

Updated Clinical Classification of Pulmonary Hypertension

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The aim of a clinical classification of pulmonary hypertension (PH) is to group together different manifestations of disease sharing similarities in pathophysiologic mechanisms, clinical presentation, and therapeutic approaches. In 2003, during the 3rd World Symposium on Pulmonary Hypertension, the clinical classification of PH initially adopted in 1998 during the 2nd World Symposium was slightly modified. During the 4th World Symposium held in 2008, it was decided to maintain the general architecture and philosophy of the previous clinical classifications. The modifications adopted during this meeting principally concern Group 1, pulmonary arterial hypertension (PAH). This subgroup includes patients with PAH with a family history or patients with idiopathic PAH with germline mutations (e.g., bone morphogenetic protein receptor-2, activin receptor-like kinase type 1, and endoglin). In the new classification, schistosomiasis and chronic hemolytic anemia appear as separate entities in the subgroup of PAH associated with identified diseases. Finally, it was decided to place pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis in a separate group, distinct from but very close to Group 1 (now called Group 1'). Thus, Group 1 of PAH is now more homogeneous. (J Am Coll Cardiol 2009;54: 543–54) © 2009 by the American College of Cardiology Foundation

The classification of pulmonary hypertension (PH) has gone through a series of changes since the first classification was proposed in 1973 at an international conference on primary PH (PPH) endorsed by the World Health Organization (1,2). The initial classification designated only 2 categories,

PPH or secondary PH, depending on the presence or absence of identifiable causes or risk factors. Twenty-five years later, the 2nd World Symposium on Pulmonary Arterial Hypertension (PAH) was held in Evian, France. The “Evian classification” attempted to create categories of PH that shared pathologic and clinical features as well as similar therapeutic options (3). This was a much broader, more encompassing classification, with 5 major categories; it allowed investigators to conduct clinical trials in a well-defined group of patients with a shared underlying pathogenesis. This has led to multiple clinical trials and the approval of 8 different medications worldwide for the treatment of PAH.

The 3rd World Symposium on PAH was held in Venice, Italy, 5 years after the Evian conference. At this conference, the impact and usefulness of the “Evian classification” was reviewed, and modest changes were made. The most notable change was to abandon the term PPH in favor of idiopathic pulmonary arterial hypertension (IPAH); familial PAH if there is a family history of PAH; or associated PAH if another cause, such as connective tissue disease or human immunodeficiency virus (HIV), is present. Although the term PPH had become well ingrained in the literature after Dresdale first used it in 1951 (4), it had become clear that

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Abbreviations and Acronyms

- BM₂PR₂** = bone morphogenetic protein receptor type 2
- CHD** = congenital heart disease
- CTEPH** = chronic thromboembolic pulmonary hypertension
- ESRD** = end-stage renal disease
- HIV** = human immunodeficiency virus
- IPAH** = idiopathic pulmonary arterial hypertension
- OR** = odds ratio
- PAH** = pulmonary arterial hypertension
- PAP** = pulmonary arterial pressure
- PCH** = pulmonary capillary hemangiomatosis
- PH** = pulmonary hypertension
- POPH** = portopulmonary hypertension
- PPH** = primary pulmonary hypertension
- PVOD** = pulmonary veno-occlusive disease
- PVR** = pulmonary vascular resistance
- SCD** = sickle cell disease
- TRV** = tricuspid regurgitation jet velocity

the pathologic changes and response to therapy were similar in several other conditions or diseases. The term “secondary PH” had been abandoned at the Evian meeting because it was confusing and did not help with diagnosis or in directing treatment (5) (Table 1). The other prominent change made at the Venice meeting was to move pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) from separate categories into a single subcategory of PAH. These 2 entities have many similarities with each other, which will be discussed later in this article, as well as some similarities with PAH. The 2008 4th World Symposium on PH held in Dana Point, California, provided the opportunity to slightly modify the previous clinical classifications.

Dana Point Classification

During the 4th World Symposium on PH held in 2008 in Dana Point, California, the consensus of an international group of experts was to maintain the general philosophy and organization of the Evian-Venice classifications. However, in response to a questionnaire regarding the previous classification, a majority of experts (63%) felt that modification of the Venice classification was required to accurately reflect information published over the past 5 years, as well as to clarify some areas that were unclear. The current Dana Point classification is listed in Table 2, with major changes highlighted.

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Group 1: PAH

Pulmonary arterial hypertension has been the focus of the classification of PH since the first classification in 1973. The nomenclature of the subgroups and associated conditions has evolved since that time, and additional modifications were made in the Dana Point classification.

1.1./1.2. Idiopathic and heritable PAH. Pulmonary arterial hypertension may occur in different clinical conditions depending on associated diseases. Idiopathic PAH corresponds to sporadic disease in which there is neither a family history of PAH nor an identified risk factor. When PAH

Table 1 Venice Clinical Classification of Pulmonary Hypertension (2003)

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 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 owing to chronic thrombotic and/or embolic disease
 - 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)

occurs in a familial context, germline mutations in the bone morphogenetic protein receptor type 2 (*BM₂PR₂*) gene, a member of the transforming growth factor β signaling family, can be detected in approximately 70% of cases (6,7). More rarely, mutations in activin receptor-like kinase type 1, or endoglin, also members of the transforming growth factor β signaling family, have been identified in patients with PAH, predominantly with coexistent hereditary hemorrhagic telangiectasia. Recently, it has been suggested that patients with PAH associated with *BM₂PR₂* mutations may represent a subgroup of patients with more severe disease who are less likely to demonstrate vasoreactivity than those with IPAH without *BM₂PR₂* mutations (8–10).

Because *BM₂PR₂* mutations have also been detected in 11% to 40% of apparently idiopathic cases with no family history (11,12), the distinction between idiopathic and familial *BM₂PR₂* mutations is artificial. All patients with *BM₂PR₂* mutations have heritable disease, whether the patient is the first identified case, possibly with a de novo mutation, or other family members were previously diagnosed with PAH. In addition, in 30% or fewer families with PAH, no *BM₂PR₂* mutation has been identified. Thus, it was decided to abandon the term “familial PAH” in the new classification and to replace it with the term “heritable PAH.” Heritable forms of PAH include IPAH with germline mutations (mainly *BM₂PR₂* but also activin receptor-

Table 2 Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic PAH
1.2. Heritable
1.2.1. BMPR2
1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3. Unknown
1.3. Drug- and toxin-induced
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Schistosomiasis
1.4.6. Chronic hemolytic anemia
1.5. Persistent pulmonary hypertension of the newborn
1'. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
2. Pulmonary hypertension owing to left heart disease
2.1. Systolic dysfunction
2.2. Diastolic dysfunction
2.3. Valvular disease
3. Pulmonary hypertension owing to lung diseases and/or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1. Hematologic disorders: myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis; lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Main modifications to the previous Venice classification are in bold.
ALK1 = activin receptor-like kinase type 1; BMPR2 = bone morphogenetic protein receptor type 2; HIV = human immunodeficiency virus.

like kinase 1 or endoglin) and familial cases with or without identified germline mutations (13,14). The new category of “heritable PAH” does not mandate genetic testing in patients with IPAH or in familial cases of PAH. Genetic testing, when called for, should be performed as a part of a comprehensive program that includes genetic counseling and discussion of the risks, benefits, and limitations of such testing (15).

1.3. Drug- and toxin-induced PAH. A number of risk factors for the development of PAH have been identified and were included in the previous Evian and Venice classifications (3,5). Risk factors for PAH include “any factor or condition that is suspected to play a predisposing or facilitating role in the development of the disease. Risk factors may include drugs and chemicals, diseases, or phenotype (age, gender).” Risk factors were categorized as definite, very likely, possible, or unlikely, based on the “strength of their association with PH and their probable causal role.” In the current classification, the categorization

of risk factors and the likelihood of developing PAH have been modified. Updated risk factors and associated conditions for PAH are presented in Table 3. A “definite” association is defined as an epidemic, such as occurred with appetite suppressants in the 1960s, or large, multicenter epidemiologic studies demonstrating an association between a drug and PAH. A “likely” association is defined as a single-center, case-control study demonstrating an association or a multiple-case series. “Possible” is defined as drugs with similar mechanisms of action as those in the “definite” or “likely” categories but which have not yet been studied (e.g., drugs used to treat attention-deficit disorder). Lastly, an “unlikely” association is defined as one in which a drug has been studied in epidemiologic studies and an association with PAH has not been demonstrated.

Aminorex, fenfluramine derivatives, and toxic rapeseed oil represent the only identified “definite” risk factors for PAH (3,5). A recent retrospective analysis of more than 100 cases of PAH associated with fenfluramine exposure showed that this category shares clinical, functional, hemodynamic, and genetic features with IPAH, suggesting that fenfluramine exposure represents a potential trigger for PAH without influencing its clinical course (16).

The most recent surveillance study of PH, Surveillance of Pulmonary Hypertension in America (SOPHIA), enrolled 1,335 subjects at tertiary PH centers in the U.S. between 1998 and 2001 (17). This study confirmed the association of fenfluramine and dexfenfluramine intake with the development of PAH. The average monthly number of IPAH cases did not change during the study, which was, however, conducted after fenfluramine and its derivatives had been withdrawn from the U.S. market. A novel finding was that St. John’s Wort (odds ratio [OR]: 3.6, vs. thromboembolic PH) and over-the-counter antiobesity agents containing phenylpropanolamine (OR: 5.2, vs. thromboembolic PH) also increased the risk of developing IPAH.

The SOPHIA study examined intake of a variety of nonselective monoamine reuptake inhibitors, selective serotonin reuptake inhibitors, antidepressants, and anxiolytics, and found no increased risk for developing PAH (17). However, a recent case-control study of selective serotonin

Table 3 Updated Risk Factors for and Associated Conditions of PAH

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	St. John’s Wort
Toxic rapeseed oil	Chemotherapeutic agents SSRI
Likely	Unlikely
Amphetamines	Oral contraceptives
L-tryptophan	Estrogen
Methamphetamines	Cigarette smoking

PAH = pulmonary arterial hypertension; SSRI = selective serotonin reuptake inhibitor.

reuptake inhibitor use in pregnant women after 20 weeks of gestation showed an increased risk (OR: 6.1) in the offspring of developing persistent PH of the newborn, a form of PAH (18). Based on this study, selective serotonin reuptake inhibitors may play a role in the development of PH, at least in association with pregnancy, and therefore they have been reclassified in the “possible” category.

Amphetamine use represents a “likely” risk factor for PAH, although they are rarely taken as a single agent and are frequently used in combination with fenfluramine. A recent comprehensive retrospective study suggested a strong relationship with the use of methamphetamine (inhaled, smoked, oral, or intravenous) and the occurrence of IPAH (19). Based primarily on the results of this study, methamphetamine use is now considered a “very likely” risk factor for the development of PAH. Additional changes in drug- and toxin-induced PAH will be discussed later. With the exception of hereditary hemorrhagic telangiectasia associated with PAH, the first 3 subcategories of Group 1, idiopathic, heritable, and drug- and toxin-induced PAH, are all associated with the development of isolated pulmonary arterial diseases.

1.4.1. PAH associated with connective tissue diseases.

PAH associated with connective tissue diseases represents an important clinical subgroup. The prevalence of PAH has been well established only for systemic sclerosis. Two recent prospective studies using echocardiography as a screening method and right heart catheterization for confirmation found a prevalence of PAH of between 7% and 12% (20,21). Several long-term studies suggest that the outcome of patients with PAH associated with systemic sclerosis is markedly worse than that of patients with IPAH, despite the use of modern therapies.

Importantly, PAH does not represent the only cause of PH in systemic sclerosis. Pulmonary hypertension owing to lung fibrosis is also frequent (22), and diastolic left heart dysfunction is not uncommon (23). There is also primary cardiac involvement in the disease process (24). These observations emphasize the importance of a complete evaluation when PH is suspected in patients with systemic sclerosis and the need for right heart catheterization to confirm the diagnosis of PH and to accurately classify its etiology to determine appropriate treatment.

In systemic lupus erythematosus (25,26) and mixed connective tissue disease (27,28), the prevalence of PAH remains unknown but likely occurs less frequently than in systemic sclerosis. In the absence of fibrotic lung disease, PAH has been reported infrequently in other connective tissue diseases such as Sjögren syndrome (29), polymyositis (30), or rheumatoid arthritis (31).

1.4.2. HIV infection. Pulmonary arterial hypertension is a rare but well-established complication of HIV infection (32,33). Epidemiologic data in the early 1990s, a time when therapy with highly active antiretroviral therapy was not yet available, indicated a prevalence of 0.5% (95% confidence interval: 0.10% to 0.50%) (34). The prevalence of HIV-

associated PAH was evaluated more recently and showed a stable prevalence of 0.46% (95% confidence interval: 0.32% to 0.64%) (35). Human immunodeficiency virus-associated PAH has clinical, hemodynamic, and histologic characteristics similar to those seen in IPAH. The mechanism for the development of PH remains unclear. Because neither the virus nor viral DNA has been found in pulmonary endothelial cells, an indirect action of virus through secondary messengers such as cytokines, growth factors, endothelin, or viral proteins is strongly suspected.

Uncontrolled studies suggest that patients with severe HIV-associated PAH could benefit from bosentan or long-term infusion of epoprostenol (36,37). Interestingly, in a substantial number of cases, normalization of pulmonary vascular hemodynamics can be obtained with therapy indicated for PAH; this is very rarely seen in IPAH (38).

1.4.3. Portopulmonary hypertension. The development of PAH in association with elevated pressure in the portal circulation is known as portopulmonary hypertension (POPH) (39,40). Portal hypertension, rather than the presence of underlying liver disease, is the main determining risk factor for the development of POPH. Prospective hemodynamic studies have shown that 2% to 6% of patients with portal hypertension have PH (41,42). Right heart catheterization is absolutely mandatory for the definitive diagnosis of POPH because several factors may increase pulmonary arterial pressure (PAP) in the setting of advanced liver disease (e.g., high flow associated with the hyperdynamic circulatory state and increased pulmonary capillary wedge pressure owing to fluid overload and/or diastolic dysfunction). Pulmonary vascular resistance (PVR) is usually normal in these cases. Pathologic changes in the small arteries appear identical to those seen in IPAH. A recent multicenter case-control study identified 2 risk factors for the development of POPH: female sex and autoimmune hepatitis (43). Interestingly, hepatitis C infection was associated with a decreased risk. A recent, large cohort study of POPH showed that long-term prognosis was related to the presence and severity of cirrhosis and to cardiac function (44).

1.4.4. Congenital heart diseases. A significant proportion of patients with congenital heart disease (CHD), in particular those with relevant systemic-to-pulmonary shunts, will develop PAH if left untreated. Persistent exposure of the pulmonary vasculature to increased blood flow, as well as increased pressure, may result in pulmonary obstructive arteriopathy, which leads to increased PVR that will result in shunt reversal. Eisenmenger syndrome is defined as CHD with an initial large systemic-to-pulmonary shunt that induces progressive pulmonary vascular disease and PAH, with resultant reversal of the shunt and central cyanosis (45,46). Eisenmenger syndrome represents the most advanced form of PAH associated with CHD. The histopathologic and pathobiologic changes seen in patients with PAH associated with congenital systemic-to-pulmonary shunts (e.g., endothelial dysfunction of the

Table 4 Anatomic-Pathophysiologic Classification of Congenital Systemic-to-Pulmonary Shunts Associated With Pulmonary Arterial Hypertension (Modified From Venice 2003)

1. Type
 - 1.1. Simple pre-tricuspid shunts
 - 1.1.1. Atrial septal defect (ASD)
 - 1.1.1.1. Ostium secundum
 - 1.1.1.2. Sinus venosus
 - 1.1.1.3. Ostium primum
 - 1.1.2. Total or partial unobstructed anomalous pulmonary venous return
 - 1.2. Simple post-tricuspid shunts
 - 1.2.1. Ventricular septal defect (VSD)
 - 1.2.2. Patent ductus arteriosus
 - 1.3. Combined shunts (describe combination and define predominant defect)
 - 1.4. Complex congenital heart disease
 - 1.4.1. Complete atrioventricular septal defect
 - 1.4.2. Truncus arteriosus
 - 1.4.3. Single ventricle physiology with unobstructed pulmonary blood flow
 - 1.4.4. Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent ductus arteriosus
 - 1.4.5. Other
2. Dimension (specify for each defect if >1 congenital heart defect)
 - 2.1. Hemodynamic (specify Qp/Qs)*
 - 2.1.1. Restrictive (pressure gradient across the defect)
 - 2.1.2. Nonrestrictive
 - 2.2. Anatomic
 - 2.2.1. Small to moderate (ASD ≤2.0 cm and VSD ≤1.0 cm)
 - 2.2.2. Large (ASD >2.0 cm and VSD >1.0 cm)
3. Direction of shunt
 - 3.1. Predominantly systemic-to-pulmonary
 - 3.2. Predominantly pulmonary-to-systemic
 - 3.3. Bidirectional
4. Associated cardiac and extracardiac abnormalities
5. Repair status
 - 5.1. Unoperated
 - 5.2. Palliated (specify type of operation[s], age at surgery)
 - 5.3. Repaired (specify type of operation[s], age at surgery)

*Ratio of pulmonary (Qp) to systemic (Qs) blood flow.

pulmonary vasculature) are similar to those observed in idiopathic or other associated forms of PAH.

It has been reported that a large proportion of patients with CHD develop some degree of PAH (47–49). The prevalence of PAH associated with congenital systemic-to-pulmonary shunts in Europe and North America has been estimated to range between 1.6 and 12.5 cases per million adults, with 25% to 50% of this population affected by Eisenmenger syndrome (50). Following the Dana Point meeting, it was decided to update the pathologic and pathophysiologic classification of CHD with systemic-to-

pulmonary shunts (Table 4) to provide a more detailed description of each condition. This anatomic and pathophysiologic classification may be too complex to be used in clinical practice; however, 4 quite distinct phenotypes can be recognized (Table 5).

1.4.5. Schistosomiasis. Another important modification of the new classification is the inclusion of PH associated with schistosomiasis in Group 1.

In the previous classification, this form of PH was subcategorized in Group 4 as PH owing to chronic thrombotic and/or embolic disease. Embolic obstruction of pulmonary arteries by schistosoma eggs was thought to be the primary mechanism responsible for the development of PH (51). However, more recent publications indicate that PH associated with schistosomiasis can have a similar clinical presentation to IPAH (52), with similar histologic findings, including the development of plexiform lesions (53). The mechanism of PAH in patients with schistosomiasis is probably multifactorial. It may include POPH, a frequent complication of this disease (54), and local vascular inflammation as a result of impacted schistosoma eggs, whereas mechanical obstruction by schistosoma eggs seems to play a minor role. PAH associated with schistosomiasis represents a frequent form of PAH, especially in countries in which the infection is endemic. It is estimated that more than 200 million people are infected with any of the 3 species of schistosoma and that 4% to 8% of patients will develop hepatosplenic disease. Data from a recent study based on invasive hemodynamics showed that the prevalence of PAH in patients with hepatosplenic disease was 4.6%; also important was the prevalence of post-capillary hypertension (3.0%), reinforcing the need for invasive hemodynamics for the proper diagnosis of PAH in schistosomiasis (55).

1.4.6. Chronic hemolytic anemia. The chronic hemolytic anemias represent a new subcategory of PAH; these were previously categorized under “other” as conditions associated with the development of PAH. Since the Venice classification, there has been increasing evidence that PAH is a complication of chronic hereditary and acquired hemolytic anemias, including sickle cell disease (SCD) (56,57), thalassemia (58), hereditary spherocytosis (59), stomatocytosis (60), and microangiopathic hemolytic anemia (61).

Pulmonary hypertension has been described most frequently in patients with SCD with histologic lesions similar

Table 5 Clinical Classification of Congenital Systemic-to-Pulmonary Shunts Associated to PAH

A. Eisenmenger syndrome	Includes all systemic-to-pulmonary shunts resulting from large defects and leading to a severe increase in PVR and a reversed (pulmonary-to-systemic) or bidirectional shunt; cyanosis, erythrocytosis, and multiple organ involvement are present
B. PAH associated with systemic-to-pulmonary shunts	Includes moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunt is still prevalent, and no cyanosis is present at rest
C. PAH with small defects	Small defects (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echocardiography); clinical picture is very similar to idiopathic PAH
D. PAH after corrective cardiac surgery	Congenital heart disease has been corrected, but PAH is still present immediately after surgery or recurs several months or years after surgery in the absence of significant postoperative residual lesions

PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance.

to those found in IPAH, including plexiform lesions in 1 case series (62). However, the prevalence of PAH in SCD is not clearly established. The largest study of patients with SCD, which defined PH echocardiographically by the presence of tricuspid regurgitation jet velocity (TRV) ≥ 2.5 m/s, found that 32% of patients had PH (57). However, using a TRV > 2.5 m/s on echocardiography to define PH can lead to a substantial number of false positive cases of PH not confirmed by right heart catheterization (35,63). When a TRV > 3.0 m/s was used, corresponding to an estimated systolic PAP of > 41 mm Hg, only 9% of the cohort met the criteria for PH. Right heart catheterization was carried out in only 18 of 63 patients with TRV > 2.5 m/s. In this subpopulation, PH defined by a mean PAP > 25 mm Hg was confirmed in 17 patients; however, pulmonary wedge pressure was elevated in some patients. A substantial proportion of patients with SCD have pulmonary venous hypertension: 46% in 1 study of 26 patients with SCD and PH (64). In addition, some patients present with a hyperkinetic state with moderate elevation in mean PAP and normal PVR. Thus, although it appears that some patients with SCD do develop PAH, the prevalence of PAH in SCD is undoubtedly much lower than 32%. Prospective epidemiologic studies using echocardiographic screening and direct hemodynamic confirmation with right heart catheterization in all patients with suspected PH are ongoing and will evaluate the precise prevalence of PAH in SCD. The mechanism of PAH in SCD remains uncertain. A probable hypothesis is that chronic hemolysis results in high rates of nitric oxide consumption and produces a state of resistance to nitric oxide bioactivity (65). Consequently, smooth muscle guanosine monophosphate, a potent vasodilator/antiproliferative mediator, is not activated (66).

Group 1': PVOD and/or PCH

The conditions of PVOD and PCH are uncommon, but they are increasingly recognized as causes of PH (67). In the Evian classification, these 2 entities were placed in 2 different groups, both distinct from PAH: PVOD was included in the pulmonary venous hypertension category, and PCH was included in the heterogeneous group of disorders believed to directly affect the pulmonary vasculature. Pathologic studies indicate, however, that PVOD and PCH are often quite similar in terms of changes in the pulmonary parenchyma (i.e., pulmonary hemosiderosis, interstitial edema, and lymphatic dilation) and the development of pulmonary arterial intimal fibrosis and medial hypertrophy. Similarities in pathologic features and clinical presentation suggest that these disorders may overlap. Accordingly, in the Venice classification, PVOD and PCH were placed together as a subgroup of PAH.

PVOD and PCH were included in Group 1 for a number of reasons. First, the histologic changes in the small pulmo-

nary arteries (i.e., intimal fibrosis and medial hypertrophy) are also found in PAH. Second, the clinical presentations of PVOD/PCH and PAH are often indistinguishable and unrecognized antemortem (5). Third, PVOD/PCH and PAH share similar risk factors. These include the scleroderma spectrum of disease (68), HIV infection (69,70), and the use of anorexigens. Fourth, in addition to the well-described familial association with PAH, familial occurrence has been reported with both PVOD and PCH (67). Lastly, mutations in *BMPR2*, the gene associated with familial PAH and IPAH, have been documented in patients with PVOD (71,72). These findings suggest that PVOD, PCH, and PAH may represent different components of a single spectrum of disease.

The present decision to leave PVOD and PCH together in the same subgroup is supported by a recent clinicopathologic study (73) analyzing 38 specimens (autopsies [$n = 15$], surgical biopsies [$n = 15$], explants [$n = 7$], and pneumonectomy [$n = 1$]) from 35 patients diagnosed as having either PVOD ($n = 30$) or PCH ($n = 5$). PCH was identified in 24 (73%) patients diagnosed as having PVOD, either as perivenular foci or diffuse involvement of the pulmonary parenchyma. In 5 patients diagnosed with PCH, 4 showed the venous and arterial changes characteristic of PVOD. These findings suggest that PCH could be an angioproliferative process frequently associated with PVOD.

Recent evidence supports leaving PVOD and PCH together; however, it is apparent that although they may present similarly to IPAH, there are a number of important differences. These include the presence of crackles and clubbing on examination, ground glass opacities, septal thickening, mediastinal adenopathy on chest computed tomography (74-76), hemosiderin-laden macrophages on bronchoalveolar lavage (77), and a lower carbon monoxide diffusing capacity and PaO₂ in patients with PVOD or PCH (71). In addition, the management, response to medical therapy, and prognosis of PVOD/PCH are quite different than that of PAH. A recent study compared 24 patients with histologic evidence of PVOD with or without PCH and 24 randomly selected patients with idiopathic, familial, or anorexigen-associated PAH (71). Among the 16 patients with PVOD who received PAH-specific therapy, 7 (43.8%) developed pulmonary edema. These patients were treated mainly with continuous intravenous epoprostenol, but also with oral therapies, bosentan, and calcium channel blockers. Clinical outcomes were worse in patients with PVOD than those with PAH.

PVOD/PCH remains a difficult disorder to categorize because it shares characteristics with IPAH but also has a number of distinct differences. Given the current evidence, it was decided that PVOD/PCH should be a distinct category but not completely separated from PAH. Therefore, in the current classification, PVOD/PCH is designated as 1'.

Group 2: PH Owing to Left Heart Disease

Left heart disease probably represents the most frequent cause of PH (78). Left-sided ventricular or valvular diseases may produce an increase in left atrial pressure, with passive backward transmission of the pressure leading to increased PAP. In this situation, PVR is normal or near normal (<3.0 Wood units) and there is no gradient between mean PAP and pulmonary wedge pressure (transpulmonary gradient <12 mm Hg). In the Venice classification, 2 broad subcategories were recognized in this group based on the presence or absence of valvular disease: PH owing to left atrial or ventricular disease and PH owing to left-sided valvular disease (mitral and/or aortic). In the Venice classification, this category was referred to as PH with left heart disease. The new heading for this classification more appropriately denotes cause and effect for this group of heterogeneous disorders on the development of PH. In addition, with increasing recognition of left-sided heart dysfunction with preserved ejection fraction, the subcategories of Group 2 have been modified and now include 3 distinct etiologies: left heart systolic dysfunction, left heart diastolic dysfunction, and left heart valvular disease.

Importantly, in some patients with left heart disease, the elevation of PAP is out of proportion to that expected from the elevation of left arterial pressure (transpulmonary gradient >12 mm Hg) and PVR is increased to >3.0 Wood units. In patients referred to cardiac transplant clinics, PH with PVR >3.0 Wood units is reported in 19% to 35% of patients (78,79). Some patients with left heart valvular disease or even left heart dysfunction can develop severe PH of the same magnitude as that seen in PAH (80–82). The elevation of PAP and PVR is due to either the increase of pulmonary artery vasomotor tone and/or pulmonary vascular remodeling (83,84). No studies using medications approved for PAH have been performed in this patient population, and the efficacy and safety of PAH medications remain unknown.

Group 3: PH Owing to Lung Diseases and/or Hypoxia

In this category, the predominant cause of PH is alveolar hypoxia as a result of lung disease, impaired control of breathing, or residence at high altitude. The prevalence of PH in all of these conditions remains largely unknown. In the present classification, the structure of this group was for the most part unchanged. The heading has been modified, again to denote cause and effect on the development of PH. The primary modification in this group was to add a category of lung disease characterized by a mixed obstructive and restrictive pattern. This new subgroup includes chronic bronchiectasis, cystic fibrosis (85), and a newly identified syndrome characterized by the combination of pulmonary fibrosis, mainly of the lower zones of the lung, and emphysema, mainly of the upper zones of the lung (86). In the

syndrome of combined pulmonary fibrosis and emphysema, the prevalence of PH is almost 50% (86).

In patients with parenchymal lung disease, PH is generally modest (mean PAP 25 to 35 mm Hg) (87). However, in some patients, PAP elevations can be more substantial (mean PAP 35 to 50 mm Hg) (88). In such patients, particularly those with only moderate pulmonary mechanical impairment, this is considered “out-of-proportion” PH. In a recent retrospective study of 998 patients with chronic obstructive pulmonary disease who underwent right heart catheterization, only 1% had severe pulmonary hypertension (mean PAP >40 mm Hg) (89). The authors described an unusual pattern of cardiopulmonary abnormalities in the patients with more severe PH, including mild to moderate airway obstruction, severe hypoxemia, hypocapnia, and a very low diffusing capacity for carbon monoxide. As with PH out of proportion to left heart disease, large randomized, controlled studies of medications approved for PAH are not available for PH out of proportion for parenchyma lung disease.

Group 4: Chronic Thromboembolic PH

In the Venice classification, Group 4 was very heterogeneous and included obstruction of pulmonary arterial vessels by thromboemboli, tumors, or foreign bodies. However, depending on the origin of the obstruction, the clinical presentation and radiologic findings are often different, and management is unique to each etiology. Chronic thromboembolic pulmonary hypertension (CTEPH) represents a frequent cause of PH. The incidence of CTEPH is uncertain, but it occurs in up to 4% of patients after an acute pulmonary embolism (90,91). In contrast, other obstructive etiologies are very rare. It was decided, therefore, to maintain only CTEPH in Group 4. In the Venice classification, CTEPH was divided into 2 subgroups: proximal CTEPH, accessible to pulmonary thromboendarterectomy, and distal CTEPH, which is not accessible to surgery. In practice, however, this distinction may be quite unclear, and it may vary depending on individual centers. Currently there is no consensus among experts about the definitions of proximal and distal CTEPH (92). Thus, it was further decided to maintain in Group 4 only a single category of CTEPH and not to attempt to distinguish between proximal and distal forms.

Importantly, it is strongly recommended that patients with suspected or confirmed CTEPH be referred to a center with expertise in the management of this disease to consider the feasibility of performing pulmonary thromboendarterectomy, currently the only curative treatment. The decision depends on the location of the obstruction (central vs. more distal pulmonary arteries), the correlation between hemodynamic findings and the degree of mechanical obstruction assessed by angiography, comorbidities, the willingness of the patient, and the experience of the surgeon (93,94). Patients who are not candidates for surgery may benefit from PAH-specific medical therapy (95,96); however, the

use of these medications in CTEPH requires further evaluation in randomized, controlled trials (97).

Group 5: PH With Unclear or Multifactorial Etiologies

Group 5 consists of several forms of PH for which the etiology is unclear or multifactorial.

5.1. The first subgroup comprises several hematologic disorders. PH has been reported in chronic myeloproliferative disorders including polycythemia vera, essential thrombocythemia, and chronic myeloid leukemia (98). Chronic myeloproliferative disorders can cause PH by various potential mechanisms. High cardiac output, auto or surgical asplenia, direct obstruction of pulmonary arteries by circulating megakaryocytes (99), CTEPH (100), POPH, and congestive heart failure may all play a role. Splenectomy as a result of trauma or as a treatment for hematologic disorders may increase the risk of developing PH (101). CTEPH (102,103) and several cases of PAH (102,104) with medial hypertrophy, internal fibrosis, and plexiform lesions in the pulmonary vasculature have been reported in association with splenectomy.

5.2. The second subgroup includes systemic disorders that are associated with an increased risk of developing PH (105). Sarcoidosis is a common systemic granulomatous disease of unknown origin. PH is an increasingly recognized complication of sarcoidosis (106), with a reported prevalence of 1% to 28% (107). PH is often attributed to the destruction of the capillary bed by the fibrotic process and/or to the resultant chronic hypoxemia (108). However, the severity of PH does not always correlate well with the degree of parenchymal lung disease and blood gas abnormalities, suggesting that other mechanisms may be contributing to the development of PH (105). In this setting, such mechanisms could include extrinsic compression of large pulmonary arteries by mediastinal and hilar adenopathy, and direct granulomatous infiltration of the pulmonary vasculature, especially the pulmonary veins, which sometimes mimic PVOD (109). More rarely, POPH secondary to hepatic involvement with sarcoidosis can be associated with the pathogenesis.

Pulmonary Langerhans cell histiocytosis is an uncommon cause of infiltrative lung disease associated with destructive changes in the lung parenchyma. Severe PH is a common feature in patients with end-stage pulmonary Langerhans cells histiocytosis (110). In some patients, PH is probably related to chronic hypoxemia and/or abnormal pulmonary mechanics; in others, especially those patients with more severe elevation of PAP, PH is unrelated to lung parenchymal injury. Histopathologic examination has shown severe diffuse pulmonary vasculopathy involving predominantly intralobular pulmonary veins and, to a lesser extent, muscular pulmonary arteries (111). These vascular changes consist of medial hypertrophy and intimal fibrosis.

Lymphangioleiomyomatosis is a rare multisystem disorder predominantly affecting women, characterized by cystic

lung destruction, lymphatic abnormalities, and abdominal tumors. PH is relatively uncommon in patients with lymphangioleiomyomatosis (112,113). Chronic hypoxemia and pulmonary capillary destruction caused by cystic lung lesions probably represent the predominant causes of PH.

Neurofibromatosis type 1, also known as von Recklinghausen disease, is an autosomal dominant disease that can be recognized by characteristic “café au lait” skin lesions and by cutaneous fibromas. The disease is occasionally complicated by systemic vasculopathy. Recently it was reported that the neurofibromatosis type 1 gene modulates protein kinase B, an important regulator of cell proliferation. Several cases of PH have recently been reported in the setting of von Recklinghausen disease (114–117). The mechanism of PH is unclear. Lung fibrosis and CTEPH are thought to play a role. In rare cases, histologic examination found both arteries and veins narrowed by medial and/or intimal hypertrophy and fibrosis (117,118).

Lastly, some rare cases of PH have been observed in antineutrophil cytoplasmic antibodies-associated vasculitis; the clinical presentation is similar to PAH, but histologic data are not available (119).

5.3. The third subgroup comprises metabolic disorders. PH has been reported in a few cases of type Ia glycogen storage disease, a rare autosomal recessive disorder caused by a deficiency of glucose-6-phosphatase (120–122). The mechanism of PH is uncertain but has been associated with portocaval shunts, atrial septal defects, or severe restrictive pulmonary function defects. Thrombosis may also play a role in this setting. In 1 case, autopsy findings revealed the presence of plexiform lesions (123).

Gaucher disease is a rare disorder characterized by a deficiency of lysosomal B glucosidase, which results in an accumulation of glucocerebroside in reticuloendothelial cells. Typical manifestations include hepatosplenomegaly and bone marrow infiltration. In a study of 134 patients with Gaucher disease who were systematically screened by echocardiography, PH was not uncommon (124). In this setting, several potential mechanisms for PH have been suggested, including interstitial lung disease, chronic hypoxemia, capillary plugging by Gaucher cells, and splenectomy (124,125). One case of histologic findings similar to idiopathic PAH has been reported (126).

The association between thyroid diseases (hypothyroidism and hyperthyroidism) and PH has been reported in a number of studies (127,128). In a recent prospective study using echocardiographic evaluation, more than 40% of patients with thyroid diseases had PH (129). One instance of PVOD confirmed by histology was observed in a patient with Hashimoto thyroiditis (130). Interestingly, a recent prospective study of 63 consecutive adult patients with PAH found a 49% prevalence of autoimmune thyroid disease, including both hypothyroidism and hyperthyroidism, suggesting that these conditions may be linked by a common immunogenetic susceptibility (131).

5.4. The last subgroup in category 5 includes a number of miscellaneous conditions. In tumor obstruction, a tumor grows into the central pulmonary arteries, with additional appositional thrombosis leading to a progressive obstruction of proximal pulmonary arteries and PH. Such cases are due principally to pulmonary artery sarcomas, occur rarely, and are usually rapidly fatal (132,133). The differential diagnosis with CTEPH can be difficult. Computed tomography and magnetic resonance imaging angiography are the most useful diagnostic modalities for differentiation between tumor and thrombotic material (132,134,135).

Occlusion of the microvasculature by metastatic tumor emboli represents another rare cause of rapidly progressive PH (136). The initial laboratory evaluation shows hypoxemia, often severe, with a clear lung field (137). Computed tomography scanning does not show proximal thrombi but often shows thickening of septa. In contrast, the V/Q lung scan is generally abnormal with multiple subsegmental perfusion defects. Pulmonary microvascular cytology sampling through a pulmonary artery catheter in the wedge position is an important diagnostic tool (137). The majority of reported cases occur in association with breast, lung, or gastric carcinomas.

Patients with mediastinal fibrosis may present with severe PH owing to compression of both pulmonary arteries and veins (138,139). V/Q scan, computed tomography, and pulmonary angiography are very useful for accurate diagnosis, but findings can mimic proximal thrombotic obstruction. The predominant etiology is histoplasmosis (139), although mediastinal fibrosis has been reported with other fungal organisms, with tuberculosis (140), and in patients with sarcoidosis.

Lastly, PH has been reported in patients with end-stage renal disease (ESRD) maintained on long-term hemodialysis. Based on echocardiographic studies, the prevalence of PH in this patient population is estimated at up to 40% (141). There are several potential explanations for the development of PH in patients with ESRD. Hormonal and metabolic derangement associated with ESRD might lead to pulmonary vascular constriction. The PAP may also be increased by high cardiac output (resulting from the arteriovenous access itself and often concomitant anemia) as well as fluid overload. In addition, diastolic and systolic left heart dysfunctions are frequent in this setting (142).

Conclusions

In updating the classification of PH, we incorporated recent findings and sought to clarify areas of ambiguity. We believe that this version is both more comprehensive and more comprehensible and hope that it will also be more useful to clinicians, pending further research into this diverse disease.

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