

Clinical Classification of Pulmonary Hypertension

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In 1998, during the Second World Symposium on Pulmonary Hypertension (PH) held in Evian, France, a clinical classification of PH was proposed. The aim of the Evian classification was to individualize different categories sharing similarities in pathophysiological mechanisms, clinical presentation, and therapeutic options. The Evian classification is now well accepted and widely used in clinical practice, especially in specialized centers. In addition, this classification has been used by the U.S. Food and Drug Administration and the European Agency for Drug Evaluation for the labeling of newly approved medications in PH. In 2003, during the Third World Symposium on Pulmonary Arterial Hypertension held in Venice, Italy, it was decided to maintain the general architecture and philosophy of the Evian classification. However, some modifications have been proposed, mainly to abandon the term “primary pulmonary hypertension” and to replace it with “idiopathic pulmonary hypertension”; to reclassify pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis; to update risk factors and associated conditions for pulmonary arterial hypertension and to propose guidelines in order to improve the classification of congenital systemic-to-pulmonary shunts. (J Am Coll Cardiol 2004;43:5S–12S) © 2004 by the American College of Cardiology Foundation

Pulmonary hypertension (PH) was previously classified into two categories: primary pulmonary hypertension (PPH) or secondary pulmonary hypertension, depending on the absence or the presence of identifiable causes or risk factors. The diagnosis of PPH was one of exclusion after ruling out all causes of PH (1,2).

In 1998, during the Second World Symposium on Pulmonary Hypertension held in Evian, France, a clinical classification of PH was proposed (3–5). The aim of the “Evian classification” was to individualize different categories sharing similarities in pathophysiological mechanisms, clinical presentation, and therapeutic options. Such a clinical classification is essential in communicating about individual patients, in standardizing diagnosis and treatment, in conducting trials with homogeneous groups of patients, and in analyzing novel pathobiological abnormalities in well-characterized patient populations. Obviously, a clinical classification does not preclude other classifications such as a pathological classification based on histological findings, or a functional classification based on the severity of symp-

toms. The 2003 Third World Symposium on Pulmonary Arterial Hypertension (PAH) held in Venice, Italy, provided the opportunity to assess the impact and the usefulness of the Evian classification and to propose some modifications.

EVIAN CLASSIFICATION

The Evian classification (3,4) consisted of five categories (Table 1) in which PH diseases were grouped according to specific therapeutic interventions directed at dealing with the cause of: 1) PAH, 2) pulmonary venous hypertension, 3) PH associated with disorders of the respiratory system or hypoxemia, 4) PH caused by thrombotic or embolic diseases, and 5) PH caused by diseases affecting the pulmonary vasculature. Within each category are subsets that reflect diverse causes and sites of injury.

Pulmonary arterial hypertension. The first category, termed PAH, included a first subgroup without identifiable cause, or so-called PPH. It incorporated both the familial and sporadic forms of the disease. The second subgroup included a number of conditions or diseases of known causes that have in common the localization of lesions to the small pulmonary muscular arterioles. Among these are drug-related PH, porto-pulmonary hypertension, HIV-related PH, collagen vascular diseases, congenital systemic-to-pulmonary shunts, and persistent PH of the newborn.

Although the mechanisms responsible for remodeling of pulmonary arterioles in these conditions are unknown, they share similar morphological findings, clinical presentation, and clinical responsiveness to treatment with the continuous infusion of epoprostenol (particularly PPH and PAH asso-

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Abbreviations and Acronyms

ALK1	=	activin-receptor-like kinase-1
APAH	=	pulmonary arterial hypertension related to risk factors or associated conditions
BMPR2	=	bone morphogenetic protein receptor type II
FPAH	=	familial pulmonary arterial hypertension
IPAH	=	idiopathic pulmonary arterial hypertension
PAH	=	pulmonary arterial hypertension
PCH	=	pulmonary capillary hemangiomatosis
PH	=	pulmonary hypertension
PPH	=	primary pulmonary hypertension
PVOD	=	pulmonary veno-occlusive disease
TGF- β	=	transforming growth factor- β

Pulmonary venous hypertension. This category consisted predominantly of left-sided valvular or myocardial diseases requiring therapies directed at improving myocardial performance or relieving valvular mechanical defects rather than pulmonary vasodilator therapy. Indeed, epoprostenol therapy in patients with pulmonary venous hypertension can be harmful (8). This category also included extrinsic compression of the pulmonary veins (9) and pulmonary veno-occlusive disease (PVOD), which clinically mimics PPH (10).

PH associated with disorders of the respiratory system or hypoxemia. Within this category, the predominant cause is inadequate oxygenation of arterial blood as a result of either lung disease, impaired control of breathing, or residence at high altitude. In this category, the increase in mean pulmonary artery pressure is generally modest (<35 mm Hg) (11). As a rule, survival depends on the severity of the pulmonary disease rather than on pulmonary hemodynamics. Long-term oxygen therapy (16 or 24 h/day) improves survival in patients with chronic obstructive lung disease (12,13). In native residents who develop PH at high altitude, relocation to sea level rapidly improves PH and its associated symptoms.

PH caused by thrombotic or embolic diseases. This category included either chronic thromboembolic PH due to proximal organized clot in major pulmonary arteries, which can benefit from pulmonary endarterectomy (14,15), or more peripheral emboli or thrombi that are indistinguishable from thrombotic lesions observed in PPH and can be treated with chronic pulmonary vasodilator therapy (16). In all cases, life-long anticoagulation is indicated.

PH caused by diseases affecting the pulmonary vasculature. This category involved PH stemming from inflammatory processes or mechanical obstruction (e.g., schistosomiasis, sarcoidosis). Pulmonary capillary hemangiomatosis (17) was also included in this group, although it usually presents clinically, as with PVOD (18).

ASSESSMENT OF THE EVIAN CLASSIFICATION

The 2003 World Symposium on PH provided the oppor-

Table 1. The Evian Clinical Classification

1. Pulmonary arterial hypertension
 - 1.1 Primary pulmonary hypertension
 - (a) Sporadic
 - (b) Familial
 - 1.2 Related to
 - (a) Collagen vascular disease
 - (b) Congenital systemic-to-pulmonary shunts
 - (c) Portal hypertension
 - (d) Human immunodeficiency virus infection
 - (e) Drugs/toxins
 - (1) Anorexigens
 - (2) Other
 - (f) Persistent pulmonary hypertension of the newborn
 - (g) Other
2. Pulmonary venous hypertension
 - 2.1 Left-sided atrial or ventricular heart disease
 - 2.2 Left-sided valvular heart disease
 - 2.3 Extrinsic compression of central pulmonary veins
 - (a) Fibrosing mediastinitis
 - (b) Adenopathy/tumors
 - 2.4 Pulmonary veno-occlusive disease
 - 2.5 Other
3. Pulmonary hypertension associated with disorders of the respiratory system or hypoxemia
 - 3.1 Chronic obstructive pulmonary disease
 - 3.2 Interstitial lung disease
 - 3.3 Sleep-disordered breathing
 - 3.4 Alveolar hypoventilation disorders
 - 3.5 Chronic exposure to high altitude
 - 3.6 Neonatal lung disease
 - 3.7 Alveolar-capillary dysplasia
 - 3.8 Other
4. Pulmonary hypertension caused by chronic thrombotic or embolic disease
 - 4.1 Thromboembolic obstruction of proximal pulmonary arteries
 - 4.2 Obstruction of distal pulmonary arteries
 - (a) Pulmonary embolism (thrombus, tumor, ova, or parasites, foreign material)
 - (b) In situ thrombosis
 - (c) Sickle-cell disease
5. Pulmonary hypertension caused by disorders directly affecting the pulmonary vasculature
 - 5.1 Inflammatory
 - (a) Schistosomiasis
 - (b) Sarcoidosis
 - (c) Other
 - 5.2 Pulmonary capillary hemangiomatosis

classification and to propose modifications. A questionnaire was sent to all the experts (n = 56) who attended the Venice meeting. The first question was: "Do you think the Evian classification is now well accepted and widely used in clinical practice in place of the previous classification?" Among responders (n = 30), a total of 88% considered the Evian classification to be well accepted and widely used in clinical practice, especially in centers with the largest clinical experience. In contrast, nonexpert physicians apparently still use the old classification (primary vs. secondary).

The second question was: "Do you think the Evian classification is useful for drug evaluation and registration, clinical practice, basic science?" Respectively, 88%, 96%, and 66%

drug evaluation and registration, for clinical practice, and for basic science.

Lastly and probably the best evidence of the impact of the Evian classification is that both the U.S. Food and Drug Administration and the European Agency for Drug Evaluation have recently used this clinical classification for the labeling of newly approved drugs: bosentan (19,20), treprostinil (21), and iloprost (22).

Considering the globally favorable opinion of the Evian classification, the task force on epidemiology and classification decided to maintain the general architecture and philosophy of this clinical classification. However, to improve and to update the Evian classification according to the recent advances in our understanding of PH, it was proposed that some important issues be addressed, including: 1) the need to include a genetic classification, 2) discontinuing use of the term "primary pulmonary hypertension," 3) the reclassification of PVOD and pulmonary capillary hemangiomas (PCH), 4) the update on new risk factors for PAH, and 5) reassessment of the classification of congenital systemic-to-pulmonary shunts.

DO WE NEED A GENETIC CLASSIFICATION OF PH?

In light of the recent advances in our understanding of the genetic basis of PPH, it has been suggested that a genetic classification of PH be considered. Before addressing this question further it may be worthwhile to outline briefly what is known and unknown regarding the genetics of severe PH. Mutations in the gene encoding the bone morphogenetic protein receptor type II (BMPR2), localized to chromosome 2q33, have been suggested to underlie approximately 50% of cases of familial PPH (23). Although many of the other 50% of families show some evidence of linkage to the BMPR2 locus, specific mutations have not been identified in the coding region, or the promoter region (R. Trembath, personal communication, June 2003). Moreover, mutations in BMPR2 have been identified in up to 26% of sporadic cases of PPH (24). Although some of these cases may arise *de novo* by mutation, the majority represent familial transmission of mutant BMPR2, with low penetrance of the gene for the disease (25). However, the frequency of mutation has not yet been reproduced in larger studies, and so far fewer than 70 BMPR2 mutations have been reported. In addition, there is some evidence for a second locus mapping to 2q31, although this locus has been mapped using a phenotype that includes an abnormal pulmonary vascular response to exercise, rather than manifest PPH.

So far, mutations in BMPR2 gene seem to be quite specific for so-called PPH; however, mutations in BMPR2 have also been identified in rare cases of PAH associated with appetite-suppressant drugs (26) and one patient with PVOD (27). Thus far, a search for BMPR2 mutations in other forms of PH has been negative (28).

BMPR2 are not sufficient *per se* to cause clinical disease. Hence, the chance of a disease gene carrier developing clinical PPH is as low as 20%. This observation highlights the critical role of other genetic/environmental factors in conferring susceptibility to PH (29).

In summary, because our knowledge of the role of genes in various forms of PH remains at an early stage it is probably premature to recommend a classification of PH based on genetic defects. Further studies are needed to identify other genes, modifiers, and regulatory genes of PH and to determine whether PAH patients with BMPR2 mutations differ from PAH patients without identified mutations with respect to response to treatment, age of onset, severity, and natural course of the disease.

TO ABANDON THE TERM "PRIMARY PULMONARY HYPERTENSION"

Primary pulmonary hypertension means unexplained or idiopathic PH.

Initially described by Romberg (30) as "sclerosis of pulmonary arteries" more than a century ago this disease has been the subject of great interest and has successively undergone several name changes. The term "primary pulmonary hypertension" was coined by Dresdale *et al.* (31) more than 50 years ago, to characterize a condition in which hypertensive vasculopathy existed exclusively in the pulmonary vasculature without a demonstrable cause.

In the last 20 years, it has become recognized that several conditions or diseases, including the intake of appetite-suppressant medications, connective tissue disease, portal hypertension, or HIV infection, may be associated with pulmonary vascular disease, and that they share similar pathologic and clinical features with PPH. These conditions were commonly grouped as "secondary pulmonary hypertension" in contrast with primary forms. As a result, the term "secondary pulmonary hypertension" comprised very heterogeneous forms of diseases including other intrinsic pulmonary vascular diseases that resemble PPH as well as disorders that either affect the pulmonary venous circulation or conditions that affect the pulmonary circulation by altering respiratory structure or function.

Thus, the term "secondary pulmonary hypertension" in the Evian classification was abandoned because it was found confusing and without value for diagnosis and treatment. In contrast, the term "primary pulmonary hypertension" was retained because of its common use and familiarity, and because it was emblematic of 50 years of intense scientific and clinical research. However, the main problem with the term "primary" is that it requires use of the modifier "secondary" to distinguish this condition from others. Thus, during the Venice meeting, it was proposed to abandon "primary pulmonary hypertension" and to replace it with "idiopathic pulmonary arterial hypertension." The first category in the modified Evian classification termed "pulmo-

subgroups: 1) idiopathic pulmonary arterial hypertension (IPAH), 2) familial pulmonary arterial hypertension (FPAH), and 3) pulmonary arterial hypertension related to risk factors or associated conditions (APAH).

TO RECLASSIFY PVOD AND PCH

Both PVOD and PCH are uncommon conditions, but they are increasingly recognized as causes for PH. In the Evian classification, these two entities were included in separate groups, both distinct from the PAH category: PVOD was included in the pulmonary venous hypertension category, which consists predominantly of left-sided valvular or myocardial diseases; PCH was included in the last and heterogeneous group of PH caused by diseases directly affecting the pulmonary vasculature.

As discussed in the pathology report by Pietra *et al.* (32) in this supplement, PVOD and PCH are similar in some respects, particularly in relation to the changes in the pulmonary parenchyma (i.e., pulmonary hemosiderosis, interstitial edema, and lymphatic dilation) and to pulmonary arterial intimal fibrosis and medial hypertrophy (18, 33, 34). Similarities in the pathological features and clinical presentation, along with the possible occurrence of pulmonary edema during epoprostenol therapy (35,36), suggest that these disorders may overlap. Accordingly, it seems logical to include PVOD and PCH within the same group, most appropriately within the category of PAH. Indeed, PVOD and PCH, as well as PAH, show similar histological changes in the small pulmonary arteries, including intimal fibrosis, medial hypertrophy, and plexiform lesions. Moreover, the clinical presentation of PVOD and PCH is generally similar to that of PPH.

Finally, the risk factors or conditions associated with PAH and PVOD/PCH are similar and include the scleroderma spectrum of the disease (37), HIV infection (38,39), and the use of anorexigens (F. Capron, personal communication, June 2003). Of particular interest are reports of a familial occurrence in both PVOD (40) and PCH (41) as well as in PAH. Lastly, *BMPR2* mutation, the gene associated with familial and IPAH, has been documented in a patient with PVOD (27). These findings suggest that PVOD, PCH, and PAH may represent components of a spectrum of a single disease. Thus, in the new classification, the PAH category comprises another subgroup termed "PAH associated with significant venous or capillary involvement." This subgroup probably requires similar management to the other PAH subgroups. However, the prognosis seems worse, with a more rapid downhill course. In addition, vasodilators and especially epoprostenol have to be used with great caution because of the high risk of pulmonary edema. As a result, as soon as recognized, these patients should be placed on the list for lung transplanta-

UPDATED RISK FACTORS AND ASSOCIATED CONDITIONS FOR PULMONARY ARTERIAL HYPERTENSION

A risk factor for PAH is 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). The term "associated conditions" is used when it is not possible to determine whether a predisposing factor was present before PH onset. Because the absolute risk of known risk factors for PAH is generally low, individual susceptibility or genetic predisposition is likely to play an important role. During the Evian meeting, different risk factors and associated conditions were categorized according to the strength of their association with PH and their probable causal role. "Definite" indicates an association based on several concordant observations including a major controlled study or an unequivocal epidemic. "Very likely" indicates several concordant observations (including large case series and studies) that are not attributable to identified bases. "Possible" indicates an association based on case series, registries, or expert opinions. "Unlikely" indicates risk factors that were suspected but for which controlled studies failed to demonstrate any association. According to the strength of the evidence, Table 2 summarizes, risk factors and associated conditions that were identified during the Evian meeting.

RECENT EPIDEMIOLOGIC STUDIES

Ever since the Evian meeting, two prospective epidemiologic studies have been performed in the United States.

The SNAP (Surveillance of North American Pulmonary Hypertension) study was a voluntary collaborative survey conducted on 559 patients with PH over a 14-month period (42). This study confirmed the causal role of fenfluramine derivatives in the development of PAH. It showed a clear association between the use of fenfluramine and the diagnosis of PPH but not secondary PH. The adjusted odds ratio (OR) for the use of fenfluramine for more than six months was 7.5. Another interesting observation in the SNAP study was the unexpectedly high reported rate of anorexigen use in secondary PH (11.4%). This finding suggested that the use of anorexigens increased the likelihood of developing PH in patients with other conditions that cause secondary PH.

The Sophia (Surveillance Of Pulmonary Hypertension In America) study enrolled 13 tertiary-care PH centers within the U.S. and included 1,335 patients with newly diagnosed PH between January 1998 and June 2001 (43). This study demonstrated that the use of fenfluramine during the past five years was preferentially associated with PPH rather than chronic thromboembolic PH (OR, 2.7; 95% confidence interval [CI]: 1.5 to 4.8); Interestingly, this study also

Table 2. Risk Factors and Associated Conditions for PAH Identified During the Evian Meeting (1998) and Classified According to the Strength of Evidence

A. Drugs and Toxins
1. Definite
• Aminorex
• Fenfluramine
• Dexfenfluramine
• Toxic rapeseed oil
2. Very likely
• Amphetamines
• L-tryptophan
3. Possible
• Meta-amphetamines
• Cocaine
• Chemotherapeutic agents
4. Unlikely
• Antidepressants
• Oral contraceptives
• Estrogen therapy
• Cigarette smoking
B. Demographic and Medical Conditions
1. Definite
• Gender
2. Possible
• Pregnancy
• Systemic hypertension
3. Unlikely
• Obesity
C. Diseases
1. Definite
• HIV infection
2. Very likely
• Portal hypertension/liver disease
• Collagen vascular diseases
• Congenital systemic-pulmonary-cardiac shunts
3. Possible
• Thyroid disorders

both “St. John’s wort” and over-the-counter antiobesity agents that contain phenylpropanolamine.

CASE SERIES AND CASE REPORTS

Ever since the Evian meeting, several case series or case reports have been published that provide some evidence of novel “possible” risk factors for PAH.

Hematologic conditions. Recently, a high prevalence (11.5%) of *asplenia secondary to surgical splenectomy* has been reported in a series of 61 patients with unexplained PAH, suggesting that patients with splenectomy may be at increased risk for developing PAH (44). At the time of diagnosis, PAH was generally severe, and the interval between splenectomy and diagnosis ranged from 4 to 32 years. Histological examination of the lungs in three patients showed pulmonary vascular changes similar to those of IPAH. However, these patients also had many thrombotic lesions in small pulmonary arteries. The underlying pathogenetic mechanisms are unclear; it was hypothesized that because of the loss of the filter function of the spleen, abnormal erythrocytes remained longer in the circulation

Certain *hemoglobinopathies* represent other possible risk factors for PAH. Pulmonary hypertension is a well-recognized complication of sickle-cell disease. It is a severe complication that significantly reduces the survival rate of these patients as compared with those without PH. It represents the cause of death in 3% of patients with sickle-cell disease. Classically, in situ thrombosis of elastic and small pulmonary arteries was considered to be the predominant finding at autopsy. Recently, a clinical-pathologic study of 20 patients reported pulmonary vascular abnormalities consistent with those of PAH, including plexiform lesions, in 60% of patients (45). Increased shear stress from deformed erythrocytes passing through the pulmonary microvasculature has been proposed as the underlying mechanism of vascular injury. In addition, the bioavailability of nitric oxide is reported to be decreased in these patients (46,47).

Other *hemoglobin abnormalities* may be associated with PAH, especially *beta-thalassemia* (48). In some patients, histologic examination at postmortem has found the lesions of IPAH and/or thrombotic pulmonary arteriopathy. The mechanism of PAH in patients with hemoglobinopathy is unclear, but a possible role has been suggested for liver disease, splenectomy, and thrombosis.

The possible association of PAH with chronic myeloproliferative disorders has been reported by several case reports (49,50) and in one cohort of six patients (51). A recent report from the Mayo Clinic dealt with 26 patients seen in that institution between 1987 and 2000 (52). The chronic myeloproliferative disorders included polycythemia vera, essential thrombocytosis, and myelofibrosis with myeloid metaplasia accompanying chronic myeloid leukemia or the myelodysplastic syndrome. In all patients, PH was moderate or severe at diagnosis. In these patients, the main causes of PH, particularly chronic thromboembolism, were excluded on clinical grounds and ventilation-perfusion lung scan. Unfortunately, autopsies were not performed. The etiology of PAH in these patients is probably multifactorial, including splenectomy, portal hypertension, chemotherapy-induced PVOD, and infiltration of the pulmonary parenchyma by hematopoietic cells and extramedullary hemopoiesis.

Rare genetic or metabolic diseases. Unexplained PAH has been reported in patients with certain rare genetic or metabolic diseases. These observations suggest new pathobiologic mechanisms for the pulmonary hypertension (e.g., an alternative role for a known mutated gene, genetic defects in chromosomal regions adjacent to a mutated gene, or a consequence of a new metabolic pathway).

Pulmonary arterial hypertension has been associated with type *Ia glycogen storage disease* (Von Gierke disease) in fewer than 10 patients since the initial description (53). It is a rare autosomal recessive disorder caused by a deficiency of glucose-6-phosphatase (54). Pulmonary histology is typical of PAH, and the clinical course is that of rapidly developing right heart

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