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Review

A Critical Appraisal of the Updated 2014 Nice Pulmonary Hypertension Classification System

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ABSTRACT

In 2013, the Fifth World Symposium on Pulmonary Hypertension (PH) was held in Nice, France. This meeting has been held every 5 years since the Second World Symposium in 1998, when the modern-day classification system of PH was initially conceived. PH is a pathophysiologic state of the pulmonary circulation characterized by an increased mean pulmonary artery pressure ≥ 25 mm Hg at rest, and can be the consequence of a variety of distinct disease entities. The rationale of a classification system for PH was to group together disease entities that share similar pathomechanisms, clinical presentation, and therapeutic approaches. Refinements of the classification system have been made at each subsequent World Symposium, reflecting the ongoing research and new knowledge acquired in the science of PH. We provide an update of the recent changes made to the PH classification system from the Nice meeting.

RÉSUMÉ

En 2013, le 5e Symposium mondial sur l'hypertension pulmonaire (HP) était tenu à Nice, en France. Cette rencontre a eu lieu tous les 5 ans depuis le 2e Symposium mondial de 1998, où le système actuel de classification de la HP était conçu. La HP est un état physiopathologique de la circulation pulmonaire caractérisé par une augmentation de la pression artérielle pulmonaire moyenne ≥ 25 mm Hg au repos et peut être la conséquence de diverses entités pathologiques distinctes. Les raisons justifiant un système de classification de la HP étaient de regrouper les entités pathologiques qui partagent des pathomécanismes, un tableau clinique et des approches thérapeutiques similaires. Les améliorations au système de classification ont été faites à chaque Symposium mondial subséquent, et reflètent la recherche en cours et les nouvelles connaissances acquises dans le domaine de l'HP. Nous offrons une mise à jour sur les changements récents du système de classification de la rencontre tenue à Nice.

A definition of biological classification is the "arrangement of entities in a hierarchical series of nested classes, in which similar or related classes at one hierarchical level are combined comprehensively into more inclusive classes at the next higher level."[1] More than 40 separate disease entities are now included in the current clinical classification of pulmonary hypertension (PH),[2] and the classification system grew out of the need for clinicians, researchers, epidemiologists, and approval bodies to share a common descriptive language. The fundamental principle was that conditions should be categorized according to similarities in pathobiology, clinical features, and therapeutic options. A classification system for PH was also necessary to provide a framework for standardizing diagnosis and treatment, and to define relatively homogeneous populations for inclusion into clinical trials and registries. The recent Fifth World Symposium on PH (Nice, France, 2013) provided an opportunity for a consensus update of the PH classification system, and this review will provide an appraisal of the changes introduced in the new classification system.

Historical Perspective and Structure of the Current Classification

The First World Symposium, organized and endorsed by the World Health Organization, was held in Geneva, Switzerland in 1973. The meeting was a response to the sudden increase in the incidence of so-called "primary PH," related to the use of the anorexigen, aminorex. As an indication of the immense progress that has been made in PH, only 17 participants attended the first World Health Organization meeting in Geneva. In the First World Symposium, PH was simply classified into "primary" or "secondary" causes,[3] with primary PH encompassing what is termed today as idiopathic, heritable, and drug-induced pulmonary arterial hypertension (PAH).

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See page 7 for disclosure information.

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Table 1. Updated classification of PH (Nice, 2013)

1. PAH
   1.1 Idiopathic PAH
   1.2 Heritable PAH
      1.2.1 BMPR2
      1.2.2 ALK-1, ENG, SMAD9, **CAV-1, KCNK3**
      1.2.3 Unknown
   1.3 Drugs or toxins 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 disease
      1.4.5 Schistosomiasis

1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1″. Persistent pulmonary hypertension of the newborn

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

4. Chronic thromboembolic pulmonary hypertension

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

Changes introduced at Fifth World Symposium (Nice, 2013) are highlighted in bold.

ALK-1, activin receptor-like kinase 1; BMPR2, bone morphogenetic protein receptor 2; CAV-1, caveolin-1; ENG, endoglin; KCNK3, potassium channel subfamily K member 3; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; SMAD9, mothers against decapentaplegic 9.

Modified from Simonneau et al.[2] with permission from Elsevier.

Table 2. Hemodynamic definition of PH

Definition	Characteristics	Clinical group(s)*
PH	Mean Ppa $\geq$ 25 mm Hg	All
Precapillary PH	Mean Ppa $\geq$ 25 mm Hg; Ppw $\leq$ 15 mm Hg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	Mean Ppa $\geq$ 25 mm Hg; Ppw $>$ 15 mm Hg	2. PH due to left heart disease

PH, pulmonary hypertension; Ppa, pulmonary artery pressure; Ppw, pulmonary artery wedge pressure.

*Clinical groups according to Table 1.

During the Second World Symposium (Evian, France, 1998),[4] the foundation for the modern-day classification was laid out, and it was proposed that PH should be divided into 5 main categories as follows: group 1, PAH; group 2, pulmonary venous hypertension or PH due to left heart diseases; group 3, PH due to lung diseases and/or hypoxia; group 4, chronic thromboembolic PH; and group 5, miscellaneous disorders that can affect the pulmonary vasculature with unclear and/or multifactorial mechanisms. This basic structure has since been maintained in subsequent revisions of the classification system, and gradual refinements have been made as new knowledge and insights emerged.[5,6] The current Nice clinical classification is provided in Table 1.[2]

Hemodynamically, PH is defined according to a mean pulmonary artery pressure (Ppa) $\geq$ 25 mm Hg at rest assessed using right heart catheterization. Furthermore, PH is divided according to the pulmonary artery wedge pressure (Ppw) into precapillary (Ppw $\leq$ 15 mm Hg) and postcapillary PH (Ppw $>$ 15 mm Hg).[7] All PH groups, with the exception of group 2 left heart diseases, represent precapillary forms of PH (Table 2).

One important theme that emerged from the Nice meeting was that based on the recommendation of the Pediatric Task Force, a common PH classification system should exist for children and adults.[8] Many children with PH diagnosed during neonatal through to adolescent periods are now surviving into adulthood, and will thus require transition to adult care. Furthermore, some adult PH conditions develop as a consequence of lesions or substrates that have origins during childhood (such as congenital heart defects). Consistent with this philosophy, pediatric PH conditions have now been included to provide a comprehensive and unified classification system appropriate for all ages.

Group 1: PAH

Entities classified according to group 1 PAH consist of conditions that primarily affect the pulmonary arterial circulation, characterized by a vasculopathy of the distal pulmonary arteries consisting of luminal obliteration by vascular cell proliferation and functional rarefaction of vessels (ie, direct loss of distal arterioles). Other common features include pulmonary artery endothelial dysfunction leading to vasomotor imbalance favouring vasoconstriction[9] and therapeutic response to currently approved PAH drugs (Fig. 1).[10] This group has been the main focus of recent drug trials with PAH agents (such as endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, soluble guanylate cyclase stimulators, and prostanoids); although these trials have predominantly enrolled patients with idiopathic, heritable, drug-induced, and connective tissue disease-associated PAH. One randomized controlled trial has specifically addressed the congenital heart disease (CHD) population.[11] Patients with portopulmonary hypertension have conventionally been excluded from randomized controlled trials of PAH agents, although a favourable therapeutic response has been demonstrated in multiple observational studies.[12,13]

Updates From the Nice Classification

New subcategory for persistent PH of the newborn

Persistent PH of the newborn (PPHN), previously classified as group 1 PAH in the Dana Point Classification, has now been placed into a separate subcategory designated 1″. PPHN