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## Pulmonary Arterial Hypertension

Vallerie V. McLaughlin, MD; Michael D. McGoon, MD

Most practicing cardiologists see patients with pulmonary hypertension (PH) on a regular basis. Although this is most commonly in the form of pulmonary venous hypertension related to elevated left heart pressures, the explosion in knowledge of and treatment for pulmonary arterial hypertension (PAH) over the past decade obligates cardiologists to be more cognizant of this disorder. In this review, we will discuss the pathobiology, classification, diagnosis, and treatment of PAH in adults. The term PAH in this context refers specifically to a pulmonary hypertensive state limited predominantly to the arterial component of the pulmonary vasculature and constitutes one of the main classifications of clinical PH diseases.

### Pathobiological Changes in PH

The normal pulmonary vasculature is a low-pressure system with less than one tenth the resistance to flow observed in the systemic vascular bed. The mechanistic and structural alterations underlying the development and progression of pulmonary vasculopathy have become increasingly well characterized. Some or all of these perturbations may play a role in all forms of PAH, but some molecular and cellular substrates, and the histopathologic consequences, have been associated with particular clinical types of PH.

PH refers to the hemodynamic state in which the pressure measured in the pulmonary artery is elevated. By expert consensus, PAH is regarded as a mean pulmonary artery pressure (mPAP) greater than 25 mm Hg in the setting of normal or reduced cardiac output and a normal pulmonary capillary wedge pressure.<sup>1</sup> The evolution of pulmonary vascular disease frequently originates with the interaction of a predisposing state and 1 or more inciting stimuli, a concept referred to as the "multiple-hit hypothesis."<sup>2,3</sup> Two or more hits may consist of a genetic substrate combined with an additional genetic condition (either a mutation or polymorphism), a coexisting disease, or an environmental exposure. Once a constellation of permissive and provocative factors exists, various mechanisms are activated that lead to vascular constriction, cellular proliferation, and a prothrombotic state in varying degrees, which results in PAH and its clinical sequelae.

### Genetic Substrates

Several genotypes have been confirmed to be associated with the occurrence of PAH. The presence of these genotypes, or

the observation of more than 1 member of a family, represents one form of PAH.

### *Bone Morphogenetic Protein Receptor II*

Bone morphogenetic protein receptor II (BMPR2) is a component of the heteromeric vascular smooth muscle cell BMPR receptor, a member of the transforming growth factor- $\beta$  family. Exonic mutations of the gene encoding for BMPR2 were identified in 2000 to be associated with familial PAH (FPAH).<sup>4,5</sup> The effect of a mutation in the BMPR2 receptor protein is an aberration of signal transduction in the pulmonary vascular smooth muscle cell, which in turn results in a postulated alteration of apoptosis that favors cellular proliferation.

### *Activin-Like Kinase Type-1*

Another transforming growth factor- $\beta$ , the activin-like kinase type-1 receptor on endothelial cells, has mutations in some patients with hereditary hemorrhagic telangiectasia and PAH.<sup>6</sup>

### *5-Hydroxytryptamine (Serotonin) Transporter*

5-Hydroxytryptamine (serotonin; 5-HT) transporter (5-HTT) activity is associated with pulmonary artery smooth muscle cell proliferation, and the L-allelic variant of the 5-HTT gene promoter, which is associated with increased expression of 5-HTT,<sup>7,8</sup> is present in homozygous form in 65% of patients with idiopathic PAH (IPAH) compared with 27% of controls.<sup>9</sup>

## Molecular and Cellular Mechanisms

### *Prostacyclin*

Prostacyclin (PGI<sub>2</sub>) is produced by the action of prostacyclin synthase on arachidonic acid in endothelial cells. Prostacyclin synthase activity and prostacyclin levels (as determined by excretion of the metabolite PGF<sub>2 $\alpha$</sub> ) are reduced in patients with PAH, which leads to a relative deficiency of its potent vasodilatory and antiproliferative effects.<sup>10</sup> Moreover, levels of the vasoconstrictor thromboxane are increased.<sup>10</sup>

### *Endothelin*

Endothelin-1 (ET-1) is a 21-amino acid peptide that is produced from big endothelin by endothelium-converting enzymes in endothelial cells and that possesses potent vasoconstrictor and mitogenic effects.<sup>11,12</sup> Endothelin levels are

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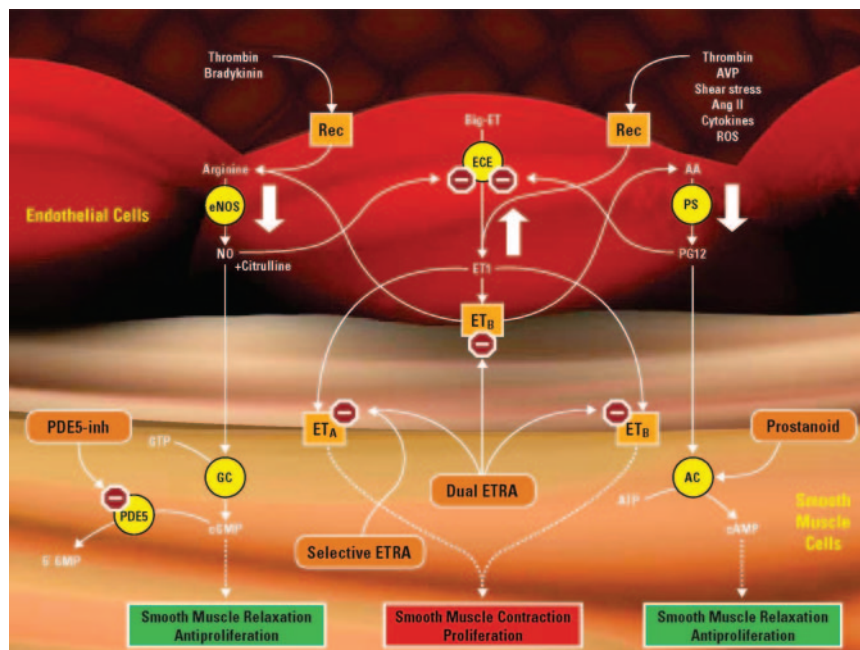
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**Figure 1.** Three major mechanistic pathways are known to be perturbed in patients with PAH. (1) The NO pathway: NO is created in endothelial cells by type III NO synthase (eNOS), which in turn induces guanylate cyclase (GC) to convert guanosine triphosphate (GTP) to cGMP, a second messenger that constitutively maintains pulmonary artery smooth muscle cell (PASM) relaxation and inhibition of PASM proliferation. (2) The endothelin (ET) pathway: Big-ET (or pro-ET) is converted in endothelial cells to ET-1 (21 amino acids) by endothelin-converting enzyme (ECE). ET-1 binds to PASM  $ET_A$  and  $ET_B$  receptors, which ultimately leads to PASM contraction, proliferation, and hypertrophy. ET-1 also binds to endothelial cell  $ET_B$  receptors. (3) The prostacyclin pathway: The production of  $PGI_2$  (prostacyclin) is catalyzed by prostacyclin synthase (PS) in endothelial cells. In PSMs,  $PGI_2$  stimulates adenylate cyclase (AC), thus increasing production from ATP of cAMP, another second messenger that maintains PASM relaxation and inhibition of PASM proliferation. Importantly, the pathways interact as illustrated, modulating the effect of any single pathway. They also are impacted by transmitters and stimuli that act at cell membrane receptors (Rec). Examples of these include but are not limited to thrombin, bradykinin, arginine vasopressin (AVP), vessel-wall shear stress, angiotensin II (Ang II), cytokines, and reactive oxygen species (ROS). In addition, the effect of a transmitter depends on its specific site of action (such as PASM  $ET_A$  or  $ET_B$  receptors vs endothelial cell  $ET_B$  receptor). The large white arrows depict aberrations observed in these pathways among patients with PAH. The orange boxes represent agents that have reported clinically beneficial effects in patients with PAH. PDE5-inh indicates PDE-5 inhibitor, eg, sildenafil; ETRA, endothelin receptor antagonist, eg, bosentan (dual), ambrisentan, and sitaxsentan (receptor A selective). Prostanoids, eg, epoprostenol, treprostinil, and iloprost, supplement exogenously deficient levels of  $PGI_2$ . Red stop signs signify an inhibitory effect of depicted agents. Dotted arrows depict pathways with known and unknown intervening steps that are not shown.

elevated in patients with PAH,<sup>13</sup> and clearance of endothelin in the pulmonary vasculature is reduced.<sup>14</sup> Endothelin acts at 2 different receptors:  $ET_A$  receptors on vascular smooth muscle cells and  $ET_B$  receptors on vascular smooth muscle cells and endothelial pulmonary vascular cells. Both  $ET_A$  and  $ET_B$  receptors mediate vascular smooth muscle cell proliferation.  $ET_A$  receptors mediate vasoconstriction.  $ET_B$  receptors may have a role in either vasoconstriction, via actions on smooth muscle cell receptors, or release of both vasodilators (nitric oxide [NO] and  $PGI_2$ ) and vasoconstrictors (thromboxane), via actions on endothelial cells, and also clear ET-1. Plasma levels of ET-1 correlate with severity of PAH and prognosis.<sup>14,15</sup>

#### NO Pathway

NO, produced in endothelial cells from arginine by NO synthase, leads to vasodilation via a complex pathway that involves the production in vascular smooth muscle cells of cGMP. cGMP activates cGMP kinase, which in turn opens cell membrane potassium channels to allow potassium ion efflux, membrane depolarization, and calcium channel inhibition. Decreased calcium entry and reduced release of sarcoplasmic calcium stores diminishes activation of the

contractile apparatus and leads to vasodilation. Phosphodiesterase-5 (PDE-5), 1 of 11 superfamilies of PDE enzymes, degrades cGMP, thus counteracting the vasodilatory pathway initiated by NO.

Patients with PAH have evidence of decreased NO synthase expression, thus promoting vasoconstriction and cell proliferation.<sup>16</sup> Potential sites of intervention include increased substrate (arginine), NO or nitrate donor agents, inhibition of PDE-5, or calcium channel blockade. The prostacyclin, endothelin, and NO pathways are depicted in Figure 1.

#### 5-HT (Serotonin)

Serotonergic mechanisms have been implicated in PAH. Elevated plasma 5-HT and relatively depleted platelet 5-HT have been observed. 5-HTT facilitates the induction of proliferation by transporting 5-HT into pulmonary vascular smooth muscle cells. In addition, the 5-HT<sub>1B</sub> receptor, the expression of which is increased in PAH, mediates vasoconstriction.<sup>17</sup>

#### Ion Channels

Voltage-dependent potassium channels (Kv) are inhibited by a number of stimuli that promote PAH, including hypoxia and

fenfluramine derivatives.<sup>18,19</sup> Kv1.5 channels are downregulated in patients with PAH.

### Inflammation

A number of observations suggest that inflammation may be involved as a mechanism in some forms of PAH.<sup>20,21</sup> Auto-antibodies, proinflammatory cytokines, and inflammatory infiltrates have been observed in some cases of PAH.

### Coagulation

A wide array of procoagulant aberrations have been identified in PAH patients, in part related to endothelial dysfunction and to abnormalities of the coagulation cascade and disordered platelet function. These include increased levels of von Willebrand factor, plasma fibrinopeptide A, plasminogen activator inhibitor-1, serotonin, and thromboxane and decreased levels of tissue plasminogen activator, thrombomodulin, NO, and PGI<sub>2</sub>.

### Endothelial Cell Dysfunction

A common denominator of many of the molecular mechanisms underpinning PAH is dysfunction of endothelial processes provoked by various possible sources of injury: shear stress, inflammation, toxins, hypoxia, and other causes yet to be discovered. The epitome of endothelial dysfunction is reflected by the plexiform lesion, a disordered proliferation of endothelial cells that in IPAH appears to be monoclonal in origin, which have been characterized as “tumorlets.”<sup>22</sup>

## Classification of PH

The first attempt to organize the nosology of PH was published as a result of the World Health Organization (WHO) Conference on PH in 1973. This was followed by reclassification in 1998 at the 2nd WHO Conference in 1998 in Evian, France, and most recently at the 3rd World Conference in Venice in 2003 (Table 1).<sup>23</sup>

### Pulmonary Arterial Hypertension

All forms of PAH reduce survival (Figure 2A)<sup>24</sup> and produce symptomatic sequelae (Table 2).

#### Idiopathic Pulmonary Arterial Hypertension

IPAH is PAH of undetermined cause characterized histopathologically by angioproliferative plexiform lesions of endothelial cells, muscularization of precapillary arterioles, intimal endothelial cell proliferation, and medial thickening due to vascular smooth muscle cell proliferation. IPAH is rare, with an incidence of approximately 2 to 5 per million per year when strictly defined in the absence of any possible contributing substrates. The female:male ratio is 1.7:1, and the mean age at diagnosis is 37 years (in the national registry of 1987),<sup>25</sup> although the age range of affected individuals appears to be increasing, perhaps owing to enhanced longevity after advances in treatment. Dyspnea is the most common presenting symptom and is virtually universally present during the course of the illness, as is fatigue, followed by anginal chest pain, near-syncope or syncope, and ultimately, manifestations of right ventricular failure.

**TABLE 1. WHO Classification of Pulmonary Hypertension**

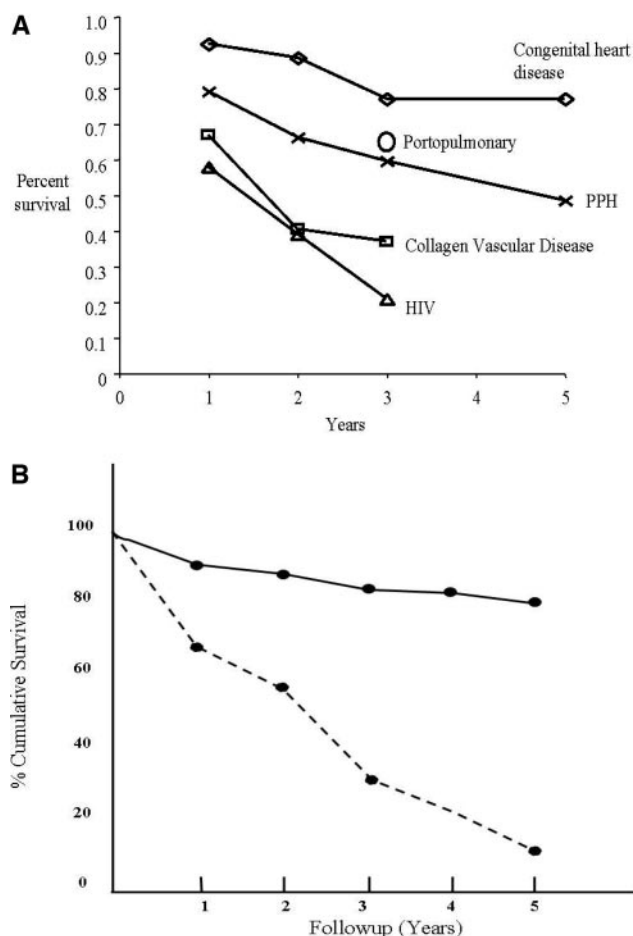
1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic (IPAH)
1.2. Familial (FPAH)
1.3. Associated with (APAH):
1.3.1. Collagen vascular disease
1.3.2. Congenital systemic-to-pulmonary shunts
1.3.3. Portal hypertension
1.3.4. HIV infection
1.3.5. Drugs and toxins
1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
1.4. Associated with significant venous or capillary involvement
1.4.1. Pulmonary veno-occlusive disease (PVOD)
1.4.2. Pulmonary capillary hemangiomatosis (PCH)
1.5. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension with left heart disease
2.1. Left-sided atrial or ventricular heart disease
2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung diseases and/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. Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)
4.1. Thromboembolic obstruction of proximal pulmonary arteries
4.2. Thromboembolic obstruction of distal pulmonary arteries
4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous
Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Reproduced from Simonneau et al<sup>23</sup> with permission from the American College of Cardiology Foundation. Copyright 2004.

#### Familial Pulmonary Arterial Hypertension

Hereditary transmission of PAH is suspected or documented in approximately 6% to 10% of patients with PAH. BMPR2 mutations have been identified in 50% to 90% of patients diagnosed with FPAH.<sup>26,27</sup> BMPR2 mutations have been identified in 25% of patients with IPAH<sup>28</sup> and in 15% of PAH related to fenfluramine use, which raises the possibility that these individuals experienced spontaneous mutations or are from a family with as-yet-undiscovered genetic transmission in the absence of clinically evident disease. FPAH is characterized by genetic anticipation, in which members of successive generations who develop PAH do so at earlier ages and may develop more severe and rapidly progressive disease, and by incomplete penetrance.





**Figure 2.** A, Survival with various origins of PAH. Reproduced from McLaughlin et al<sup>24</sup> with permission from the American College of Chest Physicians. Copyright 2004. B, Survival of scleroderma patients with and without PAH. Five-year probability of survival for limited scleroderma patients with (dashed line; n=106) or without (solid line; n=106) PH. Reproduced from Steen and Medsger<sup>33</sup> with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Copyright 2003, American College of Rheumatology.

#### PAH With Significant Venous or Capillary Involvement

In rare instances, a “pan-vasculopathy” is present, which includes the typical findings of PAH. Both pulmonary occlusive venopathy (formerly pulmonary veno-occlusive disease) and pulmonary microvasculopathy (formerly pulmonary capillary hemangiomatosis) can cause PH and also share with PAH features of arterial intimal fibrosis, medial hypertrophy, and plexiform lesions, as well as exhibiting hallmarks of pulmonary venous hypertension (pulmonary hemosiderosis, interstitial edema, and lymphatic dilation).<sup>29</sup> The clinical presentation can be indistinguishable from PAH, but the development of rapid-onset pulmonary edema after administration of epoprostenol has been reported for both entities.<sup>30,31</sup>

#### PAH Associated With Other Diseases

PAH, as defined by typical pathobiological features, occurs with sufficient frequency in the course of certain other diseases that it is considered to be an associated, although not necessarily observed, feature of the disease, and this is termed APAH. The associated disease may be appropriately regarded as one of the “hits” that leads to PAH.

**TABLE 2. Symptoms of PAH**

Symptom	Potential Causes
Dyspnea	Decreased oxygen transport Hypoxemia Low cardiac output Low DLCO Low mixed venous oxygen saturation Increased work of breathing
Angina	Increased myocardial oxygen demand Elevated right ventricular wall stress (volume, pressure) Inadequate oxygen delivery Reduced aorta-to-right ventricular systolic gradient Left main coronary artery compression
Syncope	Hemodynamic Systemic vasodilation (exertion, orthostatic, vasodepressor) and low fixed cardiac output due to high pulmonary resistance
Arrhythmic	“Benign” arrhythmias (atrial fibrillation) result in loss of atrial contribution to cardiac output Malignant arrhythmias provoked by wall stretch, ischemia
Edema	Right ventricular failure Tricuspid regurgitation Sedentary lifestyle Chronic deep venous insufficiency

DLCO indicates diffusing capacity of the lung for carbon monoxide.

Connective tissue disease (CTD), especially the scleroderma spectrum, is an important subgroup of the APAH classification. PH, defined as a Doppler echocardiographically estimated right ventricular systolic pressure >40 mm Hg, is present in 23% of patients with scleroderma or mixed CTD identified in community-based rheumatology practices.<sup>32</sup> Isolated PAH is more frequently observed in limited scleroderma than in diffuse scleroderma, in which PH usually manifests with pulmonary fibrosis and generally becomes evident later in the course of the illness. The development of PAH in limited scleroderma initially may be symptomatically unapparent or nonspecific, is characteristically preceded by a progressive decline in diffusing capacity, and markedly attenuates survival compared with that of scleroderma patients without PAH (Figure 2B).<sup>33</sup>

PAH is a well-recognized outcome of uncorrected high pulmonary blood flow associated with congenital heart disease and systemic-to-pulmonary shunts. Although the development of PAH and attendant reversal of flow (Eisenmenger syndrome) is most predictable when flow is high and the shunt lesion exposes the pulmonary vasculature to systemic pressure (as with ventricular septal defect, patent ductus arteriosus, or truncus arteriosus), PAH may also occur with atrial septal defect. Portopulmonary hypertension refers to PAH that occurs in conjunction with liver disease and portal hypertension; it is reported in 4% to 15% of patients undergoing evaluation for liver transplantation.<sup>34,35</sup> PAH may be minimally symptomatic and relatively mild, but it has major implications for survival (50% to 72% over 2 years<sup>36</sup>) and risk of liver transplantation (35% perioperative mortality<sup>37</sup>).

The risk of developing PAH is increased by exposure to certain toxic agents. Toxic PAH has been convincingly associated with drugs structurally derived from amphetamine, most notably, the appetite suppressants aminorex, fenfluramine, and dexfenfluramine, all of which have been removed from the market after epidemiological studies or reports of widespread observations connected them to PAH (and in the case of the fenfluramines/dexfenfluramines, to cardiac valvular abnormalities). A case-control population study revealed that exposure to fenfluramine/dexfenfluramine increased the odds of developing PAH by a factor of 6.3.<sup>38</sup> The widespread illicit use of methamphetamine poses a potential ongoing environment for the perpetuation of toxic PAH. Approximately 1 of 200 patients with human immunodeficiency virus (HIV) infection exhibit features of PAH.<sup>39</sup>

### PH and Left Heart Disease

PH in the context of left heart disease is an initially passive process of back pressure, producing upstream elevation in pulmonary venous and arterial pressure. Prolonged duration of pulmonary venous hypertension may eventually lead to what teleologically can be considered as an adaptive increase in pulmonary arteriolar resistance. Amelioration of the underlying cause is the primary approach, although persistent vascular changes may persist after complete normalization of the cardiac lesion or dysfunction.

### PH and Lung Diseases or Hypoxemia

The development of PH in hypoxic states and ventilatory disorders is well recognized but in the past has largely been relegated to the status of an epiphenomenon. Although some degree of PH is present in up to 66% of patients with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage IV chronic obstructive lung disease, it is generally mild.<sup>40</sup> Similarly, sleep-disordered breathing is associated with mild PH unless coupled with obesity-hypoventilation syndrome or associated with obstructive pulmonary disease.<sup>41</sup> It has become increasingly apparent that (1) patients with obstructive pulmonary disease have worse survival when PH intervenes,<sup>42</sup> and (2) a subset of patients have PH that is disproportionately severe compared with their obstructive pulmonary disease.<sup>43</sup> Deficient NO synthase<sup>44</sup> and prostacyclin levels<sup>10</sup> and elevated pulmonary vascular ET-1<sup>13</sup> have been implicated as mechanisms. Although patients with hypoxic lung disease have been excluded from treatment studies of PAH, they represent a population in which exploration of vasoactive treatment modalities may be warranted. Studies of interstitial lung disease with or without associated PH are currently under way.

### PH and Chronic Embolic Occlusive Disease

Chronic thromboembolic PH (CTEPH) is observed in up to 3% of patients who survive an acute embolism<sup>45</sup> and may occur because of persistently reduced cross-sectional luminal area, continuing platelet activation and release of vasoconstrictors, recurrent thromboemboli, superimposed *in situ* thrombosis, or development of small-vessel arteriopathy.<sup>46</sup> The occurrence of CTEPH portends a poor prognosis if untreated, with 30% probability of survival for 5 years when

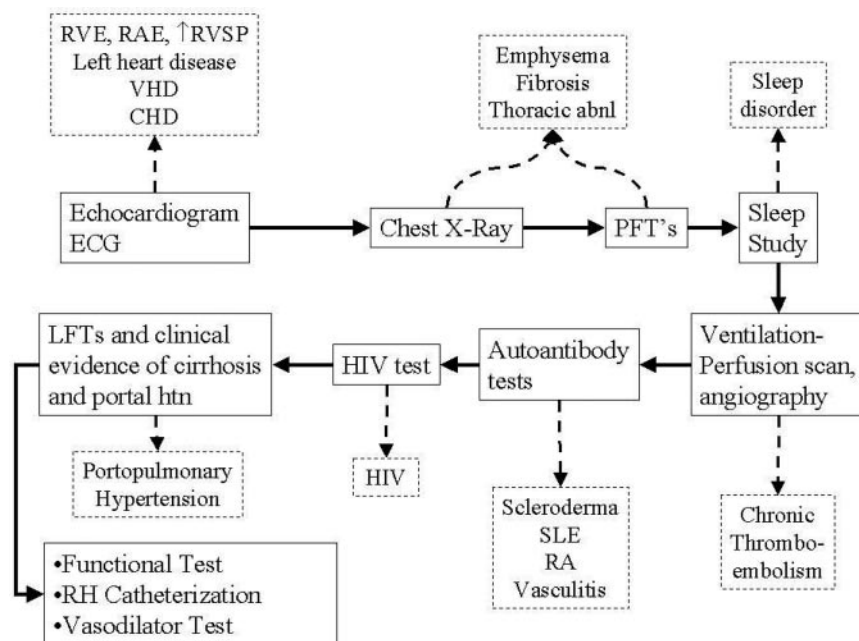
the mPAP is >40 mm Hg.<sup>47</sup> CTEPH may occur in the absence of a clear history of acute pulmonary embolism. In patients with a history of pulmonary embolism, a relatively asymptomatic interval may precede presentation when more advanced arteriopathy or right ventricular failure has developed. Recognition of CTEPH in the course of evaluation with screening ventilation-perfusion scintigraphy and anatomic definition with contrast-enhanced computerized tomography and pulmonary angiography is vital because PH and right ventricular dysfunction can be markedly improved or reversed by successful pulmonary thromboendarterectomy in appropriately selected patients. Candidates are patients with symptoms and substantial elevations of pulmonary arterial resistance due to occlusive disease that is sufficiently proximal to be surgically accessible and who do not have prohibitive comorbidities, particularly advanced left ventricular dysfunction.

### Natural History and Prognostic Factors

The natural history of IPAH was well described by the National Institutes of Health (NIH) registry, which enrolled 194 patients at 32 clinical centers from 1981 to 1985, before the availability of any disease-specific therapy.<sup>25</sup> The median survival was 2.8 years, with 1-, 3-, and 5-year survival rates of 68%, 48%, and 34%, respectively.<sup>48</sup> Other series have demonstrated similar outcomes in untreated IPAH.<sup>49–51</sup> Associated conditions influence outcomes: Patients with CTD- and HIV-associated PAH tend to have a worse prognosis, whereas those with congenital heart disease-associated PAH tend to have a better prognosis (Figure 2A).

Important prognostic indicators in PAH have recently been reviewed and include symptoms (as assessed by functional class [FC]), exercise endurance, and hemodynamics.<sup>24</sup> Most of these prognostic variables are related to right ventricular function. In the NIH registry, the median survival among patients presenting with FC I and II symptoms was nearly 6 years versus 2.5 years for patients with FC III symptoms and just 6 months for patients who presented with FC IV symptoms.<sup>48</sup> Two large retrospective series have confirmed the importance of FC as a prognostic variable, even during treatment.<sup>52,53</sup> Among IPAH patients treated with intravenous epoprostenol, prognosis was worse for patients who commenced therapy with more advanced symptoms. Moreover, in both series, patients who improved to FC I or II status after 3 to 17 months of intravenous epoprostenol therapy had a better prognosis than patients who remained in FC III or IV.

Exercise tolerance in PAH is commonly assessed by means of the 6-minute-walk distance (6MWD), which has served as an entry criterion and primary end point of many clinical trials of therapeutic agents for PAH. In one of the first controlled trials, a 6MWD of <150 m was associated with a very poor prognosis.<sup>54</sup> Two observational series of IPAH patients undergoing therapy have reinforced the prognostic importance of the 6MWD.<sup>53,55</sup> In a series of 178 IPAH patients treated with epoprostenol, those who walked further than the median value of 380 m after 3 months of therapy had a better prognosis than those who did not.<sup>53</sup> Although used less commonly in clinical practice, one study has demonstrated that maximum oxygen consumption of >10.4 mL ·



**Figure 3.** Diagnostic algorithm for the evaluation of PAH, as discussed in text. RVE indicates right ventricular enlargement; RAE, right atrial enlargement; RVSP, right ventricular systolic pressure; VHD, valvular heart disease; CHD, congenital heart disease; LFTs, liver function tests; htn, hypertension; RH, right heart; abnl, abnormality; PFT's, pulmonary function tests; SLE, systemic lupus erythematosus; and RA, rheumatoid arthritis.

$\text{kg}^{-1} \cdot \text{min}^{-1}$  and peak systolic blood pressure  $>120$  mm Hg as measured by cardiopulmonary exercise testing are favorable prognostic indicators.<sup>56</sup>

The NIH registry found that 3 measured hemodynamic variables (right atrial pressure, cardiac index, and mPAP) were associated with an increased risk of death by both univariate and multivariate analysis.<sup>48</sup> These data were used to formulate a regression equation, which was subsequently validated in a prospective cohort of 61 patients by Sandoval et al.<sup>49</sup> Most but not all historical series have demonstrated similar findings in untreated patients.<sup>24</sup>

### Clinical Assessment of the Patient With Suspected PH

The process of evaluating suspected PH is oriented toward confirming its presence, defining the specific hemodynamic configuration (ie, precapillary versus postcapillary), identifying the underlying cause or associated disease substrate, determining prognosis, and identifying the most appropriate therapy. The portion of the assessment designed to characterize the syndrome is easily conceptualized as a systematic process of examining the differential diagnoses and is depicted in the algorithm in Figure 3.

### Screening and Detection

#### At-Risk Populations

Because PAH has a low prevalence in the general population, global screening is inadvisable. The frequency of PAH in certain populations, however, warrants periodic assessment. These populations include individuals with multiple affected family members, who have a known BMPR2 mutation, or those with CTD or HIV. The recommended method of screening is Doppler echocardiography. The optimal frequency of screening in various populations is unclear. Among those at highest risk (eg, those with limited scleroderma or HIV), annual assessment is probably reasonable. Because the

likelihood of developing PAH in patients exposed to appetite suppressants is low, routine screening is not recommended in these patients.

#### Physical Examination

Findings on physical examination are useful to guide the need for further assessment in at-risk populations or in patients with any symptom that may be indicative of PAH. Features that should raise the suspicion of PAH or resulting right ventricular dysfunction have been summarized elsewhere.<sup>57</sup>

#### Chest Roentgenography

Chest roentgenography may provide the first clue to the presence of PAH (Figure 4A).

#### Electrocardiogram

The ECG may suggest underlying PAH (Figure 4B), although it is relatively insensitive and nonspecific.

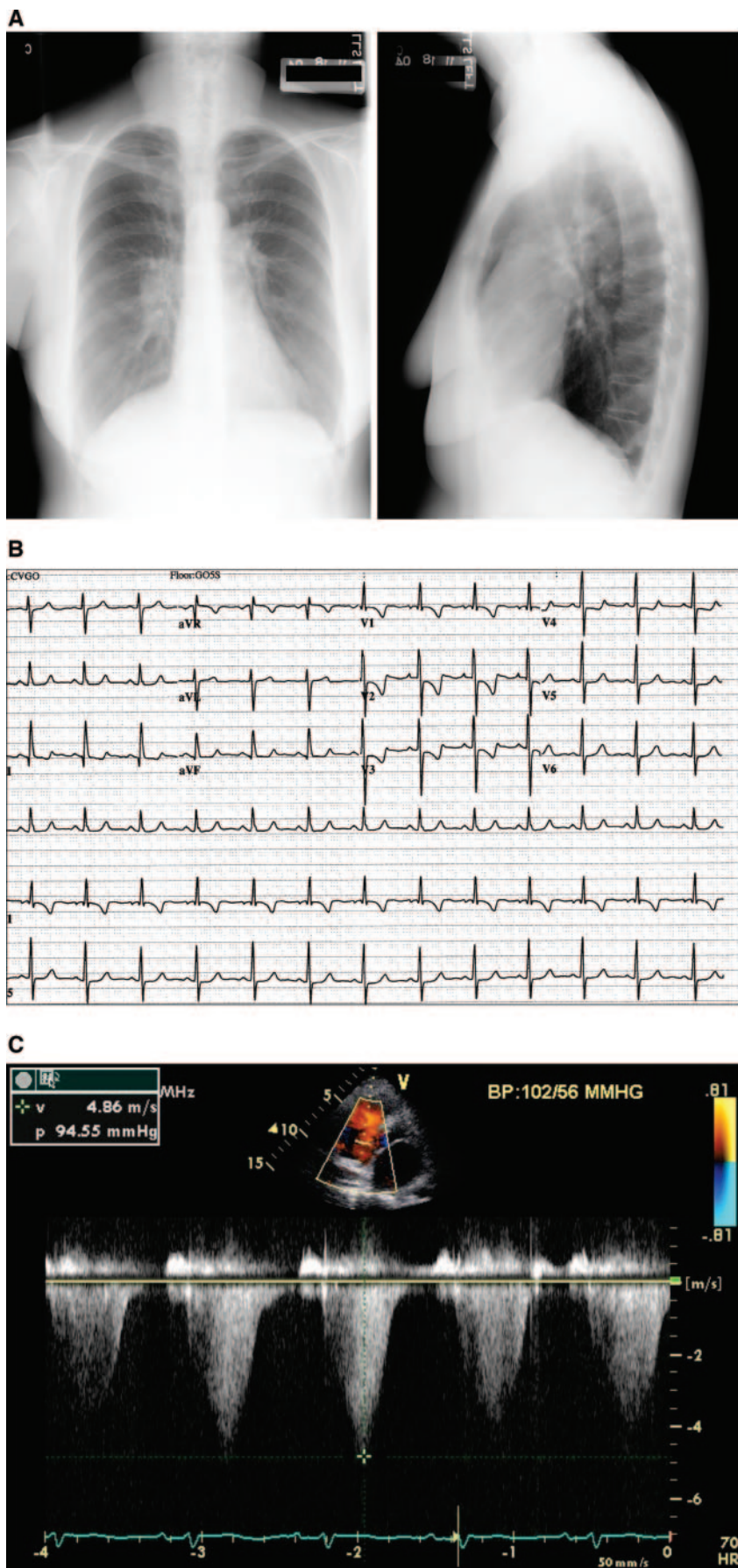
#### Echocardiogram

Transthoracic Doppler echocardiography is the essential screening tool for the presence of PAH because of the high level of correlation of estimated right ventricular systolic pressure (Figure 4C) with invasively measured pulmonary artery pressure.<sup>58</sup> Like any screening test, individual results may overestimate or underestimate actual pulmonary artery systolic pressures, and further confirmation with invasive studies is required. Echocardiography provides additional data important in the evaluation of PAH, including assessment of right ventricular size and function.

#### Mild PH

Emphasis on screening and early detection raises the question of how the discovery of relatively mild PH, with or without associated symptoms, should be managed. Clinical drug studies have used a criterion of symptomatic PAH (at least WHO FC II; Table 3) with an mPAP  $\geq 25$  mm Hg for enrollment. Most patients in these studies actually had sig-





**Figure 4.** A, Chest radiography in PAH demonstrating enlargement of the central pulmonary arteries with peripheral pruning of the pulmonary vasculature on the posteroanterior view and reduction in retrosternal air space on the lateral view. B, ECG in PAH demonstrating right-axis deviation, right ventricular hypertrophy, and anterior ST- and T-wave abnormalities consistent with a right ventricular strain pattern. C, Doppler echocardiogram of tricuspid regurgitant velocity signal for estimation of right ventricular systolic pressure. BP indicates blood pressure.



**TABLE 3. WHO Functional Classification of PAH**

Class	Description
I	Patients with PH in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope.
II	Patients with PH who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
III	Patients with PH who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope.
IV	Patients with PH who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest, and symptoms are increased by almost any physical activity.

nificantly higher pressures. Consequently, it remains unclear whether treatment with complex, expensive medications yields an advantageous benefit-to-risk or benefit-to-cost strategy for patients with either mildly elevated pressure or any degree of abnormal hemodynamics with absence of symptoms.

### Exercise-Related PH

Some symptomatic patients exhibit normal resting pulmonary hemodynamics but have an exaggerated pulmonary hypertensive response to exercise. Peak Doppler echocardiographic pulmonary systolic pressure with exercise has been reported to be  $\approx 50$  mm Hg among a cohort of athletes and  $<30$  mm Hg among healthy male volunteers.<sup>59</sup> The long-term implications of asymptomatic exercise-induced PH and the effect of any form of treatment have not been determined.

### Role of Genetic Evaluation and Counseling

Although BMPR2 mutations are clearly associated with heritable PAH, the use of genetic screening poses potential clinical difficulties. Only  $\approx 10\%$  to  $20\%$  of carriers of the gene mutation actually exhibit PAH. Thus, a genetic mutation confers the risk of transmitting the mutant gene to offspring, but it does not predict with certainty that the carrier will develop manifestations of clinical disease. Clinical testing for BMPR2 mutations is currently available at a limited number of institutions (Vanderbilt University Medical Center, Nashville, Tenn, and Columbia University Medical Center, New York, NY), but its role in the management of patients and families is evolving.

### Right Heart Catheterization and Vasodilator Testing

Right heart catheterization remains the standard by which the diagnosis of PAH is made. Right heart catheterization pro-

vides important prognostic information and is essential to exclude pulmonary venous hypertension by measuring the pulmonary capillary wedge pressure (PCWP). If an adequate PCWP tracing cannot be obtained, the left ventricular end-diastolic pressure should be measured. In addition, the mixed venous saturation should be sampled, and measurements of cardiac output should be obtained. The hemodynamic definition of PAH is an mPAP  $\geq 25$  mm Hg with a PCWP of  $\leq 15$  mm Hg and a pulmonary vascular resistance of  $>3$  Wood units.

The degree to which mPAP and pulmonary vascular resistance can be decreased acutely by the administration of fast-acting, short-duration vasodilators reflects the extent to which vascular smooth muscle constriction is contributing to the hypertensive state. Because the vasodilator response has considerable therapeutic implications in IPAH, most patients should undergo a vasodilator trial at the time of initial cardiac catheterization. Intravenous epoprostenol, intravenous adenosine, and inhaled NO are commonly used for acute vasodilator testing (Table 4). On the basis of retrospective data, the consensus definition of a positive response is defined as a reduction of mPAP by at least 10 mm Hg to a value of 40 mm Hg or less, given the observation that patients with this response are most likely to have a beneficial hemodynamic and clinical response to treatment with calcium channel blockers. Those failing to achieve this response are unlikely to improve with calcium channel blocker therapy, whereas those achieving this response may be treated with calcium channel blockers and followed up closely for both safety and efficacy of therapy. A significant vasodilator response may reflect an earlier stage of disease or a qualitatively different disease process. Patients in whom calcium channel blockers would not be considered as therapy, such as those with FC IV symptoms, overt right heart failure, or advanced hemodynamics (markedly elevated right atrial pressure or reduced cardiac output), need not undergo vasodilator testing, because the risks outweigh the benefits.

### Treatment of PAH

Treatment of PAH includes lifestyle modifications, conventional treatments, and disease-specific treatments. Over the past decade, 5 agents have received Food and Drug Administration (FDA) approval for the treatment of PAH. Many others are under active investigation. Goals of treatment include alleviation of symptoms, with improvements in quality of life and survival. Response to therapy is commonly evaluated with a variety of methods, including assessment of FC, exercise tolerance, echocardiography, and right heart catheterization. Both the American College of Chest Physicians and the European Society of Cardiology have recently

**TABLE 4. Agents for Vasodilator Testing**

	Epoprostenol	Adenosine	NO
Route of administration	Intravenous	Intravenous	Inhaled
Dose range	2–10 ng $\cdot$ kg <sup>-1</sup> $\cdot$ min <sup>-1</sup>	50–250 $\mu$ g $\cdot$ kg <sup>-1</sup> $\cdot$ min <sup>-1</sup>	10–80 ppm
Dosing increments	2 ng $\cdot$ kg <sup>-1</sup> $\cdot$ min <sup>-1</sup> every 15 min	50 $\mu$ g $\cdot$ kg <sup>-1</sup> $\cdot$ min <sup>-1</sup> every 2 min	10–80 ppm for 5 min
Common side effects	Headache, flushing, nausea	Chest tightness, dyspnea	None

published guidelines for the medical treatment of PAH.<sup>60,61</sup> Table I in the Data Supplement summarizes selected prospective, controlled clinical trials in PAH.

### Lifestyle Modifications

Although there are few data on which to base recommendations about exercise, heavy physical activity or isotonic exercises can evoke exertional syncope. We encourage low-level graded aerobic exercise, such as walking, as tolerated. We recommend against exposure to high altitudes because this may produce hypoxic pulmonary vasoconstriction and may not be well tolerated. Similarly, some patients may require oxygen on commercial aircraft. Patients should follow a sodium-restricted diet (<2400 mg per day) because excessive sodium ingestion can predispose to right heart failure. Because respiratory infections are particularly troublesome in this population, immunizations against influenza and pneumococcal pneumonia are advised. Concomitant medications that should be avoided include vasoconstricting sinus or cold preparations and anorexigens. Certain PAH medications have specific medication interactions, such as glyburide or cyclosporine with bosentan and organic nitrates with sildenafil, and are consequently contraindicated for simultaneous use. Patients receiving warfarin anticoagulation should be counseled about the many agents that interact with this medication.

The hemodynamic fluctuations of pregnancy, labor, delivery, and the postpartum period are potentially devastating in PAH patients, resulting in a 30% to 50% maternal mortality rate.<sup>62</sup> Most experts recommend that pregnancy be avoided or terminated early in women with PAH.<sup>60</sup> Although effective methods of birth control are advocated, the preferred method of birth control for PAH patients is not clear. Estrogen-containing contraceptives may increase the risk of venous thromboembolism; however, the use of currently available lower-dose preparations with concomitant warfarin anticoagulation may reduce this risk. Surgical sterilization and barrier methods are also options.

The risk-benefit ratio of elective surgery should be weighed carefully in PAH patients because they are particularly susceptible to vasovagal events, hemodynamic fluctuations, and ventilatory compromise. In a study of 145 PH patients who underwent surgery, Ramakrishna et al<sup>63</sup> found the following to be independent predictors of short-term morbidity: history of a pulmonary embolism ( $P=0.01$ ), FC  $\geq 2$ , ( $P=0.02$ ), intermediate- to high-risk surgery ( $P=0.04$ ), and duration of anesthesia >3 hours ( $P=0.04$ ).

### Conventional Treatments

Diuretics are indicated to manage volume overload due to right ventricular failure. In some cases, intravenous diuretics are required. As in left heart failure, serum electrolytes and renal function should be monitored closely. Because hypoxemia is a potent pulmonary vasoconstrictor, most experts recommend oxygen supplementation to maintain arterial oxygen saturation above 90%. The use of supplemental oxygen in patients with Eisenmenger physiology is controversial. Few data are available on the use of digoxin, although some experts prescribe digoxin in patients with right ventricular failure or low cardiac output.

Anticoagulation has been studied in 2 small, uncontrolled trials, one prospective and one retrospective, both of which described improved survival in IPAH patients receiving warfarin.<sup>64,65</sup> On the basis of these reports, most experts recommend warfarin anticoagulation targeted to an international normalized ratio of 2.0 to 2.5, although some experts recommend a range of 1.5 to 2.0, and others recommend a range of 2.0 to 3.0. Anticoagulation of patients with associated forms of PAH is more controversial because few data exist in these populations. Additionally, the risk of gastrointestinal bleeding may be increased in patients with disorders such as CTD or portal hypertension. We generally recommend warfarin anticoagulation in APAH patients being treated with intravenous prostanoids in the absence of contraindications.

### Calcium Channel Blockers

Some IPAH patients who experience a response to an acute vasodilator on testing at the time of cardiac catheterization will do well with calcium blocker therapy. Recently, Sitbon and colleagues<sup>66</sup> reported results of a retrospective analysis of 557 IPAH patients tested acutely with intravenous epoprostenol or inhaled NO. Only 12.8% of patients displayed vaso-reactivity using a criterion of a >20% decrease in both mPAP and pulmonary vascular resistance, and only 6.8% had a favorable clinic response to chronic calcium channel blocker therapy. The patients who responded to long-term calcium channel blocker therapy exhibited a more pronounced reduction in mPAP, reaching an absolute mPAP of  $33 \pm 8$  mm Hg with acute vasodilator testing. As a result, the consensus definition of a response is now defined as a fall in mPAP of  $\geq 10$  mm Hg, to an mPAP  $\leq 40$  mm Hg, with an unchanged or increased cardiac output. Patients with IPAH who meet these criteria may be treated with calcium channel blockers. Long-acting nifedipine or diltiazem or amlodipine is suggested. Owing to its potential negative inotropic effects, verapamil should be avoided. Patients should be followed up closely for both safety and efficacy of calcium channel blocker therapy. If a patient does not improve to FC I or II with calcium channel blocker therapy, the patient should not be considered a chronic responder, and alternative PAH therapy should be instituted.

### Prostacyclins

Intravenous epoprostenol improves FC, 6MWD, hemodynamics, and survival in IPAH. An open-label, randomized trial of 81 FC III and FC IV IPAH patients demonstrated significant improvements in 6MWD and hemodynamics.<sup>54</sup> Eight patients, all of whom were randomized to conventional therapy alone, died over the course of the 12-week trial, which resulted in a survival benefit ( $P=0.003$ ). Longer-term observational studies have confirmed the chronic benefits of intravenous epoprostenol in IPAH patients. In a series of 178 FC III and FC IV IPAH patients, Sitbon and coworkers<sup>53</sup> reported improved survival with intravenous epoprostenol compared with historical controls, with 1-, 2-, 3-, and 5-year survival rates of 85%, 70%, 63%, and 55%, respectively. Similarly, in a series of 162 FC III and FC IV patients, intravenous epoprostenol resulted in improved survival com-

pared with predicted survival based on the NIH equation, with 1-, 2-, 3-, and 5-year survival rates of 88%, 76%, 63%, and 56%, respectively.<sup>52</sup> Improvements in FC, exercise endurance, and hemodynamics were also noted.

Intravenous epoprostenol has also been evaluated in PAH related to CTD. A multicenter, open-label, randomized trial demonstrated marked improvements in 6MWD and hemodynamics but no effect on mortality after 12 weeks of therapy.<sup>67</sup> Observational series have also reported favorable effects of intravenous epoprostenol in patients with PAH related to CTD, congenital heart disease, HIV, and portal hypertension.<sup>68–72</sup>

Intravenous epoprostenol must be delivered by continuous intravenous infusion. Each patient must learn the techniques of sterile preparation of the medication, operation of the ambulatory infusion pump, and care of the central venous catheter. Intravenous epoprostenol is commonly started in the hospital at a dose of  $2 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . The dose is further adjusted upward on the basis of symptoms of PAH and side effects of the drug. Chronic overdose can lead to high cardiac output failure.<sup>73</sup> Most experts believe that the optimal dose range for chronic therapy is between 25 and  $40 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Common side effects include headache, jaw pain, flushing, nausea, diarrhea, skin rash, and musculoskeletal pain. Infections and infusion interruptions can be life-threatening. Given its considerable complexity, epoprostenol use should be limited to centers experienced with its administration. Intravenous epoprostenol is currently FDA-approved for FC III and FC IV IPAH and PAH related to the scleroderma spectrum of diseases.

Treprostinil is a stable prostacyclin analogue with a half-life of 4 hours that was first developed for continuous subcutaneous use. In a 12-week, placebo-controlled, multicenter, randomized trial of 470 patients with FC II, III, or IV PAH (IPAH, CTD, or congenital heart disease related), subcutaneous treprostinil resulted in a modest but statistically significant median increase of 16 m in 6MWD.<sup>74</sup> The improvement was dose related, and patients in the highest dose quartile experienced a nearly 40-m improvement in 6MWD. However, 85% of patients experienced pain or erythema at the site of the subcutaneous infusion. Other common side effects include headache, diarrhea, rash, and nausea. The FDA approved subcutaneous treprostinil in 2002 for use in FC II, III, and IV PAH. Given the potential advantages over intravenous epoprostenol, including a longer half-life, intravenous treprostinil has been studied recently. In an open-label study, Tapson et al<sup>75</sup> initiated 16 FC III or IV PAH patients on intravenous treprostinil. After 12 weeks of therapy, the 6MWD improved by a mean of 82 m, and there were also improvements in hemodynamics, including mPAP, cardiac index, and pulmonary vascular resistance. In a similar open-label trial, Gomberg-Maitland et al<sup>76</sup> transitioned 31 FC II and III PAH patients from intravenous epoprostenol to intravenous treprostinil. Twenty-seven patients completed the transition, and 4 were transitioned back to epoprostenol. Exercise endurance as measured by the 6MWD was maintained among the patients completing the transition, although there was a modest increase in mPAP and a decrease in cardiac index. Notably, the dose of intravenous treprostinil at the end of 12 weeks was more than twice the dose of

intravenous epoprostenol at the start of the study. In 2004, the FDA approved the use of intravenous treprostinil in FC II, III, and IV PAH patients in whom subcutaneous infusion is not tolerated. Investigational trials with both inhaled and oral formulations of treprostinil are ongoing.

Iloprost is a chemically stable prostacyclin analogue that can be delivered by an adaptive aerosolized device 6 to 9 times per day. A 12-week multicenter, placebo-controlled, randomized trial included 207 FC III and IV patients with either IPAH, PAH associated with CTD or appetite suppressants, or PH related to inoperable chronic thromboembolic disease.<sup>77</sup> This study used a novel composite end point of improvement in FC by at least 1 level and improvement in 6MWD by at least 10% in the absence of clinical deterioration. The combined clinical end point was met by 16.8% of those receiving inhaled iloprost compared with 4.9% of those receiving placebo ( $P=0.007$ ). Longer-term outcomes with iloprost monotherapy are less clear. In a study of 24 iloprost-treated IPAH patients, Hoeper et al<sup>78</sup> reported sustained benefits in 6MWD and hemodynamics at 1 year. More recently, Opitz et al<sup>79</sup> reported event-free survival rates of 53%, 29%, and 20% at 1, 2, and 3 years, respectively, in IPAH patients treated with iloprost monotherapy. Common side effects of inhaled iloprost include cough, headache, flushing, and jaw pain. Iloprost was approved by the FDA in 2004 for FC III and IV PAH.

Beraprost is an orally active prostacyclin analogue with a short half-life of 35 to 40 minutes. A 12-week double-blind, placebo-controlled trial of 130 PAH patients performed in Europe demonstrated a modest but significant 25-m improvement in the primary end point of 6MWD.<sup>80</sup> Subsequently, a 12-month placebo-controlled, randomized trial conducted in the United States documented improvements in 6MWD at 3 and 6 months, but this effect was not sustained at 9 and 12 months.<sup>81</sup> This underscores the need for data on the long-term efficacy of PAH therapies. Beraprost is currently approved in Japan and Korea.

### Endothelin Receptor Antagonists

Bosentan is an orally active, nonselective endothelin receptor antagonist that has been studied in 2 placebo-controlled, randomized trials of FC III or IV patients with either IPAH or PAH related to CTD. Channick et al<sup>82</sup> reported a placebo-corrected increase of 76 m in the primary end point of 6MWD ( $P=0.02$ ) and significant improvements in mPAP, cardiac index, and pulmonary vascular resistance in 33 PAH patients. In the pivotal BREATHE-1 trial (Bosentan: Randomized trial of Endothelin receptor Antagonist THERapy for pulmonary hypertension), bosentan improved the primary end point of 6MWD by 36 m, whereas the 6MWD deteriorated in placebo-treated patients by 8 m ( $P=0.0002$ ).<sup>83</sup> Bosentan also improved the composite end point of time to clinical worsening, which was defined as death, initiation of intravenous epoprostenol, hospitalization for worsening PAH, lung transplantation, or atrial septostomy. A long-term observational study of IPAH patients treated as part of the placebo-controlled trials and their extension protocols suggested that first-line bosentan therapy has a beneficial effect on survival compared with the expected survival based on the NIH



registry equation.<sup>84</sup> Increases in hepatic enzymes to  $>3$  times the upper limit of normal have been observed in  $\approx 11\%$  of patients treated with bosentan in clinical trials. Other side effects include headache, flushing, lower-extremity edema, and rarely, anemia. Bosentan is teratogenic. Bosentan has been approved by the FDA for treatment of FC III and IV PAH. Careful monitoring of therapy is required, with liver function tests on a monthly basis, hemoglobin/hematocrit on a quarterly basis, and a pregnancy test in women of child-bearing potential on a monthly basis. Patients and prescribing physicians should be aware of the potential side effect of lower-extremity edema, particularly within the first several weeks after initiation of therapy, and should be prepared to adjust diuretics as needed. Ongoing investigational trials with bosentan include studies in patients with FC II symptoms, sickle cell disease, and CTEPH.

Sitaxsentan, an  $ET_A$  selective antagonist, has been studied in 2 placebo-controlled trials. The STRIDE-1 trial (Sitaxsentan To Relieve Impaired Exercise) enrolled 178 patients with FC II, III, or IV PAH, either IPAH or related to CTD or congenital heart disease.<sup>85</sup> The primary end point of maximum oxygen consumption as measured by cardiopulmonary exercise testing improved by 3.1% in the sitaxsentan 300-mg group ( $P<0.01$ ) but was unchanged in the sitaxsentan 100-mg group. There were significant improvements in the secondary end point of 6MWD. Both doses of sitaxsentan improved hemodynamics modestly. The most common side effects associated with sitaxsentan during this clinical trial were headache, peripheral edema, nausea, nasal congestion, and dizziness. There is an interaction between sitaxsentan and warfarin, and the incidence of international normalized ratio elevation was greater in the sitaxsentan groups than in the placebo group. During this placebo-controlled trial and its extension (median exposure 26 weeks), 5% of patients taking the 100-mg dose and 21% of patients taking the 300-mg dose experienced elevation of hepatic transaminases to  $>3$  times the upper limit of normal. Because of the unacceptably high incidence of hepatic enzyme elevations, evaluation of the 300-mg dose was aborted, and the subsequent placebo-controlled study evaluated doses of 50 and 100 mg. The STRIDE-2 study evaluated sitaxsentan at doses of 50 and 100 mg for PAH over 18 weeks.<sup>86</sup> The 100-mg dose resulted in a placebo-corrected improvement of 31 m, whereas the improvement in 6MWD was not significant for the 50-mg group. Sitaxsentan is currently under review by the FDA.

A phase 2 dose-ranging study with the selective  $ET_A$  antagonist ambrisentan demonstrated improvements in exercise tolerance and hemodynamics.<sup>87</sup> Sixty-four patients with IPAH or PAH related to CTD, anorexigen use, or HIV were randomly assigned to receive 1 of 4 doses of ambrisentan (1, 2.5, 5, or 10 mg daily) in a double-blind fashion. At 12 weeks, ambrisentan increased 6MWD by 36 m ( $P<0.0001$ ), with a similar improvement for each dose group (34 to 38 m). Favorable improvements in hemodynamics, which included a decrease in mPAP and an increase in cardiac index, were noted. The incidence of hepatic transaminase elevation  $>3$  times the upper limit of normal was 3.1%. Ambrisentan is currently being studied in 2 pivotal placebo-controlled trials at doses of 2.5, 5, and 10 mg daily.

### Phosphodiesterase Inhibitors

Sildenafil, a potent and highly specific PDE-5 inhibitor, was demonstrated to improve exercise capacity, FC, and hemodynamics in PAH in the Sildenafil Use in Pulmonary Hypertension (SUPER) trial.<sup>88</sup> This double-blind, placebo-controlled study enrolled 278 symptomatic PAH patients, either IPAH or PAH related to CTD or repaired congenital heart disease) and randomized them to placebo or to 1 of 3 sildenafil doses (20, 40, or 80 mg 3 times per day). The primary end point of 6MWD after 12 weeks of therapy improved by 45, 46, and 50 m in the 20-, 40-, and 80-mg groups, respectively ( $P<0.001$  for all comparisons). There was no change in the time to clinical worsening at week 12. Among the 222 patients who completed 1 year of treatment with sildenafil monotherapy, the improvement from baseline 6MWD was preserved at 51 m. Notably, however, after the 12-week, placebo-controlled trial, nearly all patients were titrated up to a dose of 80 mg 3 times per day. Side effects of sildenafil include headache, flushing, dyspepsia, and epistaxis. Sildenafil was approved for the treatment of PAH by the FDA at a dose of 20 mg 3 times per day in 2005.

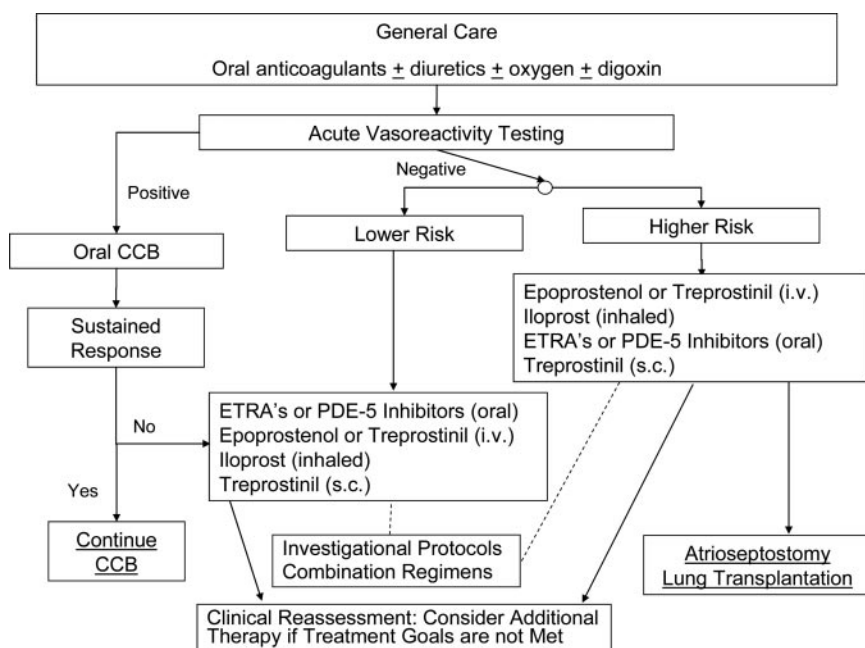
### Combination Therapy

Given the availability of medications that target different pathological processes, combination therapy is an attractive option in PAH. The goal of combination therapy should be to maximize efficacy while minimizing toxicity. Potential interactions between these agents must be considered. One small, placebo-controlled trial in which FC III or IV patients with either IPAH or PAH related to CTD who were beginning treatment with intravenous epoprostenol were randomized to receive bosentan or placebo failed to demonstrate the benefits of combination therapy, although this study was underpowered.<sup>89</sup> Several smaller, open-label observational studies have suggested a benefit of combination therapy. Studies evaluating the addition of inhaled iloprost to patients treated with bosentan and the addition of sildenafil to patients treated with intravenous epoprostenol have been completed, and results should be available in 2006. Studies to assess the combination of sildenafil and bosentan and of sildenafil and iloprost are under way. To adequately study the safety and efficacy of combination therapy, we encourage enrollment into randomized, controlled trials.

### Investigational Therapies

In addition to sitaxsentan, ambrisentan, and inhaled and oral treprostinil, discussed above, studies with novel agents are anticipated over the coming years. Vasoactive intestinal peptide, a member of the superfamily that secretes glucagon-related growth hormone-releasing factor, inhibits platelet activation and the proliferation of vascular smooth muscle cells and acts as a potent pulmonary vasodilator. In an open-label trial, inhalation of vasoactive intestinal peptide led to clinical improvements in 8 IPAH patients.<sup>90</sup> Newer agents targeted at the angiotensin and serotonin pathways and growth factor inhibitors may also provide novel treatments.<sup>9,91</sup> Although in its infancy, gene therapy may play a role in PAH. In a monocrotaline rat model, the administration of endothelial progenitor cells transfected with NO synthase





**Figure 5.** Algorithm for the medical treatment of PAH. Assessment of risk for each individual patient should include clinical variables as outlined in the table. Patients at highest risk, based on clinical assessment, should be considered for intravenous therapy as first-line therapy. Patients at lower risk are candidates for oral therapy. Patients should be followed up closely, and response to therapy should be assessed within several months. If treatment goals are not met, consider addition of a second agent, preferably as part of a randomized clinical trial. CCB indicates calcium channel blocker; ETRA, endothelin receptor antagonist; RV, right ventricular; RAP, right artery pressure; CI, cardiac index; and BNP, brain natriuretic peptide.

Lower	Determinants of Risk	Higher
No	<b>Clinical Evidence of RV Failure</b>	Yes
Gradual	<b>Progression</b>	Rapid
II, III	<b>WHO Class</b>	IV
Longer (>400 m)	<b>6 Minute Walk Distance</b>	Shorter (<300 m)
Minimally elevated	<b>BNP</b>	Very elevated
Minimal RV Dysfunction	<b>Echocardiographic Findings</b>	Pericardial Effusion Significant RV Dysfunction
Normal/Near normal RAP and CI	<b>Hemodynamics</b>	High RAP, Low CI

resulted in reductions in right ventricular systolic pressure and prolonged survival.<sup>92</sup>

### Atrial Septostomy and Lung Transplantation

Atrial septostomy involves the creation of a right-to-left interatrial shunt to increase cardiac output, which, despite reduction in systemic arterial oxygen saturation, may increase systemic oxygen transport, thus reducing the signs and symptoms of right heart failure.<sup>93</sup> Where advanced medical therapies are available, atrial septostomy is used as a palliative measure or a bridge to lung transplantation in appropriately selected patients with refractory right heart failure or syncope/near syncope despite therapy. In regions of the world without access to current medical therapies, atrial septostomy is sometimes used as primary therapy. The procedure carries substantial risk and should only be performed by experienced operators.

Lung transplantation is generally reserved for those failing the best available medical therapy. Survival in patients with PAH who undergo lung transplantation is ≈66% to 75% at 1 year.<sup>94</sup> Most centers prefer double lung transplantation. Heart and lung transplantation is generally reserved for those with complex congenital heart disease.

### Treatment Algorithm

Evidence-based treatment guidelines have recently been proposed.<sup>60,61</sup> In addition to FC, we advocate the incorporation of several other clinical factors into the decision-making process. These include important prognostic factors such as low 6MWD, high right atrial pressure, and low cardiac index. In our experience, patients with rapidly progressive symptoms at presentation warrant more aggressive therapy.

Given the availability of multiple therapeutic options, assessing the response to therapy and further tailoring treat-

ment is increasingly important, although there are few controlled data by which to make recommendations on this issue. Response to therapy may be measured noninvasively, such as with assessment of FC, 6MWD, or echocardiographic parameters of right ventricular function. Some experts monitor response to therapy with hemodynamics obtained by right heart catheterization. We believe that goals of therapy should include improvement to FC I or II and improvement in 6MWD (to  $\geq 380$  m). Our proposed treatment algorithm is displayed in Figure 5.

### Future Directions and Conclusions

PAH is a constellation of diseases with catastrophic implications at an individual level and, despite its status as a relatively rare disease, with serious societal ramifications. Describing hemodynamic PH as a highly prevalent occurrence that affects millions of people would be accurate but unnecessarily alarmist. Most cases are associated with comorbid conditions, of which PH is a relatively minor component. On the other hand, it is equally clear that clinically important PH encompasses far more than the traditionally discussed population with IPAH and includes all patients with PAH (WHO classification 1), chronic thromboembolic disease, disproportionate PH in hypoxic lung conditions, residual PH after optimal treatment of left heart disease, and various miscellaneous causes.

### Disclosures

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