intern Med 1991; 114:464–469.
47. **Moncada S, Vane JR.** Pharmacology and endogenous roles of prostaglandin endoperoxides, thromboxane A2, and prostacyclin. Pharmacol Rev 1979; 30:293–331.
48. **Gorman RR, Bunting S, Miller OV.** Modulation of human platelet adenylate cyclase by prostacyclin. Prostaglandins 1977; 273:767–768.
49. **Geraci MW, Gao B, Shepherd DC, et al.** Pulmonary prostacyclin synthase overexpression in transgenic mice protects against development of hypoxic pulmonary hypertension. J Clin Invest 1999; 103:1509–1515.
50. **Tuder RM, Cool CD, Geraci MW, et al.** Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. Am J Respir Crit Care Med 1999; 159:1925–1932.
51. **Christman BW, McPherson CD, Newman JH, et al.** An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. N Engl J Med 1992; 327:70–75.
52. **Tuder RM, Groves B, Badesh DB, Voelkel NF.** Exuberant endothelial cell growth and elements of inflammation are present in plexiform lesions of pulmonary hypertension. Am J Pathol 1994; 144:275–285.
53. **Lee SD, Shroyer KR, Markham NE, et al.** Monoclonal endothelial cell proliferation is present in primary but not secondary pulmonary hypertension. J Clin Invest 1998; 101:927–934.
54. **Tuder RM, Chacon M, Wang J, et al.** Expression of angiogenesis-related molecules in plexiform lesions in severe pulmonary hypertension: evidence for a process of disordered angiogenesis. J Pathol 2001; 195:367–374.
55. **Newby AC, Southgate KM, Assender JW.** Inhibition of vascular smooth muscle cell proliferation by endothelium-dependent vasodilators. Herz 1992; 17:291–299.
56. **Pukac LA, Ottlinger ME, Karnovsky MJ.** Heparin suppresses specific second messenger pathways for protooncogene expression in rat vascular smooth muscle cells. J Biol Chem 1992; 267:3707–3711.
57. **Hirata Y, Takagi Y, Fukunda Y, Marumo F.** Endothelin is a potent mitogen for rat vascular smooth muscle cells. Atherosclerosis 1989; 78:225–228.
58. **Morell NW, Yang X, Upton PD, et al.** Altered growth responses of pulmonary artery smooth muscle cells from patients with primary pulmonary hypertension to transforming growth factor-β1 and bone morphogenetic proteins. Circulation 2001; 104:790–795.
59. **Lee S, Wang W, Lanzillo J, Fanburg B.** Serotonin produces both hyperplasia and hypertrophy of bovine pulmonary artery smooth muscle cells in culture. Am J Physiol 1994; 266(1 Pt 1):L46–L52.
60. **Fanburg B, Sheu-Ling L.** A new role for an old molecule: serotonin as a mitogen. Am J Physiol 1997; 272(1 Pt 1):L795–L806.
61. **Herve P, Launay J-M, Scrobohaci M-L, et al.** Increased plasma serotonin in primary pulmonary hypertension. Am J Med 1995; 99:249–254.
62. **Herve P, Drouet L, Dosquet C, et al.** Primary pulmonary hypertension in a patient with a familial platelet storage pool disease: role of serotonin. Am J Med 1990; 89:117–120.
63. **Eddahibi S, Humbert M, Fadel E, et al.** Serotonin transporter overexpression is responsible for pulmonary artery smooth muscle hyperplasia in primary pulmonary hypertension. J Clin Invest 2001; 108:1141–1150.
64. **Yuan JX, Aldinger AM, Juhaszova M, et al.** Dysfunctional voltage-gated K+ channels in pulmonary artery smooth muscle cells of patients with primary pulmonary hypertension. Circulation 1998; 98:1400–1406.
65. **Yuan XJ, Wang J, Juhaszova M, et al.** Attenuated K+ channel gene transcription in primary pulmonary hypertension. Lancet 1998; 351:726–727.
66. **Rabinovitch M.** Pathobiology of pulmonary arterial hypertension. Extracellular matrix. Clin Chest Med 2001; 22:433–449.
67. **Fuster V, Steele PM, Edwards WD, et al.** Primary pulmonary hypertension: natural history and the importance of thrombosis. Circulation 1984; 70:580–587.
68. **Farber HW, Loscalzo J.** Prothrombotic mechanisms in primary pulmonary hypertension. J Lab Clin Med 1999; 134:561–566.
69. **Chaouat A, Weitzenblum E, Higenbottam T.** The role of thrombosis in severe pulmonary hypertension. Eur Respir J 1996; 9:356–363.
70. **Welsh CH, Hassell KL, Badesch DB, et al.** Coagulation and fibrinolytic profiles in patients with severe pulmonary hypertension. Chest 1996; 110:710–717.
71. **Lopes AA, Maeda NY, Almeida A, et al.** Circulating platelet aggregates indicative of in vivo platelet activation in pulmonary hypertension. Angiology 1993; 44:701–706.

Diagnosis and evaluation of pulmonary hypertension

MARIE M. BUDEV, DO, MPH; ALEJANDRO C. ARROLIGA, MD; AND CONSTANCE A. JENNINGS, MD

ABSTRACT

The diagnosis of pulmonary hypertension (PH) relies on a high index of suspicion. In patients with symptoms or chest radiographic findings suggestive of PH, a detailed history and physical examination followed by early assessment with a transthoracic echocardiogram, ventilation-perfusion scanning, chest computed tomography, pulmonary function testing, and nocturnal oximetry screening can provide valuable information about etiology and severity. Right heart catheterization should follow in patients who are symptomatic or who demonstrate moderate to severe PH by echocardiography and are candidates for treatment. Patients at risk for developing PH should undergo serial echocardiography and pulmonary function testing to assess for disease development and progression. Genetic testing is not currently recommended in the routine evaluation of patients with a diagnosis of primary pulmonary hypertension.

Pulmonary hypertension (PH) often presents in an insidious manner, requiring a high index of suspicion by the clinician making the diagnosis. In many cases the diagnosis may be delayed because of the nonspecificity of symptoms and the relative rarity of PH. The National Institutes of Health's Primary Pulmonary Hypertension Patient Registry noted that the mean interval from the onset of symptoms to diagnosis is about 2 years.[1] Patient evaluation for PH should be directed to establish the etiology and the severity of the disease **(Table 1, Figure 1)**, both of which will influence the selection of treatment strategies. This article reviews the diagnostic workup and evaluation for patients with known or suspected PH and the role of genetic testing and screening.

From the Department of Pulmonary and Critical Care Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio.

Address: Constance A. Jennings, MD, Department of Pulmonary and Critical Care Medicine, A90, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail: jenninc@ccf.org.

Disclosure: All of the authors have indicated that they have no commercial affiliations or interests that pose a potential conflict of interest with this article.

HISTORY-TAKING: THOROUGHNESS IS KEY

The symptoms of PH are nonspecific and often are difficult to differentiate from those of other pulmonary or cardiovascular diseases, so a thorough clinical history should be taken for all patients with suspected PH. Dyspnea on exertion is by far the most common complaint. Up to one third of patients with PH and normal coronary arteries report chest pain, which probably is attributable to increased myocardial oxygen demand caused by elevated right ventricular wall stress from dilation or hypertrophy or by reduced oxygen supply from decreased myocardial blood flow.[2] Syncope or presyncope may occur in one third of patients with PH owing to a reduced, fixed cardiac output, atrial or ventricular arrhythmias, or right ventricular ischemia.[3] Syncope is an ominous sign and usually indicates severe PH with marked elevation of right heart pressures. Rarely, patients may complain of hoarseness (Ortner syndrome) attributable to impingement of the left recurrent laryngeal nerve between the aorta and a dilated left pulmonary artery.[4]

The composite effect of elevated pulmonary

TABLE 1
Hemodynamic classification of pulmonary hypertension

Precapillary pulmonary hypertension
Primary pulmonary hypertension
Pulmonary arterial hypertension due to collagen vascular disease
Eisenmenger syndrome
Portopulmonary hypertension
HIV-associated pulmonary arterial hypertension
Pulmonary arterial hypertension due to appetite suppressants
Pulmonary hypertension induced by high altitude, obstructive sleep apnea, or hypoxia
Thromboembolic pulmonary hypertension
Postcapillary pulmonary hypertension
Left ventricular systolic or diastolic dysfunction
Aortic stenosis or regurgitation
Primary mitral regurgitation
Mitral valve obstruction
Pulmonary veno-occlusive disease
Mixed pulmonary hypertension
Chronic primary systolic left ventricular failure
Aortic stenosis
Chronic aortic and primary mitral regurgitation
Mitral valve obstruction
Selective or nonselective increases in pulmonary blood flow
Atrial septal defect
Ventricular septal defect
Patent ductus arteriosus
High-output cardiac failure (thyrotoxicosis, Paget disease)
Liver disease
Chronic anemia

artery pressure, exertional hypoxemia, and reduced right ventricular performance can be gauged clinically according to the New York Heart Association (NYHA) functional classification, by which patients may report dyspnea with ordinary physical activity (class II), with less than ordinary activity (class III), or at rest (class IV).[5] Functional classification has a high correlation with prognosis and a significant impact on treatment selection.[6]

Since most patients have an underlying etiology that explains the presence of PH, careful attention should be given to symptoms related to associated diseases. In addition, patients with underlying diseases that predispose to PH should undergo a careful history directed at the symptoms of PH.[7]

Patients with connective tissue disease should be evaluated especially carefully with respect to pulmonary arterial hypertension (PAH). Patients with scleroderma who have PAH have a higher mortality than those without PAH,[8,9] and recent clinical studies have indicated a 30% to 35% prevalence of PAH in scleroderma patients,[10–12] although earlier retrospective studies based on autopsy or surgical pathology specimens reported a higher incidence.[13,14] Pulmonary arterial hypertension occurs in 9% to 14% of patients with systemic lupus erythematosus and carries a 2-year mortality rate of greater than 50% in these patients.[15] Factors associated with an increased incidence of PAH include use of cytotoxic agents, presence of Raynaud phenomenon, renal disease, ribonucleoprotein antibody, and circulating lupus anticoagulant.[16] The mean duration of systemic lupus at the time of PAH diagnosis is 2.4 years; however, because PAH may be the presenting symptom, a careful history directed toward symptoms associated with systemic lupus erythematosus is advised.[17]

History-taking in patients with possible PAH should specifically seek to identify risk factors associated with human immunodeficiency virus (HIV) infection since studies have indicated a shorter average duration of symptoms attributable to PAH and a faster disease evolution in HIV-infected patients.[18,19]

A detailed medication history should be elicited that includes use of illicit drugs, prescription medicines, over-the-counter remedies, and herbal supplements. A known association exists between PAH and a history of appetite suppressant use (dexfenfluramine, fenfluramine, and phentermine), with a relative risk for PAH after 3 months of use that is approximately 23-fold higher than that of the general population.[20]

A history suggestive of other diseases with known associations with PH should be sought, including pulmonary thromboemboli, hepatic disease, thyroid disease, sickle cell disease, congenital heart disease, conditions associated with elevated left heart pressures, and conditions associated with hypoxemia.[2]

■ THE PHYSICAL EXAMINATION: A WINDOW INTO ETIOLOGY, SEVERITY

The physical examination in a patient with suspected PH may yield valuable information about the eti-

ology and severity of the disorder. The most consistent finding in patients with PH is an increased pulmonic component of the second heart sound (P_2). Elevation of the jugular venous pulsations, murmurs of pulmonic and tricuspid insufficiency, and a right ventricular heave with an S_3 gallop are secondary findings also associated with PH.[21] Physical signs of underlying causes of PH may be present and include[21]:

- central cyanosis due to Eisenmenger syndrome (right-to-left intracardiac shunting)
- clubbing due to congenital heart disease, interstitial lung disease, or hepatic cirrhosis
- hepatomegaly, ascites, or spider angiomata, indicating underlying cirrhosis
- scleroderma, sclerodactyly, telangiectasias, or other findings indicating an underlying connective tissue disease.

DIAGNOSTIC TESTING: MANY TOOLS CAN AID ASSESSMENT

Because of the nonspecificity of symptoms and the subtlety of physical signs in most patients with PH, the history and physical examination provide only limited information on the presence and severity of disease. The following investigational tools can supplement the history and examination in assessing the presence and severity of PH.

Echocardiography

Transthoracic echocardiography should be performed as the initial study in patients suspected of having PH, owing to its sensitivity and noninvasiveness.[5] Doppler echocardiography is used to estimate the right ventricular systolic pressure by measuring tricuspid regurgitation velocity, and also provides information about the size and function of the right ventricle, as well as estimates of right atrial pressure.[21] Right ventricular systolic pressure estimates by echocardiography correlate well with pulmonary artery systolic pressure by right heart catheterization in patients with PH.[22,23] However, the right ventricular systolic pressure may be underestimated in some cases because of suboptimal tracings of the regurgitant jet, decreased tricuspid regurgitation jet velocity due to high right atrial pressures, or poor estimation of right atrial pressures.[2,24] Thus, all patients with a significantly elevated right ventricular systolic pressure on transthoracic echocardiography and those evoking a high degree of clinical suspicion for significant PH despite a normal transthoracic echocardiogram should undergo right heart catheterization for confirmation, especially if they are candidates for treatment.

Transthoracic echocardiography may also provide valuable clues about the presence of cardiac causes of PH, such as left ventricular systolic or diastolic dysfunction, mitral valve disease, and intracardiac shunting. Bubble contrast echocardiography provides information on significant intracardiac shunting, but if visualization of the atrial septum is inadequate, transesophageal echocardiography or right heart catheterization with oximetry may be required.[2] Transesophageal echocardiography is especially helpful in detecting atypically situated sinus venous atrial septal defects, anomalous pulmonary venous return, and centrally located pulmonary thrombi.[25]

Because of the high prevalence of PAH in patients with scleroderma, all patients with scleroderma should undergo screening transthoracic echocardiography.[26] However, routine echocardiographic screening is not recommended for patients with systemic lupus erythematosus unless they have symptoms consistent with PAH. First-degree relatives of patients with primary pulmonary hypertension (PPH) should undergo transthoracic echocardiography at the time of diagnosis of the index case, every 3 to 5 years thereafter, and at any time symptoms arise that are suggestive of PAH.[2]

Other laboratory investigations

Chest radiography may indicate the presence of PH. A right descending pulmonary artery width greater than 17 mm has been associated with elevated pulmonary artery pressures.[27] Linear calcification of the right pulmonary artery indicates severe longstanding PH.[21] A globular heart and decreased retrosternal air space may suggest right ventricular dilation or hypertrophy.[28] Abnormalities such as interstitial changes or emphysematous change may indicate the presence of underlying parenchymal disease, or nodular densities may suggest pulmonary vasculitis.[21] Chest radiography and spirometry are abnormal in up to 73% of patients with PAH related to scleroderma.[29]

Electrocardiography can frequently reveal evidence of right atrial or ventricular enlargement in patients with PH.[24]

The **ventilation-perfusion scan** is the most useful screening test for pulmonary thromboemboli. At

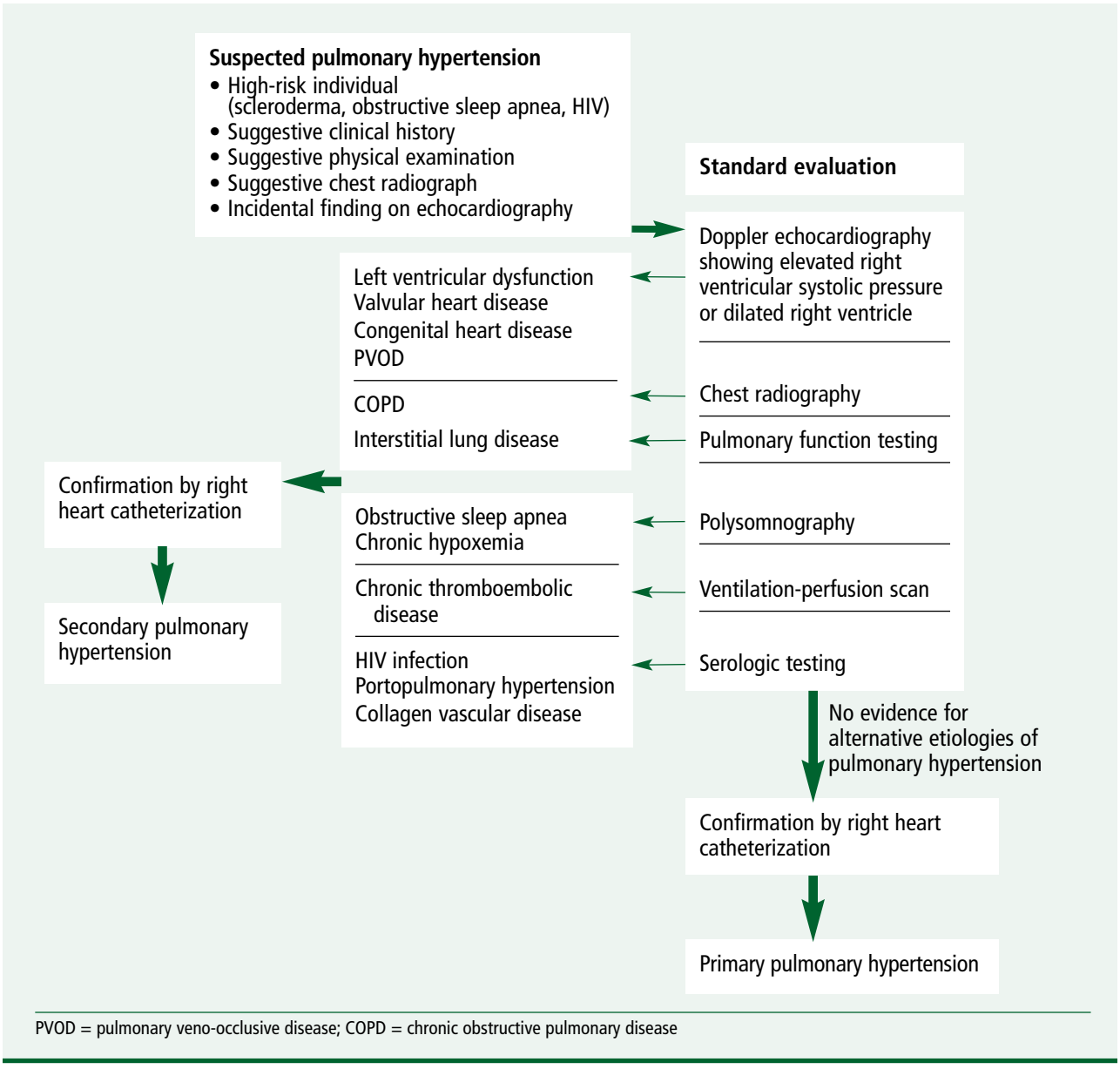


Figure 1. Clinical algorithm for the diagnosis of pulmonary hypertension.

least one segmental-sized or larger perfusion defect will be present in patients with chronic thromboembolic pulmonary hypertension, and most patients will have several segmental or lobar mismatched defects that give the scan a characteristic "moth-eaten" appearance.[30]

For patients with a ventilation-perfusion scan suggestive of chronic thromboembolic pulmonary hypertension, **pulmonary angiography** can provide additional information on the extent and the location of thromboemboli.[2] However, if residual thromboemboli are incorporated into the pulmonary arterial wall or are located distally in the small segments, conventional angiography may underestimate the extent of thrombus. In selected cases, **angioscopy** allows better visualization of thromboemboli and their surgical accessibility.[31,32] **Intravascular ultrasound** may provide useful information on proximal thrombi amenable to thromboendarterectomy or in the differentiation between

acute and chronic thromboembolic disease.[2,33,34]

Chest computed tomographic scanning is a useful part of the evaluation of patients with known or suspected PH. Helical studies with contrast are helpful in identifying proximal thromboembolic disease. An increased diameter of the main pulmonary artery (≥ 29 mm) is highly predictive of the presence of PH (sensitivity 84%, specificity 75%, positive predictive value 0.97), especially when seen in association with an artery-to-bronchus ratio greater than 1:1 in multiple lobes (specificity 100%).[35] High-resolution computed tomographic scans are helpful in diagnosing and staging interstitial lung disease and may suggest the possibility of chronic thromboemblic disease, with a "mosaic" pattern of the lung parenchyma, although this pattern is also associated with PH in the absence of thromboemboli.[36] A decreased density gradient between dependent and nondependent lung has also been described as an early indicator of PH.[37]

Magnetic resonance imaging can be used to assess the size and function of the right ventricle, myocardial thickness, the presence of chronic thromboemboli, and cardiac and pulmonary pressures.[38] In a recent study, gadolinium-enhanced pulmonary **magnetic resonance angiography** showing a right pulmonary artery diameter greater than 28 mm allowed for the diagnosis of chronic PH with a high sensitivity (89%) and a high negative predictive value (94%).[39]

Pulmonary function testing should be part of the initial evaluation of patients with known or suspected PH to assess for abnormalities of the pulmonary parenchyma or airways that may be relevant to the etiology of PH.[21] A restrictive defect with a reduction in lung volumes to less than 80% of the predicted value is present in 20% of patients with chronic thromboembolic disease.[30] A reduction of the diffusion capacity of lung for carbon monoxide (DLCO) (< 45%) out of proportion to a decline in the forced vital capacity has an 87% sensitivity in predicting PAH in patients with scleroderma[2] and may be the earliest sign of PAH in these patients.[29,40] A partial pressure of carbon dioxide (P_{CO_2}) value less than 30 mm Hg has been associated with high positive (87%) and negative (73%) predictive values for portopulmonary hypertension in patients with end-stage liver disease.[41] Evaluation by **nocturnal oximetry screening** and/or **polysomnography** for evidence of obstructive sleep apnea and nocturnal hypoxemia is also advised since the results have both diagnostic and therapeutic implications.

Maximum exercise testing is usually not performed in patients with PH because of the risk of syncope or sudden death.[42] Submaximal testing with a 6-minute walk test is recommended at the time of diagnosis to establish baseline functional impairment and at follow-up to assess response to therapy and prognosis. The mortality risk is increased 2.4-fold in patients with PPH who are able to walk less than 300 m in 6 minutes and 2.9-fold in those with a greater than 10% decline in arterial oxygen saturation.[43] The 6-minute walk distance correlates with severity by NYHA functional class in patients with PPH, and patients who walk less than 332 m have a significantly lower survival rate than those who walk farther.[44]

Lung biopsy is not without risk in patients with PH. It is usually reserved for cases in which a histopathologic diagnosis may alter treatment, such as when active vasculitis, granulomatous disease, pulmonary veno-occlusive disease, or interstitial lung disease is suspected.[45]

Right heart catheterization

Right heart catheterization remains the gold standard for the diagnosis of PH. All patients suspected of having significant PH after clinical and transthoracic echocardiographic evaluation should undergo right heart catheterization, particularly if they are candidates for treatment. Right heart catheterization establishes the pulmonary artery pressure, pulmonary vascular resistance, and cardiac output, as well as the effect of vasodilators on these parameters.

Pulmonary hypertension is defined by right heart catheterization as a mean pulmonary artery pressure greater than 25 mm Hg at rest or greater than 30 mm Hg during exercise. The severity of PH is further classified on the basis of mean pulmonary artery pressure as mild (25 to 40 mm Hg), moderate (41 to 55 mm Hg), or severe (> 55 mm Hg).[46] Pulmonary hypertension secondary to left heart disease or chronic obstructive pulmonary disease usually presents with mild to moderate elevation of mean pulmonary artery pressures (25 to 45 mm Hg). More severe PAH is typically found in PPH, in the setting of collagen vascular disease, or in chronic pulmonary thromboembolism.[6] In most cases of portopulmonary hypertension the increase in pressures is mild with minimal elevations in pulmonary vascular resistance, although a subset of patients with severe PH with elevated pulmonary vascular resistance are dis-

TABLE 2
Hemodynamic profile in pulmonary hypertension

Type	Pulmonary capillary wedge pressure	Pulmonary artery pressure (systolic, diastolic, mean)	Pulmonary vascular resistance	Pulmonary artery end diastolic pressure
Precapillary pulmonary hypertension	Normal	↑	↑	5–15 mm Hg higher than pulmonary capillary wedge pressure
Postcapillary pulmonary hypertension	↑	↑	Normal	5–15 mm Hg higher than pulmonary capillary wedge pressure
Mixed pulmonary hypertension	↑	↑	↑	Modestly higher than pulmonary capillary wedge pressure
Selective or nonselective increases in pulmonary blood flow	Inaccurate because of high pulmonary artery pressures	↑↑	Normal or ↑	↑

tinguished by right heart catheterization.[47]

A decreased mixed venous saturation consistent with low cardiac output has been found to be a strong predictor of poor outcome in some studies. Any subsequent increase in the mixed venous saturation with treatment may indicate an improvement in the cardiac index that is due to decreased right ventricular afterload.[42]

In some symptomatic patients with evidence of only mild or moderate elevation of pulmonary artery systolic pressures on echocardiography, measurement of hemodynamics at rest and during exercise by echocardiography may be needed to establish PH as the etiology of symptoms. In these patients, right heart catheterization can provide helpful additional data. In precapillary PH, the pulmonary artery pressures and resistance are elevated at rest but the pulmonary capillary wedge pressure is normal **(Table 2)**. During exercise, the pressure increases, but the normal decrease in vascular resistance does not occur.

In cases where the pulmonary capillary wedge pressure is noted to be elevated, the diagnosis of pulmonary veno-occlusive disease or left-sided heart disease should be considered.[4] In older patients, the pulmonary capillary wedge pressure may increase (>30 mm Hg) during exercise because of decreased left ventricular compliance. These patients should be treated for systemic hypertension and diastolic dysfunction but should not be aggressively treated for PH.[2,21] In certain cases a mixed hemodynamic picture may be present owing to progressive pulmonary vasculopathy in response to chronic elevation of the pulmonary capillary wedge pressure.

Some patients with mild to moderate PH can be followed or managed without right heart catheterization. Those with mild to moderate PH due to chronic hypoxemia (resting, exertional, or nocturnal) can be followed with serial echocardiography for evidence of progression on appropriate oxygen and/or nocturnal ventilatory support. For patients with mild to moderate PH by echocardiography in the setting of other known causes, such as scleroderma, who do not have NYHA class III symptoms, right heart catheterization can be reserved as a future option if PH progresses on serial echocardiography (every 3 to 6 months).

■ GENETIC TESTING ADVANCES, BUT NOT YET RECOMMENDED

Primary pulmonary hypertension is usually sporadic, but in nearly 100 families in the United States the disease has occurred in at least two first-degree relatives. Documenting familial PPH can be difficult because of skipped generations resulting from incomplete penetrance or variable expression. Many individuals in families with PPH may inherit

the gene and have children with PPH yet never develop PPH themselves. The female-to-male ratio, age at disease onset, and natural history of PPH are similar between patients with the familial form of PPH and those with the sporadic form.[48]

The locus designation gene for familial PPH, known as *PPH1*, is on chromosome 2q31–32 and is transmitted in an autosomal dominant manner. Familial PPH is caused by mutations in the bone morphogenetic protein receptor type II gene (*BMPR2*), which encodes a transforming growth factor beta (TGF-β) receptor. The TGF-β signaling pathway appears to be involved in the pathogenesis of PPH and may provide a target for future therapies.[49]

A complete family history should be obtained in every patient with PPH. Because there is a lifetime penetrance of 10% to 20%, the likelihood of a first-degree relative being affected by PPH is about 0.6% to 1.2% when only one individual in the family has PPH, even if the *PPH1* gene is present. If there is a second case in the family, the lifetime risk rises to 5% to 10%. Offspring of an affected parent have a 5% to 10% lifetime risk of developing PPH.[48]

Most experts advise against genetic testing of family members of patients with PPH because knowledge of the gene and its interaction with other factors contributing to PH is still in its infancy and because the overall risk in first-degree relatives is low. When genetic testing *is* performed, it is critical to ensure both appropriate genetic analysis and appropriate genetic counseling.[50]

Primary pulmonary hypertension has also been associated with autoimmune phenomena, but the genetic significance remains unclear.[50]

■ SPECIAL SITUATIONS

Certain diseases and clinical states are associated with an increased prevalence of PH. We conclude by presenting the following recommendations on screening strategies for select population subgroups with factors that put them at risk for PH.

Systemic autoimmune disease

An elevated erythrocyte sedimentation rate and increased immunoglobulin G levels have been reported in patients with PAH due to scleroderma.[51–53] Serologic studies show that antiphospholipid antibodies are almost twice as prevalent (60% to 68%) in systemic lupus erythematosus patients with PAH as compared to those patients without PAH.[54] Assessing lupus anticoagulant and anticardiolipin antibodies may identify patients with systemic lupus erythematosus who are at increased risk for venous thromboemboli and PH.[54]

Liver disease

The prevalence of PH is approximately 1% in patients with chronic liver disease or portal hypertension but is approximately 4% in patients undergoing orthotopic liver transplantation.[55] All patients being evaluated for liver transplantation should undergo transthoracic echocardiography to assess for portopulmonary hypertension since the presence of PH increases the risk of complications during transplantation. Transthoracic echocardiography is reported to be 97% sensitive and 77% specific in diagnosing moderate to severe PAH in patients with portal hypertension.[56,57]

HIV infection, intravenous drug abuse

Pulmonary arterial hypertension is reported in 0.5% of HIV-infected patients.[58] It is not related to the degree of immunodeficiency or the duration of the disease. Diagnostic screening with transthoracic echocardiography is recommended only in HIV-infected patients who have symptoms consistent with PAH.[59,60]

Pulmonary hypertension in patients with a history of intravenous drug abuse is caused by embolization of foreign particles that are injected with the drug. Because the presence of PH is variable in this population, screening with transthoracic echocardiography is recommended only in individuals with symptoms consistent with PH.[61] Open lung biopsy is generally not indicated unless a confirmatory diagnosis of PH due to intravenous drug use needs to be established.

Hyperthyroidism

Pulmonary hypertension in patients with hyperthyroidism may be due to a high cardiac output state, endothelial damage, increased metabolism of intrinsic pulmonary vasodilating substances, or increased cholinergic output and reduced vasodilator response.[62,63] The usefulness of screening echocardiography in these patients is unclear.

Obstructive sleep apnea and parenchymal lung disease

There is a well-described association between obstructive sleep apnea and PH. Prevalence rates of

PH in patients with obstructive sleep apnea range from 17% to 79%; PH is usually mild in these patients but may be severe.[64] The etiology is most likely multifactorial and related to a combination of daytime and nocturnal hypoxemia, changes in pleural pressure, alveolar hypoventilation, and elevated endothelin levels.[65] Patients with sleep apnea documented by polysomnography with symptoms of dyspnea should be screened for PH with echocardiography.[66] One recent study found that 22% of patients with severe obstructive sleep apnea (defined as an apnea-hypopnea index > 30) had evidence of daytime PH.[67]

Patients with parenchymal lung disease leading to resting, nocturnal, or exertional hypoxemia may also develop PH. Echocardiographic screening in this setting is based on abnormal cardiac auscultation, rapid exertional desaturation, and progression of dyspnea or hypoxemia in the context of stable lung volumes and flows.

Other conditions

Pulmonary hypertension has been associated with other conditions, including hypothyroidism, L-tryptophan use, hyperuricemia, and sickle cell disease, but the predictive value of early screening is not yet clear.[2] A recent clinicopathologic study of 20 cases of sickle cell hemoglobinopathy noted a high prevalence of PH and high mortality. These groups of patients may benefit from regular periodic assessments for PH with directed history, physical examination, and transthoracic echocardiography.[68]

REFERENCES

1. **Rich S, Danzker DR, Ayres S, et al.** Primary pulmonary hypertension: a national prospective study. Ann Intern Med 1987; 107:216–223.
2. **McGoon M.** The assessment of pulmonary hypertension. Clin Chest Med 2001; 22:493–508.
3. **Gomez A, Bialostozky D, Zajarias A, et al.** Right ventricular ischemia in patients with primary pulmonary hypertension. Am J Coll Cardiol 2001; 38:1137–1142.
4. **Fishman A.** Pulmonary hypertension and cor pulmonale. In: Fishman A, ed. Fishman's Pulmonary Diseases and Disorders. 3rd ed. New York: McGraw Hill, 1998:1261–1296.
5. **D'Alonzo GE, Barst RJ, Ayres SM, et al.** Survival in patients with primary pulmonary artery hypertension: results from a national prospective registry. Ann Intern Med 1991; 115:343–349.
6. **Rich S, ed.** Primary pulmonary hypertension: executive summary from the World Symposium on Primary Pulmonary Hypertension. Geneva: World Health Organization, 1998.
7. **Minai OA, Dweik RA, Arroliga AC.** Manifestations of scleroderma pulmonary disease. Clin Chest Med 1998; 19:713–731.
8. **Stupi AM, Steen VD, Owens GR, et al.** Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. Arth Rheum 1986; 29:515–524.
9. **Koh ET, Lee P, Gladman DD.** Pulmonary hypertension scleroderma: an analysis of 17 patients. Br J Rheumatol 1996; 35:989–993.
10. **Morelli S, De Marzio P, Valesini G, et al.** Pulmonary hypertension in systemic sclerosis. G Ital Cardiol 1993; 23:871–876.
11. **Murata I, Kihara H, Shinohara S, et al.** Echo evaluation of pulmonary arterial hypertension in patients with progressive systemic sclerosis and related syndromes. Jpn Circ J 1992; 56:983–991.
12. **Battle RW, Davitt MA, Cooper SM, et al.** Prevalence of pulmonary hypertension in limited and diffuse scleroderma. Chest 1996; 110:1515–1519.
13. **Salerni R, Rodnan GP, Leon DF, et al.** Pulmonary hypertension in the CREST syndrome variant of progressive systemic sclerosis (scleroderma). Ann Intern Med 1977; 86:394–399.
14. **Yousem SA.** The pulmonary pathologic manifestations of the CREST syndrome. Hum Pathol 1990; 21:467–474.
15. **Orens JB, Martinez FJ, Lynch JP III.** Pleuropulmonary manifestations of systemic lupus erythematosus. Rheum Dis Clin North Am 1994; 20:159–193.
16. **Asherson RA, Hackett D, Gharavi AE, et al.** Pulmonary hypertension in systemic lupus erythematosus (editorial). J Rheumatol 1986; 13:1–5.
17. **Quismorio FP, Sharma O, Koss M, et al.** Immunopathologic and clinical studies in pulmonary hypertension associated with systemic lupus erythematosus. Semin Arth Rheum 1984; 13:349–359.
18. **Petitpretz P, Brenot F, Azarian R, et al.** Pulmonary hypertension in patients with human immunodeficiency virus infection. Comparison with primary pulmonary hypertension. Circulation 1994; 89:2722–2727.
19. **Mehta NJ, Khan IA, Mehta RN, et al.** HIV-related pulmonary hypertension: analytic review of 131 cases. Chest 2000; 118:1133–1141.
20. **Abenhaim L, Moride Y, Brenot F, et al.** International primary pulmonary hypertension study group. Appetite suppressant drugs and the risk of primary pulmonary hypertension. N Engl J Med 1996; 335:609–616.
21. **Chatterjee K, De Marco T, Alpert J.** Pulmonary hypertension: hemodynamic diagnosis and management. Arch Intern Med 2002; 162:1925–1933.
22. **Homma A, Anzueto A, Peters JI, et al.** Pulmonary artery systolic pressures estimated by echocardiogram vs cardiac catheterization in patients awaiting lung transplantation. J Heart Lung Transplant 2001; 20:833–839.
23. **Berger M, Haimowitz A, van Tosh A, Berdoff RL, Goldberg E.** Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous-wave Doppler ultrasound. J Am Coll Cardiol 1985; 6:359–365.
24. **Peacock AJ.** Primary pulmonary hypertension. Thorax 1999; 54:1107–1118.
25. **Pruszczyk P, Torbicki A, Pacho R, et al.** Noninvasive diagnosis of suspected severe pulmonary thromboembolism: transesophageal echocardiography vs. spiral CT. Chest 1997; 112:722–728.
26. **Smith JW, Clements PJ, Levisman J, et al.** Echocardiographic features of progressive systemic sclerosis (PSS): correlation with hemodynamic and postmortem studies. Am J Med 1979; 66:28–33.
27. **Matthay R, Berger H.** Cardiovascular function in cor pulmonale. Clin Chest Med 1983; 4:269–295.
28. **Restrepo CI, Tapson VF.** Pulmonary hypertension and cor pulmonale. In: Topol EJ,ed. Textbook of Cardiovascular Medicine. 2nd ed. Philadelphia: Williams &Wilkins, 2002:647–665.
29. **Young RH, Mark GJ.** Pulmonary vascular changes in scleroderma. Am J Med 1978; 64:998–1004.
30. **Viner SM, Bagg BR, Auger WR, et al.** The management of pulmonary hypertension secondary to chronic thromboembolic disease. Prog Cardiovasc Dis 1994; 37:79–92.

31. **Shure D, Gregoratos G, Moser KM.** Fiberoptic angioscopy: role in the diagnosis of chronic pulmonary arterial obstruction. Ann Intern Med 1985; 103:844–850.
32. **Uchida Y, Oshima T, Hirose J, et al.** Angioscopic detection of residual pulmonary thrombi in the differential diagnosis of pulmonary embolism. Am Heart J 1995; 130:854–859.
33. **Stahr P, Rupprecht HJ, Voigtlander T, et al.** Comparison of normal and diseased pulmonary artery morphology by intravascular ultrasound and histological examination. Int J Card Imaging 1999; 15:221–31.
34. **Bressollette E, Dupuis J, Bonan R, et al.** Intravascular ultrasound assessment of pulmonary vascular disease in patients with pulmonary hypertension. Chest 2001; 120:809–815.
35. **Tan RT, Kuzo R, Goodman L.** Utility of CT scan for predicting pulmonary hypertension in patients with parenchymal lung disease. Chest 1998; 113:1250–1256.
36. **Sherrick AD, Swensen SJ, Hartman TE.** Mosaic pattern of lung attenuation of CT scans: frequency among patients with pulmonary artery hypertension of different causes. Am J Roentgenol 1997; 169:79–82.
37. **Cailes JB, du Bois RM, Hansell DM.** Density gradient of the lung parenchyma on computed tomography scanning in patients with pulmonary hypertension and systemic sclerosis. Acad Radiol 1996; 3:724–730.
38. **Frank H, Globits S, Glogar D, et al.** Detection and quantification of pulmonary artery hypertension with MR imaging: results in 23 patients. Am J Roentgenol 1993; 161:27–31.
39. **Kruger S, Haage P, Hoffman R, et al.** Diagnosis of pulmonary arterial hypertension and pulmonary embolism with magnetic resonance angiography. Chest 2001; 120:1556–1561.
40. **Steen VD, Graham G, Conte C, et al.** Isolated diffusing capacity reduction in systemic sclerosis. Arth Rheum 1992; 35:765–770.
41. **Kuo PC, Plotkin JS, Johnson LB, et al.** Distinctive clinical features of portopulmonary hypertension. Chest 1997; 112:980–986.
42. **McLaughlin VV, Genthner DE, Panella MM, Rich S.** Reduction in pulmonary vacular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. N Engl J Med 1998; 338:273–277.
43. **Paciocco G, Martinez FJ, Bossone E, et al.** Oxygen desaturation on the six-minute walk test and mortality in untreated primary pulmonary hypertension. Eur Respir J 2001; 17:647–652.
44. **Miyamoto S, Nagaya N, Satoh T, et al.** Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparision with cardiopulmonary exercise testing. Am J Respir Crit Care Med 2000; 161:487–492.
45. **Venkateshiah SB, Arroliga AC, Mehta AC, et al.** Safety of surgery in patients with pulmonary artery hypertension [abstract]. Am J Respir Crit Care Med 2002; 165:B53.
46. **Khan MG.** Pulmonary hypertension and cor pulmonale. In: Khan MG, Lynch JP III, eds. Pulmonary Disease Diagnosis and Therapy: A Practical Approach. Baltimore: Williams & Wilkins, 1997:603–616.
47. **Chemla D, Castelain V, Herve P, et al.** Haemodynamic evaluation of pulmonary hypertension. Eur Respir J 2002; 20:1314–1331.
48. **Humber M, Trembath RC.** Genetics of pulmonary hypertension: from bench to bedside. Eur Respir J 2002; 20:741–749.
49. **Newman J.** Treatment of primary pulmonary hypertension—the next generation. N Engl J Med 2002; 346:933–935.
50. **Thomas AQ, Gaddipati R, Newman JH, et al.** Genetics of primary pulmonary hypertension. Clin Chest Med 2001; 22:477–491.
51. **Yamane K, Ihn Y, Asano N, et al.** Clinical and laboratory features of scleroderma patients with pulmonary hypertension. Rheumatology 2000; 39:1269–1271.
52. **MacGregor AJ, Canavan C, Knight CP, et al.** Pulmonary hypertension in systemic sclerosis: risk factors for progression and consequences for survival. Rheumatology 2001; 40:453–459.
53. **Launay D, Hachulla E, Hartron PY, et al.** Pulmonary hypertension screening in systemic sclerosis: a cohort study of 67 patients. Rev Med Interne 2001; 22:819–829.
54. **Fagan KA, Budesch DB.** Pulmonary hypertension associated with connective tissue disease. Prog Cardiovasc Dis 2002; 45:225–234.
55. **Castro M, Krowka MJ, Schroeder DR, et al.** Frequency and clinical implications of increased pulmonary artery pressures in liver transplantation. Mayo Clin Proc 1996; 71:543–551.
56. **Kim WR, Krowka MJ, Plevak DJ, et al.** Accuracy of Doppler echocardiography in the assessment of pulmonary hypertension in liver transplant candidates. Liver Transplant 2000; 6:453–458.
57. **Cotton CL, Gandhi S, Vaitkus PT, et al.** Role of echocardiography in detecting portopulmonary hypertension in liver transplant candidates. Liver Transplant 2002; 8:1051–1054.
58. **Le Houssine P, Karmochkine M, Ledru E.** Primary pulmonary hypertension in human immunodeficiency virus infection. Study of 9 cases and review of the literature. Rev Med Interne 2001; 22:1196–1203.
59. **Petrosillo N, Pellicelli AM, Boumis E, Ippolito G.** Clinical manifestation of HIV-related pulmonary hypertension. Ann NY Acad Sci 2001; 946:223–235.
60. **Seoane L, Shellito J, Welsh D, et al.** Pulmonary hypertension associated with HIV infection. South Med J 2001; 94:635–639.
61. **Tomashefsk JF, Hirsch CS.** The pulmonary vascular lesions of intravenous drug abuse. Hum Pathol 1980; 11:133–145.
62. **Nakchbandi IA, Wirth JA, Inzucchi SE.** Pulmonary hypertension caused by Grave's thyrotoxicosis: normal pulmonary hemodynamics restored by (131)I treatment. Chest 1999; 116:1483–1485.
63. **Arroliga AC, Dweik RA, Rafanan AL.** Primary pulmonary hypertension and thyroid disease. Chest 2000; 118:1224–1225.
64. **Sanner BM, Doberauer C, Konermann M, et al.** Pulmonary hypertension in patients with obstructive sleep apnea syndrome. Arch Intern Med 1997; 157:2483–2487.
65. **Phillips BG, Norkiewk K, Perck CA, et al.** Effect of obstructive sleep apnea on endothelin-1 and blood pressure. J Hypertens 1999:61–66.
66. **Krowka MJ.** Pulmonary hypertension: diagnostics and therapeutics. Mayo Clin Proc 2000; 75:625–630.
67. **Yamakawa H, Shiomi T, Sasanabe R, et al.** Pulmonary hypertension in patients with severe obstructive sleep apnea. Psychiatry Clin Neurosci 2002; 56:311–312.
68. **Haque AK, Gokhale S, Rampy BA.** Pulmonary hypertension in sickle cell hemoglobinopathy. A clinicopathologic study of 20 cases. Hum Pathol 2002; 33:1037–1043.

Treatments and strategies to optimize the comprehensive management of patients with pulmonary arterial hypertension

THOMAS R. GILDEA, MD; ALEJANDRO C. ARROLIGA, MD; AND OMAR A. MINAI, MD

ABSTRACT

The management of pulmonary arterial hypertension (PAH) should aim to provide vasodilation of the pulmonary arteries, treat right ventricular failure, improve functional capacity and quality of life, and improve survival, if possible. Data from right heart catheterization and an estimation of vasoresponsiveness together guide treatment for PAH. The judicious use of calcium channel blockers, prostacyclin analogues, anticoagulation, and endothelin receptor antagonists forms the current basis of therapy. Three drugs—the prostacyclin analogues epoprostenol and treprostinil and the endothelin receptor antagonist bosentan—are currently approved for the primary treatment of PAH and have been clinically shown to improve outcomes. Coumarin derivatives, epoprostenol, and, in selected patients, calcium channel blockers are the only drugs associated with improved survival, and only epoprostenol has been shown to improve survival in a prospective randomized trial. Knowledge of the supportive therapies, indications for surgical intervention, and emerging drug therapies should provide the working armamentarium for clinicians treating this rare but devastating disease.

From the Department of Pulmonary and Critical Care Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio.

Address: Omar A. Minai, MD, Department of Pulmonary and Critical Care Medicine, A90, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail: minaio@ccf.org.

Disclosure: Dr. Minai has indicated that he has been a consultant to Actelion Pharmaceuticals. Drs. Gildea and Arroliga have indicated that they have no commercial affiliations or interests that pose a potential conflict of interest with this article.

The comprehensive management of patients with pulmonary arterial hypertension (PAH) generally includes the following goals:

- Vasodilation of the pulmonary arteries to reduce pulmonary artery pressure
- Treatment of right ventricular failure
- Improvement in functional capacity and quality of life
- Improved survival.

These goals are most efficiently and effectively achieved using a team approach centered on collaboration among the various physicians involved and a pulmonary hypertension center, including a pulmonary hypertension coordinator (see the article by Mughal et al in this supplement). In the present article, we review the various therapeutic options available for patients with PAH and issues involved in the comprehensive management of these patients. The simplified algorithm in **Figure 1** provides an overview of the management of these patients.

GENERAL CONSIDERATIONS IN THE APPROACH TO PULMONARY HYPERTENSION

Pulmonary arterial hypertension has diverse origins and may occur as a primary disease (primary pulmonary hypertension) or as a complication of systemic, pulmonary, or cardiac conditions,[1] as described earlier in this supplement. Most of the discussion in this article relates to patients with prima-

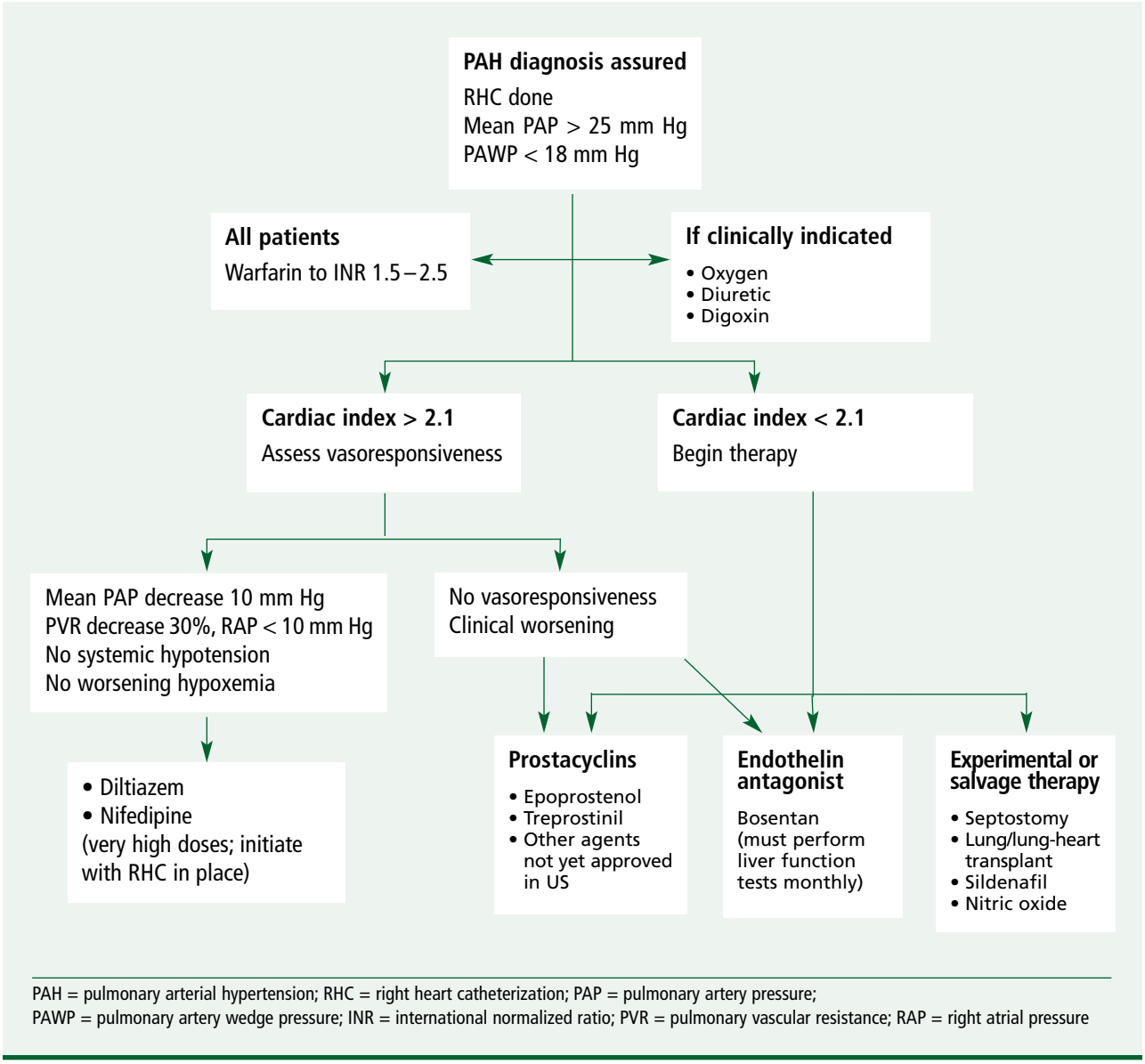


Figure 1. Algorithm for the management of patients with pulmonary arterial hypertension.

ry pulmonary hypertension, although many studies have included patients with other categories of PAH **(Table 1)**.

Secondary causes of pulmonary hypertension should be thoroughly investigated since most cases have an underlying etiology. Although some of these secondary causes may have distinguishing clinical features, a high index of suspicion is needed to make a correct and timely diagnosis of PAH, owing to its insidious onset and progression, nonspecific symptoms, and varied underlying causes.[1,2]

Although echocardiography is a useful noninvasive method of estimating the right ventricular systolic pressure,[3,4] all patients should undergo right heart catheterization for accurate measurement of hemodynamic parameters and to guide the selection of appropriate therapy.

■ ESTIMATE OF VASORESPONSIVENESS

Before vasodilator therapy is initiated for PAH, patients should be identified as "responders" or

TABLE 1
Classification of pulmonary arterial hypertension

1. Primary pulmonary hypertension
   - Sporadic
   - Familial
2. Pulmonary arterial hypertension related to:
   - Collagen vascular disease
   - Congenital systemic to pulmonary shunts
   - Portal hypertension
   - HIV infection
   - Drugs
     - —Anorexigens
     - —Other (rapeseed oil, cocaine, L-tryptophan, etc)
   - Persistent pulmonary hypertension of the newborn
   - Other

Adapted from reference 1 with permission of the World Health Organization.

"nonresponders" by measuring the change in pulmonary artery pressure and pulmonary vascular resistance in response to short-acting vasodilators such as inhaled nitric oxide,[5] intravenous prostacyclin,[6] or adenosine.[7] A decrease of 10 mm Hg in mean pulmonary artery pressure and a 25% decrease in pulmonary vascular resistance[8] is considered a positive response so long as it occurs with a stable or increased cardiac index and without a significant decrease in systemic blood pressure or oxygen saturation.[9] Because there is a 20% to 25% spontaneous variability in pressures and resistances,[10] it is reasonable to require at least a 30% reduction in pulmonary vascular resistance in order to call a vasodilator response positive.[11] Patients with a positive response are more likely to benefit from long-term vasodilator therapy[11–14] and to have fewer side effects.[11,15] Patients without an acute vasodilator response also appear to have vascular endothelial remodeling that limits vasodilatation,[16] but they still derive clinical benefit from long-term vasodilator therapy with epoprostenol.[17–19]

■ CALCIUM CHANNEL BLOCKERS

Calcium channel blockers were the first medications associated with an improvement in survival in patients with primary pulmonary hypertension. Some authors recommend at least a 50% decrease in pulmonary vascular resistance and near normalization of mean pulmonary artery pressure in response to a vasodilator trial when assessing a patient's candidacy for calcium channel blocker therapy.[20] Calcium channel blockers are best reserved for patients with a preserved cardiac index and documented vasoreactivity. Unfortunately, vasoreactivity is uncommon, existing in approximately 30% of patients.[21]

Studies have shown that high-dose calcium channel blocker therapy in carefully selected patients (ie, those with a 20% reduction in mean pulmonary artery pressure during acute titration of nifedipine or diltiazem) is associated with reducations in pulmonary artery pressure, pulmonary vascular resistance, and symptoms, as well as improved survival at 5 years.[12,13,22] Doses up to 720 mg/day of diltiazem or 240 mg/day of nifedipine were used as long-term therapy after the initial dose escalation.

Notably, patients with a right atrial pressure greater than 10 mm Hg may not derive benefit from calcium channel blocker therapy.[23]

■ PROSTACYCLIN ANALOGUES

Prostaglandins, including prostacyclin, are powerful vasodilators that have antiplatelet activity and may also contribute to pulmonary vascular endothelial remodeling.[23–27] Several prostacyclin analogues are in clinical use for pulmonary hypertension throughout the world, but only epoprostenol (Flolan) and treprostinil (Remodulin) are approved by the Food and Drug Administration (FDA) for use in the United States.

Epoprostenol is delivered by continuous intravenous infusion because of its short half-life in the circulation (3 to 5 minutes). Its main mechanism of action is a dose-dependent vasodilation that begins within a few minutes of the start of infusion. Through its actions on the arachidonic acid pathway, epoprostenol also can inhibit platelet aggregation and reduce the risk of in situ thrombosis.

Reports in the 1980s[28,29] suggested a significant sustained benefit from epoprostenol in patients with primary pulmonary hypertension. In 1996, a randomized prospective trial demonstrated the sustained effect of epoprostenol over a 3-month period in 81 patients with severe primary pulmonary hypertension (New York Heart Association [NYHA] class III or IV).[18] The mean pulmonary artery pressure decreased by 8% in the epoprostenol group while rising by 3% in the conventional therapy group. Additionally, epoprostenol therapy was associated with significant improvements in cardiac index, pulmonary vascular resistance, 6-minute walk distance,

and quality-of-life measures over the 12-week period. All of the patients who died were in the conventional therapy arm **(Figure 2)**.

Several other trials of epoprostenol have shown a sustained increase in cardiac output with reduction in pulmonary vascular resistance[30] and improvement in survival at 1, 3, and 5 years compared with historical controls.[18,31] The beneficial effects of epoprostenol can be seen even in patients without acute reduction of pulmonary artery pressure and vascular resistance.[18,19] McLaughlin et al[30] showed that the greater the reduction in pulmonary vascular resistance with acute adenosine challenge, the lower the pulmonary vascular resistance with long-term epoprostenol therapy, but even those patients with no response to the initial challenge had a reduction in pulmonary vascular resistance and an improvement in symptoms.

Epoprostenol may delay or eliminate the need for lung transplantation in some instances.[32] This drug also has benefited patients with PAH secondary to connective tissue diseases,[27] congenital heart defects,[25] portopulmonary hypertension,[23] chronic thromboembolic pulmonary hypertension,[33] HIV infection,[26] use of anorectic agents,[34] and sarcoidosis.[30,35]

Dosing of epoprostenol is based on actual body weight and is calculated in ng/kg/min. Treatment is usually started with insertion of a pulmonary artery catheter to monitor hemodynamic changes with drug titration. Optimal dosing follows either of two strategies. In one strategy, the dose may be increased if the patient experiences symptoms (ie, the lowest tolerated dose is used). The second strategy is to continue increasing the dose as long as the toxicities from treatment are tolerable. These strategies have not been compared directly.

Epoprostenol typically is initiated at a dose of 2 to 4 ng/kg/min, which is titrated up, based on side effects, toward a target dose of 8 to 15 ng/kg/min in the initial 4 to 5 weeks. Interpatient variability makes the notion of an "ideal dose" somewhat nebulous, but a recent report suggests that most patients remain on stable doses between 22 and 45 ng/kg/min.[36] Epoprostenol is delivered via a permanent central catheter, which can subject the patient to significant risk of infection[37] and thrombosis.

Changes in volume status will change the volume of distribution and may result in over- or underdosing. Symptoms of epoprostenol toxicity include flushing, jaw claudication, abdominal cramping, diarrhea, nausea/emesis, headache, and

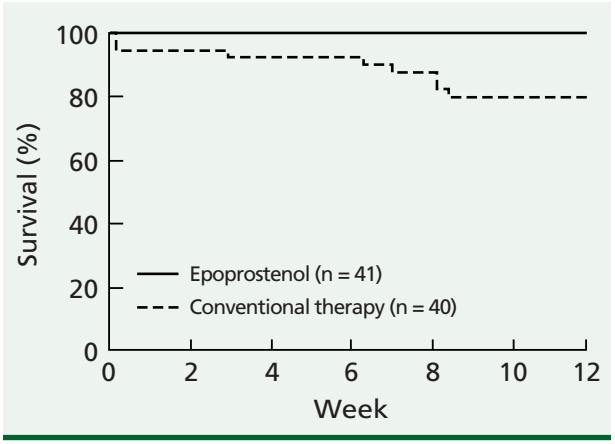


Figure 2. Survival among 41 patients treated with epoprostenol and 40 patients receiving conventional therapy in a randomized prospective trial.[18] Estimates were made by the Kaplan–Meier product-limit method. The two-sided *P* value from the log-rank test was 0.003. Reprinted with permission from reference 18. Copyright © 1996 Massachusetts Medical Society.

arthralgia; these symptoms abate with time, indicating drug tolerance.[38] Acute discontinuation of therapy for any reason may result in a rapid increase in pulmonary vascular resistance and pulmonary artery pressure, as well as potentially acute right ventricular failure and death.

Treprostinil is the prostacyclin analogue that is available for subcutaneous infusion. A recent prospective, randomized, 12-week study compared treprostinil with placebo in 470 patients with PAH (mainly primary pulmonary hypertension).[39] Treprostinil recipients showed a small improvement compared with placebo recipients in 6-minute walk distance (16 meters) and significant improvement in mean right atrial pressure, mean pulmonary artery pressure, cardiac index, pulmonary vascular resistance, mixed venous oxygen saturation, and quality-of-life measures. However, significant pain at the infusion site was a major problem, occurring in 85% of patients and causing study discontinuation in 8%. There are currently no data showing mortality benefits.

■ ENDOTHELIN RECEPTOR ANTAGONISTS

The biology of endothelin-1 and its receptors (endothelin receptors A and B) has been the focus of intense research in recent years. Endothelin-1 is the most potent known endogenous vasoconstrictor. It

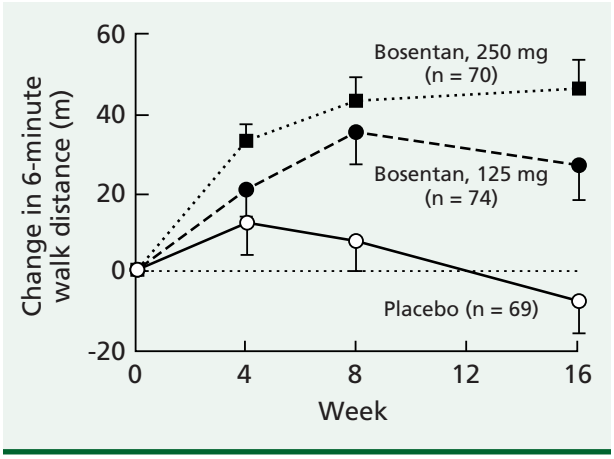


Figure 3. Mean (± SE) change in 6-minute walk distance from baseline to week 16 in patients treated with one of two doses of bosentan or placebo in a randomized prospective trial.[50] $P < 0.01$ for the comparison between the 125-mg dose of bosentan and placebo, and $P < 0.001$ for the comparison between the 250-mg dose and placebo. There was no significant difference between the two bosentan groups. Reprinted with permission from reference 50. Copyright © 2002 Massachusetts Medical Society.

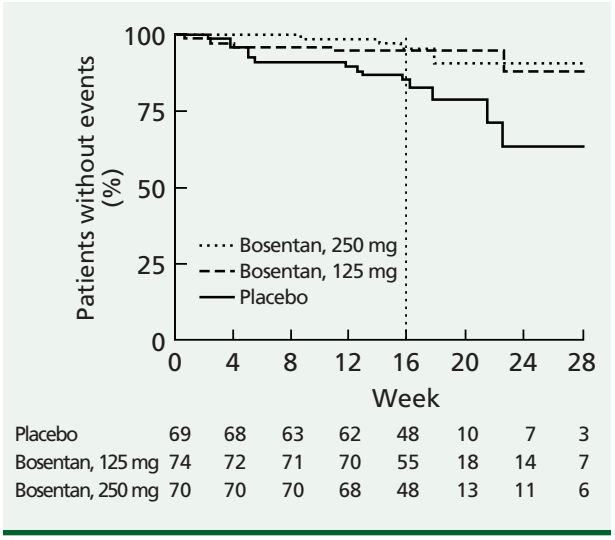


Figure 4. Kaplan–Meier estimates of the proportion of patients with clinical worsening in a randomized, prospective, placebo-controlled study of bosentan.[50] Clinical worsening was defined by the combined end point of death, lung transplantation, hospitalization, or discontinuation of the study treatment. $P < 0.05$ for the comparison of the bosentan groups with the placebo group at weeks 16 and 28. There was no significant difference between the two bosentan groups. Reprinted with permission from reference 50. Copyright © 2002 Massachusetts Medical Society.

exhibits smooth muscle mitogenic, proinflammatory, and profibrotic properties via actions on its receptors located on vascular endothelial cells and bronchial smooth muscle cells.[40] Recent evidence suggests that the vasoconstrictive action of endothelin-1 can be mediated via both endothelin receptors.[41]

Endothelin-1 has a prominent role in various forms of pulmonary hypertension. Elevated endothelin-1 levels have been found in patients with primary pulmonary hypertension[42]; PAH associated with scleroderma[43] and systemic lupus erythematosus[44]; and pulmonary hypertension due to chronic hypoxic lung diseases,[45] congenital heart diseases,[46] and congestive heart failure.[47] Endothelin-1 levels are associated with disease severity and have been shown to decrease with epoprostenol therapy.[48]

Bosentan. Because the fibrotic effects of endothelin-1 seem to be mediated via the B receptors, blockade of the B receptors with the dual endothelin receptor antagonist bosentan (Tracleer) may be desirable. Bosentan is currently the only proven effective oral therapy for PAH, as well as the only endothelin receptor antagonist that is commercially available in the United States.

Bosentan has been studied in two randomized, placebo-controlled, double-blind studies involving patients with class III or IV PAH according to the World Health Organization functional classification, which is a modification of the NYHA classification for heart failure. The first study[49] was a 12-week trial in which bosentan was associated with an improvement, compared with placebo, in 6-minute walk distance, functional capacity, score on the Borg dyspnea index, pulmonary artery pressure, pulmonary vascular resistance, and cardiac output.

The larger Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE-1)[50] enrolled 213 patients with PAH (primary pulmonary hypertension or PAH due to connective tissue diseases) who were in WHO functional classes III or IV. Patients were randomized in a 1:1:1 ratio to placebo, bosentan 125 mg twice daily, or bosentan 250 mg twice daily. At 16 weeks, patients in the combined bosentan groups walked 44.2 meters farther than those in the placebo group (95% confidence interval, 21–67 meters) **(Figure 3)** and had greater improvements in their WHO functional class and Borg dyspnea scores. Clinical worsening was noted in 20% of patients in the placebo group compared with 6% of patients in the bosentan groups **(Figure 4)**.

A recent study has also shown an improvement in

right ventricular systolic function and left ventricular early diastolic filling and reverse ventricular remodeling with bosentan therapy in patients with PAH.[51]

Although bosentan and treprostinil seem to show equivalent overall efficacy, there was a much smaller magnitude of improvement in 6-minute walk distance in the pivotal treprostinil study[39] than in studies of bosentan, which might be attributable to differences in study cohorts. Whereas the bosentan studies consisted mostly of patients with PAH related to connective tissue disease, most patients in the treprostinil study had primary pulmonary hypertension, although there were some with PAH associated with congenital disease or connective tissue disease. Also, the treprostinil study had some patients with a NYHA classification as low as II, and infusion-site pain made it difficult to reach higher doses in some patients.[39]

A dose-related rise in hepatic aminotransferase levels was noted in bosentan-treated patients in the BREATHE-1 study (3% incidence for patients receiving 125 mg twice daily, 7% for those receiving 250 mg twice daily) but resolved with dose reduction or drug discontinuation.[50] Serum aminotransferase levels must be measured in patients before starting bosentan therapy and monthly thereafter.

Because of the risk of fetal damage with bosentan use, patients should take special care not to become pregnant while on this medication.

Bosentan is approved by the FDA for all forms of PAH in patients in WHO functional classes III or IV **(Table 2)**. Adding bosentan to the regimen of patients already on epoprostenol may be a reasonable strategy in highly symptomatic patients who are deteriorating on symptom-limited doses of epoprostenol, but any recommendation for such combination therapy awaits further evidence. The practice of using bosentan to "wean patients off" epoprostenol is also currently under study.

Sitaxsentan, a specific endothelin A receptor antagonist, is currently also under study in patients with PAH.[52] This investigational agent also is administered orally. Theoretically, sitaxsentan blocks the vasoconstrictive effects of the endothelin A receptor while allowing the vasodilative effects of endothelin B receptor stimulation.

TABLE 2
World Health Organization functional classification of pulmonary hypertension

Class I—Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Class II—Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class III—Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest, but less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class IV—Patients with pulmonary hypertension who are unable to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea , fatigue, or both may be present even at rest. Discomfort is increased by any physical activity.

Adapted from reference 1 with permission of the World Health Organization.

■ OTHER VASODILATORS

Additional prostacyclin analogues are currently not available in the United States, but the possible benefits of the orally administered beraprost and the inhaled iloprost are under study in Europe.

Nitric oxide is a potent pulmonary vasodilator that is produced in the pulmonary endothelium by the metabolism of L-arginine; it has a key role in pulmonary vascular tone.[53] Inhaled nitric oxide has been used to treat persistent pulmonary hypertension of the newborn[54] as well as adult PAH. In view of its short half-life, its main role to date has been to determine vasodilator responsiveness in patients with PAH.[5,55] Long-term use of inhaled nitric oxide has also been described in patients with primary pulmonary hypertension,[56] but its clinical application has been limited because of the compound's short half-life.

Phosphodiesterase-5 (PDE-5) inhibitors act by causing cyclic GMP levels to increase, which appears to regulate pulmonary vascular tone via nitric oxide. There has been significant enthusiasm for use of the PDE-5 inhibitor sildenafil (Viagra) in PAH because it can reduce pulmonary artery pressure and pulmonary vascular resistance without significantly reducing systemic blood pressure, and also because it is orally administered and well tolerated.

A recent randomized open-label study compared sildenafil with nitric oxide and with epoprostenol in

patients with pulmonary hypertension secondary to lung fibrosis, showing a significant reduction in the pulmonary vascular resistance index with sildenafil.[57] In this preliminary study sildenafil appeared to be more potent than nitric oxide and was associated with less systemic hypotension than was epoprostenol. Sildenafil also has been used as adjunctive or rescue therapy in selected patients.[58–62] Studies of the role of sildenafil in pulmonary hypertension are currently under way in the United States and Europe.

L-Arginine is a precursor of nitric oxide in the presence of nitric oxide synthase and is a readily available nutritional supplement that can be taken orally. In a placebo-controlled study of 19 patients with PAH,[63] supplemental L-arginine produced decreases in mean pulmonary artery pressure and pulmonary vascular resistance, an increase in oxygen consumption, a decrease in CO_2 production, and a small but statistically significant decline in mean systemic arterial pressure. Further study is needed to better define the role of oral supplementation of this simple amino acid for the treatment of PAH.

■ ANTICOAGULATION AND OTHER THERAPIES

Anticoagulants. The rationale for anticoagulant therapy for PAH is based on the development of in situ thrombosis seen pathologically in patients with plexogenic pulmonary arteriopathy.[12,64] These patients are at increased risk of thrombosis because of a variety of factors, including dilated right-sided heart chambers, sluggish pulmonary vascular flow, sedentary lifestyle, and venous insufficiency. A clear and significant survival benefit has been observed at 1 and 3 years for anticoagulated over nonanticoagulated patients with PAH.[12,64] The current recommendation is that all patients with PAH should receive anticoagulation therapy with coumarin derivatives to a target international normalized ratio of between 2 and 3[65] unless they have a contraindication.

Diuretic therapy reduces plasma volume and preload and helps treat right ventricular failure, reducing the right atrial pressure. Clinically there is an improvement in jugular venous distention, ascites, peripheral edema, and dyspnea, and thereby an improvement in quality of life. Patients are typically "volume dependent," and volume depletion from overdiuresis may result in significant hypotension and dizziness. Loop diuretics are used alone or in conjunction with a thiazide diuretic or spironolactone in patients with ascites. The role of ACE inhibitors is not completely clear in this population, but sympathetic and renin-angiotensin-aldosterone activation due to severe right heart failure argues in favor of some role. Interesting animal research suggests that pulmonary angiotensin-converting enzyme is important in the pathogenesis of PAH.[66,67]

Supplemental oxygen. Hypoxemia induces pulmonary vasoconstriction in patients with PAH,[68] and hypobaric conditions such as those associated with commercial air travel should be avoided without supplemental oxygen.[69] Although no study has looked specifically at the impact of oxygen therapy in patients with PAH, the Nocturnal Oxygen Therapy Trial showed improved quality of life and survival with oxygen therapy in patients with pulmonary hypertension due to chronic lung disease.[70] Some have argued that patients with PAH, other than those with intracardiac shunts, have only a mild degree of hypoxemia and that it is explained by minimal ventilation-perfusion mismatching and a low mixed venous oxygen level that is due to low cardiac output.[20] This argument maintains that oxygen supplementation rarely, if ever, improves quality of life in patients with PAH.[20] We have shown that patients with PAH may be significantly hypoxemic during sleep and require supplemental oxygen therapy.[71] We believe that all patients with PAH should be screened for hypoxemia with exertion and, if necessary, treated with supplemental oxygen while asleep.

Digoxin and other inotropes have been used to treat pulmonary hypertension, particularly in combination with calcium channel blockers to offset the latter drugs' negative inotropic effects and to increase cardiac output.[72] Catecholamines such as dopamine, dobutamine, and norepinephrine may be used in selected patients under careful hemodynamic monitoring in an attempt to temporarily augment contractility, systemic blood pressure, or both.

■ INDICATIONS FOR SURGICAL THERAPY

Lung transplantation should be the last option in patients with PAH.[73] Improvements in medical management have lowered rates of lung transplantation for PAH and extended the time to transplantation or eliminated the need altogether.[32] Patients

in WHO functional class IV or those not responding to medical therapy should be referred for transplant evaluation. International guidelines have been published to direct this process.[74] Heart-lung transplants tend to be reserved for patients with structural cardiac abnormalities. In some circumstances a bridging procedure, such as atrial septostomy, can be used while the patient awaits lung transplantation, but such procedures are associated with significant risk.[75,76]

OTHER MANAGEMENT ISSUES

Perioperative risk. We recently reported in abstract form[77] that untreated patients with moderate to severe PAH had increased perioperative morbidity and mortality rates. Most of the complications were related to the surgical procedure or the underlying disease and not directly to PAH. The few available reports on perioperative risks in patients with PAH are case studies or series[78–80] that have looked predominantly at patients with portopulmonary hypertension undergoing liver transplantation with mixed results. We recommend perioperative pulmonary artery catheter monitoring for all patients undergoing surgery under general anesthesia.

Exercise. Pulmonary artery pressure may increase with exercise in PAH patients, precipitating dyspnea, chest pain, and syncope. The increase may be out of proportion to the rise in cardiac output, owing to exercise-induced pulmonary vasoconstriction[81] and elevated pulmonary vascular resistance.[82] We recommend that patients with PAH not lift objects heavier than 25 pounds or anything that might cause them to strain, causing elevation in intrathoracic pressure. We do encourage low-level cardiovascular, aerobic exercise to prevent deconditioning.

Immunization. Although no studies have specifically addressed the role of immunization in patients with PAH, we believe that routine pneumococcal vaccination and annual influenza vaccination are indicated. Hepatitis A vaccination should be considered in patients with congestive hepatopathy or portopulmonary hypertension.[83,84]

Pregnancy. Patients with PAH must avoid becoming pregnant. The physiologic changes associated with pregnancy severely stress an already overloaded right ventricle.[85] Some form of birth control is mandatory for women of childbearing age who have PAH. There has been concern that the estrogens in oral contraceptives might exacerbate in situ thrombosis,[86] but recent evidence suggests that there is no increased risk from the newer oral contraceptives with a lower estrogen content.[20] Which form of birth control is best remains unknown, but surgical sterilization is the safest and most effective method.

Treatment costs. Formal cost analyses have not been published for the management of PAH. In 2002, *The Medical Letter* addressed cost issues for the three FDA-approved drugs for PAH. According to that analysis,[87] the yearly costs of therapy may be $72,000 for epoprostenol, $93,000 for treprostinil, and $36,000 for bosentan. These numbers do not reflect device-related charges for epoprostenol or treprostinil, nor do they reflect the lab charges for mandatory ongoing liver function tests for bosentan. Additional costs for warfarin, digoxin, or diuretics seem minor in comparison.

Anecdotally, some patients with PAH have quit their jobs, legally separated from their spouses, or moved to other counties to become eligible for Medicaid and obtain coverage for these drugs. Nevertheless, in light of the significant clinical or mortality benefits, these drugs are recommended despite their costs.[88]

Prognosis. Discussing prognosis and end-of-life issues with patients who have PAH is often difficult. The only three therapies associated with a mortality benefit in patients with PAH to date are warfarin, calcium channel blockers, and epoprostenol, and only epoprostenol has been shown to improve survival in a prospective, randomized trial.[18] The cause of death in patients with primary pulmonary hypertension is usually progressive right heart failure or sudden death.[2] A recent study showed dismal results in the outcomes of PAH patients who underwent a circulatory arrest protocol.[89] Intense research for newer and better treatment options and continued outcomes research will help address these issues over time.

REFERENCES

1. **Rich S, ed.** Primary pulmonary hypertension: executive summary from the World Symposium on Primary Pulmonary Hypertension. Geneva: World Health Organization, 1998.
2. **D'Alonzo GE, Barst RJ, Ayres SM, et al.** Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991;115:343–349.
3. **Berger M, Haimowitz A, van Tosh A, Berdoff RL, Goldberg E.** Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous-wave Doppler ultrasound. J Am Coll Cardiol 1985; 6:359–365.
4. **Homma A, Anzueto A, Peters JI, et al.** Pulmonary artery systolic

pressures estimated by echocardiogram vs cardiac catheterization in patients awaiting lung transplantation. J Heart Lung Transplant 2001; 20:833–839.
5. **Pepke-Zaba J, Higenbottam TW, Dinh-Xuan AT, Stone D, Wallwork J.** Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. Lancet 1991; 38:1173–1174.
6. **Rubin LJ, Groves BM, Reeves JT, Frosolono M, Handel F, Cato AE.** Prostacyclin-induced acute pulmonary vasodilation in primary pulmonary hypertension. Circulation 1982; 66:334–338.
7. **Morgan JM, McCormack DG, Griffiths MJ, Morgan CJ, Barnes PJ, Evans TW.** Adenosine as a vasodilator in primary pulmonary hypertension. Circulation 1991;84:1145–1149.
8. **Klings ES, Hill NS, Ieong MH, Simms RW, Korn JH, Farber HW.** Systemic sclerosis-associated pulmonary hypertension: short- and long-term effects of epoprostenol (prostacyclin). Arth Rheum 1999; 42:2638–2645.
9. **Rich S, Dantzker DR, Ayres SM, et al.** Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987; 107:216–223.
10. **Rich S, D'Alonzo GE, Dantzker DR, et al.** Magnitude and implications of spontaneous hemodynamic variability in primary pulmonary hypertension. Am J Cardiol 1985; 55:159–163.
11. **Reeves JT, Groves BM, Turkevich D.** The case for treatment of selected patients with primary pulmonary hypertension. Am Rev Respir Dis 1986; 134:342–346.
12. **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.
13. **Rich S, Brundage BH.** High-dose calcium channel-blocking therapy for primary pulmonary hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy. Circulation 1987; 76:135–141.
14. **Barst RJ.** Pharmacologically induced pulmonary vasodilatation in children and young adults with primary pulmonary hypertension. Chest 1986; 89:497–503.
15. **Sitbon O, Humbert M, Jagot JL, et al.** Inhaled nitric oxide as a screening agent for safety identifying responders to oral calcium-channel blockers in primary pulmonary hypertension. Eur Respir J 1998; 12:265–270.
16. **Friedman R, Mears JG, Barst RJ.** Continuous infusion of prostacyclin normalizes plasma markers of endothelial cell injury and platelet aggregation in primary pulmonary hypertension. Circulation 1997; 96:2782–2784.
17. **Barst RJ, Rubin LJ, McGoon MD, et al.** Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. Ann Intern Med 1994; 121:409–415 [see comments in Ann Intern Med 1994; 121:463–464].
18. **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.
19. **Rubin LJ, Mendoza J, Hood M, et al.** Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. Ann Intern Med 1990; 112:485–491.
20. **Naeije R, Vachiery J-L.** Medical therapy of pulmonary hypertension: conventional therapies. Clin Chest Med 2001; 22:517–527.
21. **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; 114:1269–1275.
22. **Rich S, Kaufmann E.** High dose titration of calcium channel blocking agents for primary pulmonary hypertension: guidelines for short-term drug testing. J Am Coll Cardiol 1991; 18:1323–1327.
23. **Kuo PC, Johnson LB, Plotkin JS, Howell CD, Bartlett ST, Rubin LJ.** Continuous intravenous infusion of epoprostenol for the treatment of portopulmonary hypertension. Transplantation 1997; 63:604–606.
24. **Vane JR, Botting RM.** Pharmacodynamic profile of prostacyclin. Am J Cardiol 1995; 75:3A–10A.
25. **Rosenzweig EB, Kerstein D, Barst RJ.** Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. Circulation 1999; 99:1858–1865.
26. **Stricker H, Domenighetti G, Mombelli G.** Prostacyclin for HIV-associated pulmonary hypertension. Ann Intern Med 1997; 127:1043.
27. **Humbert M, Sanchez O, Fartoukh M, Jagot JL, Sitbon O, Simonneau G.** Treatment of severe pulmonary hypertension secondary to connective tissue diseases with continuous IV epoprostenol (prostacyclin). Chest 1998; 114(1 suppl):80S–82S.
28. **Jones DK, Higenbottam TW, Wallwork J.** Treatment of primary pulmonary hypertension with intravenous epoprostenol (prostacyclin). Br Heart J 1987; 57:270–278.
29. **Higenbottam T, Wheeldon D, Wells F, et al.** Long-term treatment of primary pulmonary hypertension with continuous intravenous epoprostenol (prostacyclin). Lancet 1984; 1:1046–1047.
30. **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; 338:273–277.
31. **McLaughlin VV, Shillington A, Rich S.** Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002; 106:1477–1482.
32. **Conte JV, Gaine SP, Orens JB, Harris T, Rubin LJ.** The influence of continuous intravenous prostacyclin therapy for primary pulmonary hypertension on the timing and outcome of transplantation. J Heart Lung Transplant 1998; 17:679–685.
33. **Nagaya N, Sasaki N, Ando M, et al.** Prostacyclin therapy before pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension. Chest 2003; 123:338–343.
34. **Simmoneau G, Fartoukh M, Sitbon O, et al.** Primary pulmonary hypertension associated with the use of fenfluramine derivatives. Chest 1998; 114(3 Suppl):195S–199S.
35. **Higenbottam TW, Spiegelhalter D, Scott JP, et al.** Prostacyclin (epoprostenol) and heart-lung transplantation as treatments for severe pulmonary hypertension. Br Heart J 1993; 70:366–370.
36. **McLaughlin VV, Meyer PM, Rich S.** Optimal dose range of prostacyclin for patients with primary pulmonary hypertension [abstract]. Am J Respir Crit Care Med 2000; 161:A458.
37. **Hague K, Maurer JR, Arroliga AC, et al.** Infection related to indwelling catheters for long-term delivery of epoprostenol sodium (Flolan) [abstract]. Am J Respir Crit Care Med 2001; 163:A120.
38. **Rich S, McLaughlin VV.** The effects of chronic prostacyclin therapy on cardiac output and symptoms in primary pulmonary hypertension. J Am Coll Cardiol 1999; 34:1184–1187.
39. **Simonneau G, Barst RJ, Galie N, et al.** 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.
40. **Zhao YD, Springall DR, Hamid Q, et al.** Localization and characterization of endothelin-1 binding sites in the transplanted human lung. J Cardiovasc Pharmacol 1995; 26:S336–S340.
41. **Sato K, Oka M, Hasunuma K, et al.** Effects of separate and combined ETA and ETB blockade on ET-1-induced constriction in perfused rat lungs. Am J Physiol 1995; 269(5 Pt 1):L668–L672.
42. **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.
43. **Morelli S, Ferri C, Polettini E, et al.** Plasma endothelin-1 levels, pulmonary hypertension, and lung fibrosis in patients with systemic sclerosis. Am J Med 1995; 99:255–260.
44. **Shen JY, Chen SL, Wu YX, et al.** Pulmonary hypertension in systemic lupus erythematosus. Rheumatol Int 1999; 18:147–151.
45. **Celik G, Karabiyikoglu G.** Local and peripheral plasma endothe-

lin-1 in pulmonary hypertension secondary to chronic obstructive pulmonary disease. Respiration 1998; 65:289–294.
46. **Jia B, Zhang S, Chen Z, et al.** Plasma endothelin-1 concentrations in children with congenital heart defects. Minerva Pediatr 1998; 50:99–103.
47. **Cody RJ, Haas GJ, Binkley PF, et al.** Plasma endothelin correlates with the extent of pulmonary hypertension in patients with chronic congestive heart failure. Circulation 1992; 85:504–509.
48. **Langleben D, Barst RJ, Badesch D, et al.** Continuous infusion of epoprostenol improves the net balance between pulmonary endothelin-1 clearance and release in primary pulmonary hypertension. Circulation 1999; 99:3266–3271.
49. **Channick RN, 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.
50. **Rubin LJ, Badesch DB, Barst RJ, et al.** Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002; 346:896–903.
51. **Galie N, Hinderliter AL, Torbicki A, et al.** Effects of the oral endothelin receptor antagonist bosentan on echocardiographic and Doppler measures in patients with pulmonary arterial hypertension [abstract]. J Am Coll Cardiol 2002;39(5 suppl A):224A.
52. **Barst RJ, Rich S, Widlitz A, Horn EM, McLaughlin V, McFarlin J.** Clinical efficacy of sitaxsentan, an endothelin-A receptor antagonist, in patients with pulmonary arterial hypertension: open-label pilot study. Chest 2002; 121:1860–1868.
53. **Archer S, Hampl V, McKenzie Z, et al.** Role of endothelial-derived nitric oxide in normal and hypertensive pulmonary vasculature. Semin Respir Crit Care Med 1994; 15:179–189.
54. **Peliowski A, Finer NN, Etches PC, Tierney AJ, Ryan CA.** Inhaled nitric oxide for premature infants after prolonged rupture of the membranes. J Pediatr 1995; 126:450–453.
55. **Sitbon O, Brenot F, Denjean A, et al.** Inhaled nitric oxide as a screening vasodilator agent in primary pulmonary hypertension. Am Rev Respir Dis 1995; 151:384–389.
56. **Perez-Penate G, Julia-Serda G, Pulido-Duque JM, Gorriz-Gomez E, Cabrera-Navarro P.** One-year continuous inhaled nitrous oxide for primary pulmonary hypertension. Chest 2001; 119:970–973.
57. **Ghofrani HA, Wiedemann R, Rose F, et al.** Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. Lancet 2002; 360:895–900.
58. **Zimmermann AT, Calvert AF, Veitch EM.** Sildenafil improves right-ventricular parameters and quality of life in primary pulmonary hypertension. Int Med J 2002; 32:424–426.
59. **Jackson G, Chambers J.** Sildenafil for primary pulmonary hypertension: short and long-term symptomatic benefit. Int J Clin Pract 2002; 56:397–398.
60. **Littera R, La Nasa G, Derchi G, Cappellini MD, Chang CY, Contu L.** Long-term treatment with sildenafil in a thalassemic patient with pulmonary hypertension. Blood 2002; 100:1516–1517.
61. **Watanabe H, Ohashi K, Takeuchi K, et al.** Sildenafil for primary and secondary pulmonary hypertension. Clin Pharmacol Ther 2002; 71:398–402.
62. **Prasad S, Wilkinson J, Gatzoulis MA.** Sildenafil in primary pulmonary hypertension. N Engl J Med 2000; 343:1342.
63. **Nagaya N, Uematsu M, Oya H, et al.** Short-term oral administration of L-arginine improves hemodynamics and exercise capacity in patients with precapillary pulmonary hypertension. Am J Respir Crit Care Med 2001; 163:887–891.
64. **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.
65. **Hyers TM.** Venous thromboembolism. Am J Respir Crit Care Med 1999; 159:1–14.
66. **Jeffery TK, Wanstall JC.** Perindopril, an angiotensin converting enzyme inhibitor, in pulmonary hypertensive rats: comparative effects on pulmonary vascular structure and function. Br J Pharmacol 1999; 128:1407–1418.
67. **Kanazawa H, Okamoto T, Hirata K, Yoshikawa J.** Deletion polymorphisms in the angiotensin converting enzyme gene are associated with pulmonary hypertension evoked by exercise challenge in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000; 162(4 Pt 1):1235–1238.
68. **Naeije R.** Pulmonary circulation at high altitude. Respiration 1997; 64:429–434.
69. **Naeije R.** Preflight medical screening of patients. Eur Respir J 2000; 16:197–199.
70. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med 1980; 93:391–398.
71. **Rafanan AL, Golish JA, Dinner DS, et al.** Nocturnal hypoxemia is common in primary pulmonary hypertension. Chest 2001; 120:894–899.
72. **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.
73. **Rubin LJ.** Primary pulmonary hypertension. N Engl J Med 1997; 336:111–117.
74. International guidelines for the selection of lung transplant candidates. The American Society for Transplant Physicians (ASTP)/American Thoracic Society (ATS)/European Respiratory Society (ERS)/International Society for Heart and Lung Transplantation (ISHLT). Am J Respir Crit Care Med 1998; 158:335–339.
75. **Rich S, Lam W.** Atrial septostomy as palliative therapy for refractory primary pulmonary hypertension. Am J Cardiol 1983; 51:1560–1561.
76. **Sandoval J, Rothman A, Pulido T.** Atrial septostomy for pulmonary hypertension. Clin Chest Med 2001; 22:547–560.
77. **Venkateshiah SB, Arroliga AC, Mehta AC, et al.** Safety of surgery in patients with pulmonary artery hypertension [abstract]. Am J Respir Crit Care Med 2002; 165:B53.
78. **Starkel P, Vera A, Gunson B, Mutimer D.** Outcome of liver transplantation for patients with pulmonary hypertension. Liver Transpl 2002; 8:382–388.
79. **Taura P, Garcia-Valdecasas JC, Beltran J, et al.** Moderate primary pulmonary hypertension in patients undergoing liver transplantation. Anesth Analg 1996; 83:675–680.
80. **Castro M, Krowka MJ, Schroeder DR, et al.** Frequency and clinical implications of increased pulmonary artery pressures in liver transplant patients. Mayo Clin Proc 1996; 71:543–551.
81. **Kafi SA, Melot C, Vachiery JL, et al.** Partitioning of pulmonary vascular resistance in primary pulmonary hypertension. J Am Coll Cardiol 1998; 31:1372–1376.
82. **Janicki JS, Weber KT, Likoff MJ, et al.** The pressure-flow response of the pulmonary circulation in patients with heart failure and pulmonary vascular disease. Circulation 1985; 72:1270–1278.
83. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 1996; 45(RR-15):1–30.
84. **Lemon SM, Thomas DL.** Vaccines to prevent viral hepatitis. N Engl J Med 1997; 336:196–204.
85. **Weiss BM, Zemp L, Seifert B, Hess OM.** Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. J Am Coll Cardiol 1998; 31:1650–1657.
86. **Oakley C, Somerville J.** Oral contraceptives and progressive pulmonary vascular disease. Lancet 1968; 1:890–893.
87. Treprostinil (Remodulin) for pulmonary arterial hypertension. Med Lett Drugs Ther 2002; 44:80–82.
88. **Rich S.** Prostacyclin and primary pulmonary hypertension [comment]. Ann Intern Med 1994; 121:463–464.
89. **Hoeper MM, Galie N, Murali S, et al.** Outcome after cardiopulmonary resuscitation in patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 2002; 165:341–344.

Implementing a shared-care approach to improve the management of patients with pulmonary arterial hypertension

MAJID M. MUGHAL, MD; BRIAN MANDELL, MD, PHD; KAREN JAMES, MD; KAY STELMACH, RN; AND OMAR A. MINAI, MD

ABSTRACT

Patients with pulmonary arterial hypertension (PAH) may present to internists, rheumatologists, cardiologists, or pulmonologists. This breadth of clinicians who encounter PAH patients, together with the complicated nature of PAH as a disease entity, argues for a shared-care approach to the management of these patients. This review describes the contributions of several key specialties to PAH management and outlines the collaborative PAH management model in place at our institution.

Successful approaches to pulmonary arterial hypertension (PAH) are typically collaborative approaches. Patients with PAH may present to general internists, rheumatologists, cardiologists, or pulmonologists. Moreover, centers of excellence in PAH across the United States bring together the expertise of pulmonologists in pulmonary and pulmonary vascular physiology, respiratory function testing, and pathology; the expertise of cardiologists in cardiovascular physiology, cardiac imaging, and pathology; and the expertise of rheumatologists in systemic autoimmune diseases.

These factors argue for a shared-care team approach to optimize the care of patients with PAH. An ideal way to embody this team approach is to form a pulmonary hypertension center, although the principles of this approach can apply even without such a formal center in place.

Most centers of excellence in PAH across the United States are run by either pulmonologists or cardiologists, with members of the other specialty playing a prominent role. This is natural, given that PAH has long been an area of interest for pulmonologists and cardiologists, since most patients with PAH present to these specialists by the very nature of their typical symptoms, including dyspnea on exertion and chest pain.

Nevertheless, the roles of specialists vary at different pulmonary hypertension centers, and every center needs more than just the expertise of a pulmonologist, a cardiologist, and a rheumatologist. The comprehensive care of patients with this complicated disease requires input from such team members as a pathologist with experience in pulmonary vascular diseases, an active interventional radiology program, an experienced thoracic transplant team, laboratory support, and nurses with expertise in PAH.

This article describes the contributions of key specialists to the management of patients with PAH and outlines the collaborative model for PAH patient management at the Cleveland Clinic Foundation.

From the Departments of Pulmonary and Critical Care Medicine (M.M.M., K.S., O.A.M.), Rheumatic and Immunologic Disease (B.M.), and Cardiovascular Medicine (K.J.), The Cleveland Clinic Foundation, Cleveland, Ohio.

Address: Omar A. Minai, MD, Department of Pulmonary and Critical Care Medicine, A90, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail: minaio@ccf.org.

Disclosure: Dr. Minai has indicated that he has been a consultant to Actelion Pharmaceuticals. All other authors have indicated that they have no commercial affiliations or interests that pose a potential conflict of interest with this article.

■ SCREENING AND DIAGNOSIS

At our institution, patients with PAH are referred to our pulmonary hypertension center, where their care is directed by a pulmonologist, who performs the initial evaluation. Input is sought from other specialists, including cardiologists and rheumatologists (whose roles are outlined below), if the workup reveals the possibility of a secondary etiology.

Pulmonary arterial hypertension may occur as a primary disease or as a complication of various systemic, cardiac, or pulmonary conditions,[1,2] as described earlier in this supplement. Some of these underlying diseases may be suspected on clinical grounds, but the nonspecific nature of the symptoms makes recognizing an underlying disease difficult unless the extrapulmonic symptoms or findings are evident. In most patients PAH has an underlying etiology, and the possibility of secondary causes should be vigorously explored. Because of the insidious onset and progression of PAH, its nonspecific symptoms, and its varied underlying causes, a high index of suspicion is needed for a correct and timely diagnosis.

Conditions associated with PAH should be identified to allow a focused screening strategy and effective treatment. Most patients are identified during evaluation of symptoms or incidentally during evaluation for unrelated problems. A transthoracic echocardiogram is currently the preferred screening test for PAH. Screening may be appropriate in any group of patients believed to be at increased risk of developing PAH. The biggest challenges that PAH centers and physicians who manage PAH face today are deciding whom and how to screen for this rare yet lethal disease and determining the cost-effectiveness of such a screening process. This is especially pertinent given the relative nonspecificity of the presenting symptoms and the fact that patients are typically in later stages of the disease by the time the diagnosis is finally made.

Role of the rheumatologist

Given the high incidence of PAH in patients with systemic autoimmune diseases,[3] the rheumatologist is an integral member of the PAH management team. This is especially true since many patients with systemic autoimmune diseases typically present with symptoms or findings related to their underlying rheumatologic disease long before they develop PAH. A high index of suspicion and careful attention to the patient's complaints may allow for earlier diagnosis and intervention.

TABLE 1
Systemic autoimmune diseases associated with pulmonary arterial hypertension

Scleroderma
• Diffuse[7]
• Limited (CREST syndrome)[9]
Systemic lupus erythematosus[13,14]
Mixed connective tissue disease[15]
Rheumatoid arthritis[16]
Dermatomyositis/polymyositis[17,18]
Behçet disease
Takayasu arteritis
Antiphospholipid antibody syndrome

CREST = calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias

Patients with scleroderma, systemic lupus erythematosus, and certain other systemic autoimmune diseases **(Table 1)** are considered to be at high risk for developing PAH.[3] Ungerer et al[4] estimated the prevalence of PAH to be as high as 33% in patients with scleroderma. Although early retrospective studies[5,6] based on autopsy or surgical pathology specimens reported a higher prevalence of PAH among patients with limited scleroderma, or the "CREST syndrome" (calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias), more recent clinical studies have indicated a prevalence of PAH closer to 30% to 35%.[7–9] Pulmonary arterial hypertension may occur as an isolated complication of scleroderma or secondary to interstitial fibrosis. Studies show a significant increase in mortality in scleroderma patients with PAH compared with those without PAH.[10–12]

Pulmonary arterial hypertension has been reported in a smaller proportion of patients with systemic lupus erythematosus, 4% to 14%, but is associated with a 2-year mortality rate of 25% to 50% among these patients.[13,14]

As many as 66% of patients with mixed connective tissue disease have been said to develop PAH.[15] The incidence of PAH in patients with mixed connective tissue disease may be high because this entity represents a specific clinical subset of patients with a predominant sclerodermatous pattern of disease.

Causes of elevated pulmonary artery pressure in

TABLE 2
Evaluation for pulmonary arterial hypertension in patients with systemic autoimmune disease

History and review of symptoms Raynaud phenomenon, esophageal reflux, digital ulcers, vascular bruits, rash, oral ulcers, alopecia, thyroid examination, lymph node examination, fever/sweats, edema
Laboratory studies Complete blood count, coagulation profile, liver enzyme tests, creatinine phosphokinase, urinalysis (with fresh sediment examination), autoantibody screen directed by history and physical examination
Chest radiograph
Electrocardiogram*
Pulmonary function tests* Spirometry, lung volume tests, diffusion capacity
Ventilation-perfusion lung scan
Echocardiogram*
Right heart catheterization

*Performed routinely at diagnosis and at routine follow-up intervals as discussed in the text.

patients with rheumatoid arthritis include chronic interstitial fibrosis and arterial intimal proliferation.[16] Polymyositis[17] and dermatomyositis[18] also are associated with fibrointimal proliferation and obliteration of small pulmonary arteries.

It is important to remember that patients with these diseases, especially scleroderma, may curtail their activities on account of musculoskeletal or peripheral vascular involvement and therefore may not present with dyspnea on exertion or chest discomfort. It is also extremely difficult to define the role of interstitial fibrosis as opposed to PAH in these patients, especially since a subgroup of patients may present with both.

It is critical to follow patients with limited scleroderma closely since these patients tend to present late in the course of PAH and have lower survival rates than those with coexistent interstitial fibrosis and restrictive lung disease.[12] On initial evaluation and subsequent visits, this subgroup of patients should be asked specifically about cardiopulmonary complaints, including cough, exertional dyspnea, pedal edema, chest pain, orthopnea, syncope, and presyncope.

Findings and symptoms of underlying systemic autoimmune diseases should regularly be looked for, including Raynaud phenomenon, telangiectasias, synovitis, gastroesophageal reflux disease, dysphagia, and others **(Table 2)**.

Screening tests and recommendations. All patients with scleroderma should undergo a chest radiograph, an electrocardiogram, and complete pulmonary function testing (spirometry, lung volume tests, and diffusion capacity) at baseline.[1] Ungerer et al[4] showed that, among a number of noninvasive tests studied, a diffusion capacity of lung for carbon monoxide (DLCO) below 43% of the predicted value had the greatest sensitivity (67%) for PAH and a dilated right descending pulmonary artery on chest radiograph had the greatest specificity (100%) for PAH. Both interstitial fibrosis and PAH may be associated with a decline in DLCO, but a disproportionate fall in DLCO relative to forced vital capacity should prompt an evaluation for PAH in patients with the CREST syndrome.[10,12] A DLCO less than 40% of predicted also portends a worse prognosis.[19]

Patients with scleroderma should be considered at high risk for PAH, and a transthoracic echocardiogram is recommended at baseline regardless of whether they have symptoms of PAH. Dyspnea on exertion or a declining DLCO in the absence of an alternate explanation, especially in a patient with an autoimmune disease of 10 years' or more duration, should trigger PAH evaluation with repeated transthoracic echocardiography.

There are no clear literature-based recommendations on who should be screened for PAH or how frequently, but we believe that all patients with scleroderma should have yearly pulmonary function tests and those with a declining DLCO should have a transthoracic echocardiogram. Some authorities have recommended yearly transthoracic echocardiography for all scleroderma patients.[20] In view of the lower incidence of PAH in patients with systemic lupus erythematosus, rheumatoid arthritis, and other systemic autoimmune diseases, transthoracic echocardiography is recommended only if the patient has otherwise unexplained symptoms compatible with PAH.

Serologic studies for patients with systemic autoimmune diseases should be ordered selectively on the basis of the history and physical examination. Anticentromere antibody is seen predominantly in patients with limited scleroderma and may indicate an increased risk for PAH.[3] The presence of antibodies to U3 small nucleolar ribonucleoprotein (U3 snRNP) has been associated with PAH in patients

with scleroderma[21] and may be diagnostically useful in patients suspected of having PAH. The presence of antiendothelial cell antibodies has been suggested to predict PAH in patients with systemic lupus erythematosus[22]; this is an area of ongoing study. Patients with antiphospholipid antibodies, with or without systemic lupus erythematosus, may develop PAH on the basis of occult, chronic thromboembolic disease. Some of these antibodies will also bind to endothelial cells. Many patients with primary pulmonary hypertension have elevated titers of antinuclear antibodies.[23] Debate continues on whether this represents a forme fruste of systemic lupus erythematosus or scleroderma or whether it is just a laboratory feature of primary pulmonary hypertension.

Role of the cardiologist

The cardiologist has an important role in screening and managing patients with PAH by excluding cardiac causes of secondary pulmonary hypertension **(Table 3)** and treating any that are identified.

Pulmonary arterial hypertension associated with heart disease can be caused by increased pulmonary blood flow (precapillary pulmonary hypertension) or by increased pulmonary venous pressure (postcapillary pulmonary hypertension). Eventually, the pressure or flow abnormalities cause pulmonary vascular remodeling, which perpetuates increased vascular resistance by further narrowing the pulmonary arterial tree (mixed pulmonary hypertension).[24] The category of increased blood flow includes the congenital heart defects with left-to-right shunt (atrial septal defect, ventricular septal defect, patent ductus arteriosus, transposition of great vessels, and partial anomalous pulmonary venous drainage) and conditions associated with an increase in total blood volume, cardiac output, or both, such as thyrotoxicosis and chronic renal failure.

Left ventricular failure is the most common cause of pulmonary venous hypertension in both adults and children. The more common causes of left ventricular dysfunction include coronary artery disease, cardiomyopathy, mitral valve disease, and diastolic dysfunction. Some patients with left-to-right shunts may be clinically asymptomatic, although they usually complain of fatigue, palpitations, and dyspnea on exertion and may show signs of cyanosis and cardiac failure. In contrast, patients with left ventricular dysfunction present with signs and symptoms predominantly arising from acute or subacute pulmonary edema. Examination of the heart and systemic vessels may provide valuable clues about the nature of the shunt and valvular heart diseases.

TABLE 3
Role of the cardiologist in the assessment for pulmonary arterial hypertension

Exclude cardiac causes of secondary pulmonary hypertension:
- Systolic left ventricular failure
  - —Dilated cardiomyopathy
  - —Ischemic cardiomyopathy
  - —Other (alcohol-related, peripartum, familial, etc)
- Diastolic dysfunction
  - —Hypertensive heart disease
  - —Constriction
  - —Restriction
- Valvular heart disease
- Congenital heart disease

Perform diagnostic imaging studies to assess for cardiac secondary causes of pulmonary hypertension:
- Echocardiography, including transesophageal
- Right heart catheterization (hemodynamics)
- Computed tomographic scanning or magnetic resonance imaging (used selectively)
- Adjunctive ischemia evaluation, including stress testing or coronary angiography (used selectively)

Following a thorough history and physical examination, selected cardiac studies are performed. Echocardiography, including a transesophageal echocardiogram, is an effective means of screening for the presence of valvular diseases, left ventricular dysfunction, and septal defects. When appropriate, computed tomographic scanning or magnetic resonance imaging of the pericardium may be performed to exclude restrictive and constrictive heart diseases. Right heart catheterization is recommended for all patients undergoing evaluation for PAH and is necessary to confirm the presence of PAH and to establish responsiveness to vasodilator agents. The right atrial pressure, cardiac index, and mean pulmonary artery pressure should be noted carefully because of their prognostic significance.[25]

■ A COLLABORATIVE TREATMENT MODEL

At our institution, the treatment and follow-up of patients with PAH is usually performed by the pulmonologists, cardiologists, and nurse PAH coordinators who make up the PAH team. Once PAH is diagnosed, the severity of hypertension and the underlying cause dictate further management. Most pulmonary hypertension centers manage and make treatment recom-

TABLE 4
Web sites for patient education on pulmonary arterial hypertension

Sites specific to pulmonary hypertension
www.phassociation.org (Pulmonary Hypertension Association)
General health care sites
www.nhlbi.nih.gov/health/public/lung/other/pph.htm (National Heart, Lung, and Blood Institute)
www.who.int (World Health Organization)*
www.americanheart.org (American Heart Association)*
www.clevelandclinic.org/health (Cleveland Clinic Foundation)*
www.MayoClinic.com (Mayo Clinic)*

*To obtain relevant information, patients should do a site search for "pulmonary hypertension."

mendations for patients with various forms of PAH, thromboembolic pulmonary hypertension, and PAH due to inflammatory causes.[1] Pulmonary hypertension caused by most other diseases (chronic obstructive pulmonary disease, sleep apnea, etc) is treated by treating the underlying disease.

At our institution, cardiologists from the section of heart failure perform most right heart catheterizations for PAH patients. Afterwards, patients are admitted to the heart failure unit if they are deemed to require continuous intravenous epoprostenol. The physician directing the PAH team (at our institution, a pulmonologist or sometimes a cardiologist) makes treatment decisions on the basis of the type of PAH, the patient's functional class, and the hemodynamic measurements obtained from right heart catheterization. All treatment decisions are made in consultation with the other physicians who are participating in the patient's care.

Treatment considerations

Treatment of PAH should include attempts to reverse any identified contributing factors, which often brings substantial clinical improvement. For instance, PAH associated with obstructive sleep apnea may improve with nasal continuous positive airway pressure, thromboendarterectomy may be helpful in treating accessible thromboemboli,[26] and patients with marked right ventricular dysfunction and edema often respond symptomatically to salt restriction and diuretics.

The potential therapeutic and survival benefits of oxygen supplementation in patients with chronic hypoxemia should never be overlooked. Supplemental oxygen should be prescribed for patients with chronic lung disease and arterial oxygen pressure measured below 55 to 60 mm Hg, and for patients with significant sleep-induced or exercise-induced hypoxemia.[27–29] Warfarin administration has also been associated with improved survival in patients with primary pulmonary hypertension.[30–32]

Surgical treatment, including atrial septostomy and lung or heart-lung transplantation, may be considered for patients with severe PAH who do not respond to other interventions.[33–35] In general, the need for lung transplantation in patients with primary pulmonary hypertension has declined with the newer drug therapies (epoprostenol, bosentan, treprostinil, calcium channel blockers, etc) discussed by Gildea et al earlier in this supplement. Choosing the appropriate patient as a transplant candidate and the correct time to refer to a transplant center are the crucial first steps, taken by the pulmonary hypertension center, in the transplantation process.

Pulmonary hypertension center referral and management

The PAH coordinator is usually the first contact in the referral process. While most referrals come from physicians, many patients call the pulmonary hypertension center directly. The PAH coordinator receives the medical records, reviews test results, and creates a schedule to complete the evaluation process in consultation with the pulmonologist. After the initial physical assessment, the coordinator arranges any additional testing, a cardiology consultation, and right heart catheterization, if appropriate. At our institution, patients with PAH, especially those receiving epoprostenol infusion, are assigned beds in select cardiac wards where the nurses are adept at caring for patients with cardiovascular diseases and are familiar with epoprostenol infusions.

When treatment has been determined, the PAH coordinator offers on-site teaching about the disease to the patient and his or her family, providing them with the most recent information **(Table 4)**. The coordinator also submits information for insurance verification for PAH treatments and arranges home nursing and follow-up appointments.

Patients with PAH require ongoing monitoring of their medication dosages and screening for side effects. For instance, intravenous epoprostenol has been associated with a number of adverse effects that should be monitored for, and patients receiving bosentan require liver function tests before therapy is started and monthly thereafter. The PAH coordinator keeps a log of every event and medication change, as well as a log of right heart catheterization results.

As long as patients are on therapy, they return to our pulmonary hypertension clinic every 2 to 3 months for clinical examination and a 6-minute walk test. Echocardiography and right heart catheterization are performed every 6 and 12 months, respectively, as long as patients are progressing as expected (see article by Gildea et al in this supplement). Patients' complaints and concerns are triaged over the phone by the PAH coordinator in consultation with the pulmonologist. Patients who need further attention are seen in the pulmonary hypertension clinic for evaluation.

The PAH coordinator provides an invaluable communication link between the patient and the various physicians involved in his or her care, preventing redundancy and ensuring that care is timely. The coordinator also serves a crucial function by coordinating the two essential components of PAH patient management: (1) the pulmonary hypertension center physicians and ancillary support (nursing, pathology, radiology), and (2) the patient's support network at home, consisting of local physicians, home care agencies, and family members. Keeping these two components mutually informed and working together is a key to continuing optimal care for the patient.

REFERENCES

1. **Rich S, ed.** Primary pulmonary hypertension: executive summary from the World Symposium on Primary Pulmonary Hypertension. Geneva: World Health Organization, 1998.
2. **McGoon MD.** The assessment of pulmonary hypertension. Clin Chest Med 2001; 22:493–508.
3. **Minai OA, Dweik RA, Arroliga AC.** Manifestations of scleroderma pulmonary disease. Clin Chest Med 1998; 19:713–31.
4. **Ungerer RG, Tashkin DP, Furst D, et al.** Prevalence and clinical correlates of pulmonary arterial hypertension in progressive systemic sclerosis. Am J Med 1983; 75:65–74.
5. **Salerni R, Rodnan GP, Leon DF, et al.** Pulmonary hypertension in the CREST syndrome variant of progressive systemic sclerosis (scleroderma). Ann Intern Med 1977; 86:394–399.
6. **Yousem SA.** The pulmonary pathologic manifestations of the CREST syndrome. Hum Pathol 1990; 21:467–474.
7. **Morelli S, De Marzio P, Valesini G, et al.** Pulmonary hypertension in systemic sclerosis. G Ital Cardiol 1993; 23:871–876.
8. **Murata I, Kihara H, Shinohara S, et al.** Echo evaluation of pulmonary arterial hypertension in patients with progressive systemic sclerosis and related syndromes. Jpn Circ J 1992; 56:983–991.
9. **Battle RW, Davitt MA, Cooper SM, et al.** Prevalence of pulmonary hypertension in limited and diffuse scleroderma. Chest 1996; 110:1515–1519.
10. **Stupi AM, Steen VD, Owens GR, et al.** Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. Arth Rheum 1986; 29:515–524.
11. **Steen VD, Graham G, Conte C, et al.** Isolated diffusing capacity reduction in systemic sclerosis. Arth Rheum 1992; 35:765–770.
12. **Koh ET, Lee P, Gladman DD.** Pulmonary hypertension in scleroderma: an analysis of 17 patients. Br J Rheumatol 1996; 35:989–993.
13. **Tanaka E, Harigai M, Tanaka M, et al.** Pulmonary hypertension in systemic lupus erythematosus: evaluation of clinical characteristics and response to immunosuppressive treatment. J Rheumatol 2002; 29:282–287.
14. **Li EK, Tam LS.** Pulmonary hypertension in systemic lupus erythematosus: clinical association and survival in 18 patients. J Rheumatol 1999; 26:1923–1929.
15. **Wiener-Kronish JP, Solinger AM, Warnock ML, et al.** Severe pulmonary involvement in mixed connective tissue disease. Am Rev Respir Dis 1981; 124:499–503.
16. **Helmers R, Galvin J, Hunninghake GW.** Pulmonary manifestations associated with rheumatoid arthritis. Chest 1991; 100:235–238.
17. **Bunch TW, Tancredi RG, Lie JT.** Pulmonary hypertension in polymyositis. Chest 1981; 79:105–107.
18. **Caldwell IW, Aitchison JD.** Pulmonary hypertension in dermatomyositis. Br Heart J 1956; 18:273–276.
19. **Peters-Golden M, Wise RA, Hochberg MC, et al.** Carbon monoxide diffusing capacity as predictor of outcome in systemic sclerosis. Am J Med 1984; 77:1027–1034.
20. **Fagan KA, Collier DH, Badesch DB.** Scleroderma-associated pulmonary hypertension: who's at risk and why. Adv Pulmonary Hypertens 2002; 1:5–9.
21. **Okano Y, Steen VD, Medsger TA Jr.** Autoantibody to U3 nucleolar ribonucleoprotein (fibrillarin) in patients with systemic sclerosis. Arth Rheum 1992; 35:95–100.
22. **Yoshio T, Masuyama J, Sumiya M, et al.** Antiendothelial cell antibodies and their relation to pulmonary hypertension in systemic lupus erythematosus. J Rheumatol 1994; 21:2058–2063.
23. **Rich S, Kieras K, Hart K, et al.** Antinuclear antibodies in primary pulmonary hypertension. J Am Coll Cardiol 1986; 8:1307–1311.
24. **Chatterjee K, De Marco T, Alpert JS.** Pulmonary hypertension: hemodynamic diagnosis and management. Arch Intern Med 2002; 162:1925–1933.
25. **D'Alonzo GE, Barst RJ, Ayres SM, et al.** Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991; 115:343–349.
26. **Moser KM, Auger WR, Fedullo PF.** Chronic major-vessel thromboembolic pulmonary hypertension. Circulation 1990; 81:1735–1743.
27. **Tarpy SP, Celli BR.** Long-term oxygen therapy. N Engl J Med 1995; 333:710–714.
28. **Bowyer JJ, Busst CM, Denison DM, et al.** Effect of long term oxygen treatment at home in children with pulmonary vascular disease. Br Heart J 1986; 55:385–390.
29. **Rafanan AL, Golish JA, Dinner DS, et al.** Nocturnal hypoxemia is common in primary pulmonary hypertension. Chest 2001; 120:894–899.
30. **Fuster V, Steele PM, Edwards WD, et al.** Primary pulmonary hypertension: natural history and the importance of thrombosis. Circulation 1984; 70:580–587.
31. **Frank H, Mlczoch J, Huber K, et al.** The effect of anticoagulant therapy in primary and anorectic drug-induced pulmonary hypertension. Chest 1997; 112:714–721.
32. **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.
33. **Sandoval J, Rothman A, Pulido T.** Atrial septostomy for pulmonary hypertension. Clin Chest Med 2001; 22:547–560.
34. **Kerstein D, Levy PS, Hsu DT, et al.** Blade balloon atrial septostomy in patients with severe primary pulmonary hypertension. Circulation 1995; 91:2028–2035.
35. **Rubin LJ.** Primary pulmonary hypertension. N Engl J Med 1997; 336:111–117.