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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: S43–54) © 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

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Abbreviations and Acronyms

BMPR2 = 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.

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)

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.

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 occurs in a familial context, germline mutations in the bone morphogenetic protein receptor type 2 (*BMPR2*) 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 *BMPR2* mutations may represent a subgroup of patients with more severe disease who are less likely to demonstrate vasoreactivity than those with IPAH without *BMPR2* mutations (8–10).

Because *BMPR2* 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 *BMPR2* mutations is artificial. All patients with *BMPR2* 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 *BMPR2* 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 germ-

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 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 derivates 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

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 erythematosis (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 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-

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

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