The Evolving Classification of Pulmonary Hypertension

Michelle Foshat, MD; Nahal Boroumand, MD

Context.—An explosion of information on pulmonary hypertension has occurred during the past few decades. The perception of this disease has shifted from purely clinical to incorporate new knowledge of the underlying pathology. This transfer has occurred in light of advancements in pathophysiology, histology, and molecular medical diagnostics.

Objectives.—To update readers about the evolving understanding of the etiology and pathogenesis of pulmonary hypertension and to demonstrate how pathology has shaped the current classification.

Data Sources.—Information presented at the 5 World Symposia on pulmonary hypertension held since 1973, with the last meeting occurring in 2013, was used in this review.

Conclusions.—Pulmonary hypertension represents a heterogeneous group of disorders that are differentiated based on differences in clinical, hemodynamic, and histopathologic features. Early concepts of pulmonary hypertension were largely influenced by pharmacotherapy, hemodynamic function, and clinical presentation of the disease. The initial nomenclature for pulmonary hypertension segregated the clinical classifications from pathologic subtypes. Major restructuring of this disease classification occurred between the first and second symposia, which was the first to unite clinical and pathologic information in the categorization scheme. Additional changes were introduced in subsequent meetings, particularly between the third and fourth World Symposia meetings, when additional pathophysiologic information was gained. Discoveries in molecular diagnostics significantly progressed the understanding of idiopathic pulmonary arterial hypertension. Continued advancements in imaging modalities, mechanistic pathogenicity, and molecular biomarkers will enable physicians to define pulmonary hypertension phenotypes based on the pathobiology and allow for treatment customization.

DEVELOPMENTS IN THE POSTCARDIAC CATHETERIZATION ERA

The advent of heart catheterization revolutionized the field of PH. In 1930, before cardiac catheterization, the study of PH was limited to autopsy cases that provided limited insight into the functional behavior of small pulmonary arteries and arterioles. Investigation of the functional aspect of pulmonary vasculature began in 1940, and assessment of pulmonary vascular hemodynamics by cardiac and pulmonary artery catheterization fundamentally changed the understanding of the pulmonary circulation.4

In 1950, David T. Dresdale, MD, noticed increased pulmonary artery pressure in patients with neither heart nor lung problems. He coined the term primary pulmonary hypertension (PPH) to represent this patient population without an evident cause of PH.11 Dr Dresdale made a breakthrough in the understanding of the pathophysiology of PPH by establishing that tolazoline, a pulmonary vasodilator, reduced the pressure in PH and, thus, demonstrated the role of vasoconstriction in the disease pathogenesis.12

In 1959, Heath and Edwards13 published a landmark article describing the histopathologic findings in small arteries and arterioles in patients with chronically elevated pulmonary artery pressure (PAP). They studied lung tissue from 67 patients with congenital heart disease–associated PH and 2 patients with idiopathic (primary) pulmonary artery hypertension. They divided the pathologic changes in the intima and media of small arteries and arterioles into 6 grades.13 The Heath and Edwards13 observations were a major step forward in developing the pathologic classification of PH and brought organization to a complex subject; however, because it was mainly based on PH in patients with congenital heart disease, application of their work to other types of PH was uncertain.

The most complete pathologic description of pulmonary arterial hypertension (PAH) was made by Wagenvoort and Wagenvoort,14 in 1970, of 156 PH cases collected throughout Europe.2,15 Together, Heath and Edward13 along with the Wagenvoort's developed a schema for grading the severity of arteriopathy and for describing specific lesions, including concentric intimal fibrosis, medial hypertrophy, plexiform lesions, in situ thrombosis, and dilatation lesions. These descriptions still form the basis of studies of the pathogenesis of PH.

This was the current state of knowledge when an epidemic of PH secondary to aminorex broke out. Aminorex was a popular, over-the-counter appetite suppressant, which entered into the market in Switzerland, Germany, and Austria in 1965. Shortly thereafter, catheterization laboratories in Switzerland and subsequently, in Germany and Austria suddenly noticed an increase in the number of cases of PH not associated with cardiac or pulmonary problems. Before this event, catheterization laboratories had been dedicated to patients with cardiac disease. The patients presenting with PH were generally females with real or perceived obesity who were otherwise healthy individuals. Eventually, aminorex was implicated as the causative agent of the sudden increase of PH. In 1968, the drug was withdrawn from the market, and consequently, the incidence of PH dropped. Autopsies of patients who died after exposure to aminorex revealed vascular lesions similar to the pathologic findings described in PPH (ie, plexiform lesions and concentric, cellular intimal thickening).5 These findings resulted in overlap, confusion, and ambiguity in the terminology of PPH clinically and pathologically.

THE FIRST WORLD HEALTH ORGANIZATION MEETING

The epidemic of PH induced by aminorex prompted the World Health Organization to hold its first meeting about PH in Geneva, Switzerland, in 1973. The purpose of the meeting was to assess the state of knowledge about PPH and to standardize the clinical and pathologic nomenclature.10 That meeting constituted the beginning of the attempts for the classification of PH.

The first recommendation from that meeting was that the clinical and pathologic nomenclature should be separate and distinct. From the clinical standpoint, PPH was defined as a group of patients with elevated PAP and no known underlying cause, without elevation of the pulmonary capillary wedge pressure. However, from the pathology standpoint, 3 distinct pathologic patterns might be found in those patients: plexogenic pulmonary arteriopathy, recurrent pulmonary thromboembolic disease, and pulmonary veno-occlusive disease (PVOD).17

The meeting also called for an international registry to gather standardized data regarding the disease, but the registry never materialized.18 However, in 1981, the National Heart, Lung and Blood Institute of Health (Bethesda, Maryland) created a national registry of patients with PPH. Significant achievement in clarifying the clinical, pathophysiologic, and pathologic aspects of the disease arose from the registry until it closed in 1987.

THE SECOND WORLD HEALTH ORGANIZATION MEETING

The second World Health Organization meeting was prompted by discovery of 2 effective treatments for PAH: epoprostenol (prostacyclin)19 and high doses of calcium channel blockers. The meeting was held in Evian, France, in 1998, 25 years after the first meeting. Instead of focusing only on PPH, the proceedings expanded the classification and nomenclature to reflect all etiologies of PH. The Evian classification had several goals, the first of which was to individualize different categories with similar pathophysiologic mechanisms, clinical presentations, and responses to treatment.20 Previously, the usefulness of a pathologic classification of PH lagged behind clinical and treatment developments because it was not incorporated into clinical algorithms used for diagnosis and for monitoring treatment. Therefore, the participants also wanted to standardize the diagnosis of PH and to begin conducting clinical trials.

The Evian classification divided PH into 5 categories (Table 1): (1) PAH, (2) pulmonary venous hypertension, (3) pulmonary hypertension associated with disorders of the respiratory system or hypoxemia, (4) pulmonary hypertension caused by chronic thrombotic or embolic disease, and (5) pulmonary hypertension caused by disorders directly affecting the pulmonary vasculature. In the Evian classification the term secondary PH was abandoned because the nomenclature was confusing and was neither helpful in diagnosis nor in directing treatment. Secondary pulmonary hypertension had comprised a heterogeneous group of diseases, including those with intrinsic vascular lesions associated with HIV infection, portal hypertension, drugs/toxins, and other disease, including PH secondary to left-sided heart failure, valvulopathy, respiratory failure, or...
Pulmonary Arterial Hypertension

The first category of PH outlined by the Evian classification was PAH. Hemodynamically, PAH is defined as a resting mean PAP of more than 25 mm Hg, a pulmonary vascular resistance more than 3 Wood units, and a pulmonary capillary wedge pressure less than 15 mm Hg. Aside from changes that are common to all types of PH, PAH is characterized by constrictive and complex lesions, which involve the small pulmonary arteries and arterioles. Constrictive lesions include concentric laminar intimal proliferation (Figure 1) and concentric acellular intimal proliferation, whereas complex lesions include plexiform lesions, dilation, and arteritis (Figure 2). Plexiform lesions are a network of vascular channels lined by endothelial cells with a core of myofibroblasts or less-differentiated cells and are associated with expansion and partial destruction of the arterial wall with extension of the plexiform lesion into the perivascular connective tissue. Fibrin thrombi and platelets are frequently present in plexiform lesions. Dilation lesions, which are expanded, thin-walled, veinlike vessels, are usually located distal to a plexiform lesion. In this classification, PAH was subdivided into 2 categories based on whether the cause was known.

At that time, the established conventional therapy for PAH was anticoagulant and vasodilator agents. Apart from calcium channel blockers for vasoreactive patients, the only approved therapy was epoprostenol, administered by continuous intravenous infusion. Epoprostenol had swift antiplatelet activity and vasodilatory properties, and long-term treatment was associated with significant reductions in pulmonary vascular resistance, going beyond immediate vasodilation. Epoprostenol caused a long-term reduction in pulmonary vascular resistance exceeding that which could be achieved through vasodilator challenge, which is consistent with the drug’s progressive effect on the pulmonary vasculature when administered over time.

Pulmonary Venous Hypertension

Pulmonary venous hypertension, the second group in the Evian classification, is due to left-sided ventricular or valvular disease, which results in increased left atrial pressure, passive backward transmission of pressure, and increased PAP levels. In this situation, pulmonary vascular resistance is within reference range (<3.0 Wood units), and no gradient exists between mean PAP and pulmonary wedge pressure levels. Treatment is directed toward improving myocardial performance or to relieving valvular mechanical defects. Importantly, epoprostenol therapy in these patients can be harmful. Histopathologic findings include medial hypertrophy and muscularization of arterioles, moderate intimal fibrosis, medial hypertrophy and arterialization of veins, dilatation of lymphatics, interstitial edema, interstitial fibrosis, and hemosiderosis (Figure 3).

Table 1. Evolution of Pulmonary Hypertension Classification: Second World Health Organization Meeting (Evian, France; 1998)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Subclassifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pulmonary arterial hypertension</td>
<td>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) Drug/toxins (1) Anorexigen (2) Other (f) Persistent pulmonary hypertension of the newborn (g) Other</td>
</tr>
<tr>
<td>2. Pulmonary venous hypertension</td>
<td>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</td>
</tr>
<tr>
<td>3. Pulmonary hypertension associated with disorders of the respiratory system or hypoxemia</td>
<td>3.1 Chronic obstructive pulmonary disease 3.2 Interstitial lung disease 3.3 Sleep-disordered breathing 3.4 Alveolar hyperventilation disorders 3.5 Chronic exposure to high altitude 3.6 Neonatal lung disease 3.7 Alveolar-capillary dysplasia 3.8 Other</td>
</tr>
<tr>
<td>4. Pulmonary hypertension caused by chronic thrombotic or embolic disease</td>
<td>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</td>
</tr>
<tr>
<td>5. Pulmonary hypertension caused by disorders directly affecting the pulmonary vasculature</td>
<td>5.1 Inflammatory (a) Schistosomiasis (b) Sarcoidosis (c) Other 5.2 Pulmonary capillary hemangiomatosis</td>
</tr>
</tbody>
</table>

In the Evian classification, PVOD was also placed in the category of pulmonary venous hypertension. PVOD, considered a rare cause of PH, is characterized by fibrous remodeling of the intima involving small veins, venules, and occasionally, larger veins, resulting in narrowing or complete occlusion of the lumen. Mild, medial hypertrophy of the arteries and arterioles is also seen. Interstitial edema, which ultimately progresses to interstitial fibrosis and hemosiderin in alveolar macrophages, pneumocytes type II, and the interstitium, are characteristic (Figure 4).

**Pulmonary Hypertension Associated With Respiratory Disorders or Hypoxemia**

The third group of Evian classification encompassed PH secondary to lung diseases or hypoxia. In this group, hypoxia is the predominant cause of PH, and the underlying pathogenesis is vasoconstriction of small pulmonary arterioles. The PH in these patients is modest (mean PAP levels, 25–35 mm Hg). Prognosis depends on the severity of the pulmonary disease, rather than on pulmonary hemodynamics. Survival in these patients improves with long-term oxygen therapy. Pathologic findings include medial hypertrophy of the small arteries and peripheral extension of smooth muscle.

**Pulmonary Hypertension From Chronic Thrombotic or Embolic Disease**

The fourth group of the Evian classification was chronic thromboembolic PH. Occlusion of the pulmonary arteries is usually embolic in origin, but in situ thrombosis of small pulmonary arteries may occasionally occur. Acute pulmonary thromboembolism rarely causes PH, except in massive cases; however, recurrent pulmonary thromboembolism can often lead to sustained arterial damage and PH. Pathologic findings in this group include mild or absent medial hypertrophy, intravascular fibrous septa, or webs in the large, elastic arteries. Eccentric intimal fibrosis, which often obliterates the lumen with recanalization of thrombi, is also seen (Figures 5 and 6). Treatment consisted of endarterectomy for proximal, organized blood clots in the major pulmonary arteries and chronic pulmonary vasodilator therapy for more-peripheral thromboemboli. In all cases, life-long anticoagulation is required.

**Pulmonary Hypertension From Disorders Affecting the Pulmonary Vasculature**

Rare causes of PH that are thought to cause direct injury to the pulmonary vasculature were listed in the fifth group of the Evian classification. Pulmonary capillary hemangiomatosis (PCH) was placed among this category. Characteristically, PCH is a localized capillary proliferation within the lung in which the capillaries invade the pulmonary interstitium, the pulmonary vasculature, and less commonly, the airways (Figure 7, A and B). Pulmonary hemosiderosis is a striking feature.

**THE THIRD WORLD SYMPOSIUM ON PULMONARY HYPERTENSION**

The third World Symposium on Pulmonary Hypertension was held in Venice, Italy, in 2003. The organization of this meeting was driven by a surge in the understanding of the pathophysiologic and molecular aspects of PH. The general architecture and philosophy of the Evian classifications were maintained (Table 2). The major changes in the classification included (1) The term primary pulmonary hypertension was abandoned and replaced by idiopathic and familial PH, and (2) PVOD and PCH were moved to the PAH category from the second and fifth categories, respectively. The decision to eliminate the term primary was based on confusion generated because the modifier secondary had been removed previously.

---

Figure 1. Constrictive and complex arteriolar lesions in pulmonary arterial hypertension—concentric cellular intimal proliferation (hematoxylin-eosin, original magnification ×200).

Figure 2. Constrictive and complex arteriolar lesions in pulmonary arterial hypertension—plexiform (network of vascular channels lined by endothelial cells with a core of myofibroblasts or less well differentiated cells) and dilation lesion (thin-wall, venulike vessels distal to plexiform lesion with angiomatoid features) (hematoxylin-eosin, original magnification ×80).

Figure 3. Pulmonary venous hypertension. Veins located in the interlobular septa with medial hypertrophy and arterialization (doubling of the elastic layer) suggest a diagnosis of pulmonary venous hypertension in patients with left-sided heart disease (Movat, original magnification ×40).
Similarities in clinical presentation and pathologic features between PVOD and PCH suggested that these 2 lesions might overlap. Commonalities included pulmonary hemosiderosis, pulmonary interstitial edema and fibrosis, lymphatic dilatation, pulmonary arterial intimal fibrosis, and medial hypertrophy. Both PVOD and PCH were placed in the first category with PAH because (1) the intimal fibrosis and medial hypertrophy seen in small pulmonary arteries in these 2 conditions were also seen in PAH, (2) their clinical presentations were often similar to PAH and could not be recognized before death, (3) they shared similar risk factors (ie, HIV, scleroderma, and use of appetite suppressant), and

Figure 4. Pulmonary veno-occlusive disease. Intimal thickening of small veins with near obliteration of the lumen. Surrounding lung parenchyma shows hemosiderosis with numerous hemosiderin-laden macrophages and features overlapping with pulmonary capillary hemangiomatosis, including interstitial thickening due to proliferation and congestion of capillaries. Differentiation from pulmonary venous hypertension depends upon involvement of small venules and absence of left heart disease (Movat, original magnification ×40).

Figure 5. Thrombotic arteriopathy. Obliteration of the lumen by eccentric intimal thickening, without vascular media thickening, and recanalization of the lumen (hematoxylin-eosin, original magnification ×100).

Figure 6. Thrombotic arteriopathy. Obliteration of the lumen by eccentric intimal thickening, without vascular media thickening, and recanalization of the lumen (Movat, original magnification ×100).

Figure 7. Pulmonary capillary hemangiomatosis. A, Proliferation of capillaries in the alveolar septa and the peribronchial and perivascular connective tissues. Hemosiderin-laden macrophages are seen in the alveolar spaces. B, Proliferation of dilated capillary loops in the alveolar septa (hematoxylin-eosin, original magnifications ×40 [A] and ×100 [B]).
cases. It was suggested that loss of function mutation in this underlies 80% of the familial cases and 10–30% of sporadic

It was discovered that mutations in bone morphogenetic protein receptor type 2 (BMPR2) mutation, mutations in activin receptor-like kinase 1 (ALK-1) and endoglin (EGN) proteins were also identified in hereditary cases. The term heritable PAH was preferred because it included idiopathic PAH with germline mutations and familial cases with or without identified germline mutations.24,25

During this meeting, the role of inflammation in vascular remodeling and the development of PAH was recognized and was supported by evidence, such as perivascular infiltration of inflammatory cells, elevated circulating levels of certain cytokines and chemokines, and increased incidence of PAH in certain inflammatory conditions, such as connective tissue diseases.

**THE FIFTH WORLD SYMPOSIUM ON PULMONARY HYPERTENSION**

Nice, France, hosted the most-recent World Symposium on Pulmonary Hypertension in 2013. Additional modifications were made to the classification system, especially for group 1 (Table 4). Persistent pulmonary hypertension of newborns was classified as group 1 because it was thought that its differences to PAH outweighed its similarities. The category of congenital/acquired left heart inflow/outflow obstruction and congenital cardiomyopathies was placed in the second group, and PH associated with chronic hemolytic anemia was moved from group 1 to group 5. Additionally, segmental pulmonary hypertension was introduced in category 5.26 The treatment algorithms were also discussed and updated.

Further advancements in molecular genetics were acknowledged and listed under heritable PAH. Besides mutations in the BMPR2, ALK1, and ENG genes, rare mutations that account for approximately 5% of the heritable PAHs included SMAD9, caveolin 1 (CAV1), and potassium channel, subfamily K, member 3 (KCNK3) genes. Most genetic mutations identified in PAH, including BMPR2, ALK1, ENG, and SMAD9, revolve around the transforming growth factor β (TGF-β) pathway, which modulates cell proliferation, differentiation, and apoptosis. Next-generation sequencing analysis has allowed for identification of genes associated with PAH outside the TGF-β superfamily, including CAV1 and KCNK3.27 The roles and mechanisms of these proteins are still under investiga-

### Table 2. Evolution of Pulmonary Hypertension Classification: Third World Symposium on Pulmonary Hypertension (Venice, Italy; 2003)

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pulmonary arterial hypertension</td>
<td></td>
</tr>
<tr>
<td>1.1 Idiopathic</td>
<td></td>
</tr>
<tr>
<td>1.2 Familial</td>
<td></td>
</tr>
<tr>
<td>1.3 Related to</td>
<td>(a) Collagen vascular disease (b) Congenital systemic-to-pulmonary shunts (c) Portal hypertension (d) Human immunodeficiency virus infection (e) Drugs/toxins (g) Other</td>
</tr>
<tr>
<td>1.4 Associated with significant venous or capillary involvement</td>
<td>1.4.1 Pulmonary veno-occlusive disease 1.4.2 Pulmonary capillary hemangiomatosis</td>
</tr>
<tr>
<td>1.5 Persistent pulmonary hypertension of the newborn</td>
<td></td>
</tr>
<tr>
<td>2. Pulmonary venous hypertension</td>
<td>2.1 Left-sided atrial or ventricular heart disease 2.2 Left-sided valvular heart disease</td>
</tr>
<tr>
<td>3. Pulmonary hypertension associated with disorders of the respiratory system or hypoxemia</td>
<td>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</td>
</tr>
<tr>
<td>4. Pulmonary hypertension caused by chronic thrombotic or embolic disease</td>
<td>4.1 Thromboembolic obstruction of proximal pulmonary arteries 4.2 Obstruction of distal pulmonary arteries 4.3 Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)</td>
</tr>
<tr>
<td>5. Miscellaneous</td>
<td>Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)</td>
</tr>
</tbody>
</table>


(4) similar to PAH, familial occurrence had been reported in PVOD and PCH.

Despite the similarities, PVOD and PCH differ from PAH in the presence of crinkles and clubbing on physical examination and radiographic findings of ground-glass opacities, septal thickening, and mediastinal adenopathy on chest computed tomography. Additionally, hemosiderin-laden macrophages upon bronchoalveolar lavage, and lower carbon monoxide diffusion capacity with differing PaO2 results. Management of patients with PAH, their response to treatment, and their prognosis are different from that in patients with PVOD and PCH.

This meeting also updated the risk factors and molecular associations for PAH. It was discovered that mutations in bone morphogenetic protein receptor type 2 (BMPR2) gene underlies 80% of the familial cases and 10–30% of sporadic cases. It was suggested that loss of function mutation in this gene promotes cell proliferation and suppresses apoptosis. Although evidence of possible genetic factors were being discussed, it was decided that the genetic classification of PH was still premature and further studies were required to identify other genes, modifiers, and regulatory genes involved in PH.22,23
Table 3. Evolution of Pulmonary Hypertension Classification: Fourth World Symposium on Pulmonary Hypertension (Dana Point, California; 2008)*

<table>
<thead>
<tr>
<th>1. Pulmonary arterial hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Idiopathic</td>
</tr>
<tr>
<td>1.2 Heritable</td>
</tr>
<tr>
<td>1.2.1 BMPR2</td>
</tr>
<tr>
<td>1.2.2 ALK-1, endoglin (ENG) (with or without hereditary hemorrhagic telangiectasia)</td>
</tr>
<tr>
<td>1.2.3 Unknown</td>
</tr>
<tr>
<td>1.3 Drug and toxin induced</td>
</tr>
<tr>
<td>1.4 Associated with:</td>
</tr>
<tr>
<td>1.4.1 Connective tissue disease</td>
</tr>
<tr>
<td>1.4.2 Human immunodeficiency virus infection</td>
</tr>
<tr>
<td>1.4.3 Portal hypertension</td>
</tr>
<tr>
<td>1.4.4 Congenital heart disease</td>
</tr>
<tr>
<td>1.4.5 Chronic hemolytic anemia</td>
</tr>
<tr>
<td>1.5 Persistent pulmonary hypertension of the newborn</td>
</tr>
<tr>
<td>1* Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatisis</td>
</tr>
</tbody>
</table>

2. Pulmonary hypertension owing to left heart disease
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. Pulmonary hypertension due to lung disease 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 lung disorders

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, fibrosis mediastinitis, chronic renal failure on dialysis

*a Modifications to the previous classification are represented in bold.
*b 1* indicates a distinct category, but is not completely separated from pulmonary arterial hypertension.
*Published in J Am Coll Cardiol, 2008;54(1)(suppl):S43–54, with permission from the American College of Cardiology Foundation.

Table 4. Evolution of Pulmonary Hypertension Classification: Fifth World Symposium on Pulmonary Hypertension (Nice, France; 2013)**

<table>
<thead>
<tr>
<th>1. Pulmonary arterial hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Idiopathic</td>
</tr>
<tr>
<td>1.2 Heritable</td>
</tr>
<tr>
<td>1.2.1 BMPR2</td>
</tr>
<tr>
<td>1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3</td>
</tr>
<tr>
<td>1.2.3 Unknown</td>
</tr>
<tr>
<td>1.3 Drug and toxin induced</td>
</tr>
<tr>
<td>1.4 Associated with:</td>
</tr>
<tr>
<td>1.4.1 Connective tissue disease</td>
</tr>
<tr>
<td>1.4.2 Human immunodeficiency virus infection</td>
</tr>
<tr>
<td>1.4.3 Portal hypertension</td>
</tr>
<tr>
<td>1.4.4 Congenital heart disease</td>
</tr>
<tr>
<td>1.4.5 Schistosomiasis</td>
</tr>
<tr>
<td>1* Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatisis</td>
</tr>
<tr>
<td>1** Persistent pulmonary hypertension of the newborn</td>
</tr>
</tbody>
</table>

2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. Pulmonary hypertension due to lung disease 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 hypventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorder: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosis mediastinitis, chronic renal failure, segmental pulmonary hypertension

**a Modifications to the previous classification are represented in bold.
**b 1* indicates a distinct category, but one that is not completely separated from pulmonary arterial hypertension.
**c 1** indicates a distinct category, but is not completely separated from pulmonary arterial hypertension.

Published in J Am Coll Cardiol, 2013;62(25)(suppl):D34–D41, with permission from the American College of Cardiology Foundation.

**CONCLUSIONS**

We have focused on the evolution of PH in light of historic discoveries, pharmacologic developments, and molecular advancements. Much of the focus and modifications to the previous classification are represented in bold, and genetic mutations is important because individuals with BMPR2 mutations tend to present at a younger age, have higher pulmonary vascular resistance, have a failure of response to vasodilators, and are more likely to succumb to the disease at an earlier age with more-severe disease.28

Evolving Classification of PH—Foshat & Boroumand
tions in the classification of PH have revolved around the subtleties of PAH. Additionally, PHA itself is composed of a heterogeneous group of disorders with similar clinical, hemodynamic, and histopathologic features, all of which are characterized by increased precapillary PAP due to vasoconstriction, vascular remodeling, and thrombosis. Despite current advancements, the exact pathogenesis of PAH is still not clear, but many of the predisposing and contributing factors have been identified. The current focus of research has turned toward immunologic and molecular mechanisms of cellular injury. It has been evident that inflammation has an important role in the pathogenesis of PAH. Endothelial dysfunction is another major factor resulting in vasoconstriction, thrombosis, and mitogenesis through imbalanced production of vasoconstrictors and vasodilators, prothrombotic and anti-thrombotic mediators, and activators and inhibitors of smooth muscle cell growth and migration. Metabolic reprogramming and mitochondrial abnormalities, which result in excessive cell proliferation and impaired apoptosis, are other emerging concepts in pathobiology of PAH. Attempts to identify other less-common molecular targets underlying heritable PAH, PVOD, and PCH, beyond the known mutations, are underway and may help decipher the underlying mechanisms of PH.31–33

Current classification of PH is primarily based on clinical presentation and hemodynamic features but does not allow for the customization of treatment. Rapid advancements in the understanding of the pathogenesis of the disease, new and improved imaging methods, and the discovery of new biomarkers will enable us to define different PH phenotypes based on their pathobiology. Among some of the proposed phenotypes are mixed precapillary and postcapillary PH, severe PH in respiratory disease, HIV-associated PH, portopulmonary hypertension, connective tissue disease–associated PH, and PAH in children.24 Hopefully, accurate phenotyping will increase our understanding of the mechanisms of disease that may then be used to determine clinical prognosis and to guide treatment.

References

33. Archer SL, Weir EK, Wilkins MR. The basic science of pulmonary arterial hypertension for clinicians: new concepts and experimental therapies. Circula-