# Classification of Pulmonary Hypertension

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Classification of pulmonary hypertension groups patients with similar pathological findings, hemodynamic profiles, and management strategies. Minor modifications have been made to the current classification system, particularly within Group 1 pulmonary arterial hypertension. This article summarizes the published conclusions of the Fifth World Symposium of Pulmonary Hypertension task force that addressed the updated clinical classification of pulmonary hypertension.



During the last few decades, awareness of pulmonary hypertension (PH) has improved significantly.[1] The Fifth World Symposium on Pulmonary Hypertension, held in 2013, highlighted the advances made in the last 40 years since the first international conference in 1973, sponsored by the World Health Organization (WHO). The following symposiums (Evian, France, 1998; Venice, Italy, 2003; and Dana Point, US, 2008) were clearly reflective of the significant achievements that have been made in the field, in terms of understanding the pathophysiology and clinical behavior, as well as development of new treatment modalities.[2]

The first classification of PH was described in 1973, and categorized patients as having "primary" or "secondary" hypertension according to the presence or absence of an identifiable cause for the disease. The limitations of such classifications became more evident as more associated conditions were identified. During the Second World Symposium on PH in 1998, the basis for the current classification system was proposed. The concept supporting the classification is to group patients with similar pathological findings, hemodynamic profiles, and management. Five different categories were then established: pulmonary arterial hypertension (PAH); PH due to left heart disease; PH due to chronic lung disease and/or hypoxia; chronic thromboembolic PH (CTEPH); and PH due to unclear multifactorial mechanisms (previously called "miscellanea").[3] Although minor modifications have been made during the last decade, the concept of the current classification remains the same. The updated classification for PH, derived from the last world symposium, is presented in Table 1.[4]

For the current classification, Group 1 PAH is the condition with the most significant changes and will be the focus of this review.

PAH encompasses a group of clinical conditions that present precapillary PH, defined by the presence of mean pulmonary artery pressure (mPAP) $\geq$25 mm Hg with normal pulmonary artery occlusion pressure ($<$15 mm Hg), and share similar pathological and/or clinical findings. IPAH corresponds to sporadic disease in which no family history of PAH or an identified risk factor is present[3]; therefore, an extensive investigation is needed to rule out alternative diagnoses.[5]

Since the last world symposium, heritable PAH has gained significant attention. Heritable forms of PAH include those with identified gene mutations and familial cases with or without identified mutations. Up to 80% of familial cases of PAH have been linked to germline mutations in the gene coding for the bone morphogenetic protein receptor 2 (*BMPR2*), a member of the transforming growth factor beta (TGF-$\beta$) signaling family.[6] *BMPR2* mutations have also been detected in a significant proportion of apparently idiopathic cases without familial history.[7] Other mutations in genes from the TGF-$\beta$ family were already known to be associated with particular PAH cases: ALK1,[8] endoglin,[9] and SMAD9.[10]

However, new genes not closely related to the TGF-$\beta$ family have recently been described: CAV1[11] and KCNK3.[12] The importance of these genes is that they might provide different insights in terms of pathophysiological mechanisms of the disease and may even lead to new therapeutic targets.

Besides genetic predisposition, there are a number of risk factors associated with the development of PAH. Aminorex, a potent appetite suppressant, was the first drug to drive the attention to the possible link of its use and pulmonary vascular disease.[13] Its use in the 1960s led to an outbreak of rapidly progressive PAH in Switzerland, Austria, and Germany. More than 20 years after the aminorex epidemics, fenfluramine and dexfenfluramine have been marketed as appetite suppressants, leading to a new outbreak of drug-induced PAH in the 1980s-1990s. PAH cases in patients exposed to fenfluramine derivatives share clinical, functional, hemodynamic, and genetic features with IPAH.[14]

More recently, benfluorex, a benzoate

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Table 1. Clinical Classification of PH

| |
|---|
| 1. PAH<br>1.1. Idiopathic PAH (IPAH)<br>1.2. Heritable PAH<br>• 1.2.1. BMPR2<br>• 1.2.2. ALK1, ENG, SMAD9, CAV1, KCNK3<br>• 1.2.3. Unknown<br>1.3. Drug- and toxin-induced<br>1.4. Associated with:<br>• 1.4.1. Connective tissue diseases<br>• 1.4.2. HIV infection<br>• 1.4.3. Portal hypertension<br>• 1.4.4. Congenital heart diseases<br>• 1.4.5. Schistosomiasis |
| 1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis<br>1'' Persistent PH of the newborn |
| 2. PH owing to left heart disease<br>• 2.1. Left ventricular systolic dysfunction<br>• 2.2. Left ventricular diastolic dysfunction<br>• 2.3. Valvular disease<br>• 2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies |
| 3. PH owing to lung diseases and/or hypoxia<br>• 3.1. Chronic obstructive pulmonary disease<br>• 3.2. Interstitial lung disease<br>• 3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern<br>• 3.4. Sleep-disordered breathing<br>• 3.5. Alveolar hypoventilation disorders<br>• 3.6. Chronic exposure to high altitude<br>• 3.7. Developmental lung diseases |
| 4. CTEPH |
| 5. PH with unclear multifactorial mechanisms<br>• 5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy<br>• 5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cellhistiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis<br>• 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders<br>• 5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH |

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Table 2. Updated Classification for Drug- and Toxin-Induced PAH*

| Definite | Possible |
|---|---|
| Aminorex | Cocaine |
| Fenfluramine | Phenylpropanolamine |
| Dexfenfluramine | St. John's wort |
| Toxic rapeseed oil | Chemotherapeutic agents |
| **Benfluorex** | **Interferon α and β** |
| **SSRIs†** | **Amphetamine-like drugs** |
| **Likely** | **Unlikely** |
| Amphetamines | Oral contraceptives |
| L-Tryptophan | Estrogen |
| Methamphetamines | Cigarette smoking |
| **Dasatinib** | |

*Nice 2013. †Selective serotonin reuptake inhibitor (SSRIs) have been demonstrated as a ris factor for the development of persistent pulmonary hypertension in the newborn (PPHN) in preg nant women exposed to SSRIs (especially after 20 weeks of gestation). PPHN does not strict belong to Group 1 (pulmonary arterial hypertension [PAH]) but to a separated Group 1. Mai modification to the previous Danapoint classification are in **bold**.

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ester that shares structural and pharmacologic characteristics with dexfenfluramine and fenfluramine, has been linked to the development of PAH. The active and common metabolite of each of these molecules is norfenfluramine, which itself has a chemical structure similar to that of the amphetamines. Given its pharmacological properties, benfluorex would be expected to have similar toxic effects to the fenfluramine derivatives.[15,16] An outbreak of valvular heart diseases and/or PAH induced by benfluorex use has been uncovered in France in the 2000s. Eighty-five cases of PH associated with benfluorex exposure were identified by the French PH network from June 1999 to March 2011. The analysis of these cases caused benfluorex to be withdrawn from the French market in 2009.[17]

Other classes of drugs have also been linked to the development of PAH. Cases of precapillary PH fulfilling the criteria of drug-induced PAH have been reported in chronic myelogenous leukemia patients treated with the tyrosine kinase inhibitor dasatinib. Clinical, functional, and hemodynamic improvements were observed within a few months of dasatinib discontinuation in most patients, although the majority failed to demonstrate complete clinical remission.[18]

The presence of genetic abnormalities and risk factors (such as specific drug exposures) reinforces the "multiple hit" concept for the development of PH[19] and emphasizes the importance of active investigation of PH in any symptomatic individual with known exposure to any risk factor. The list of the recognized risk factors potentially related to the development of PH is presented in Table 2.

Connective tissue disease (CTD) is one of the most important forms of PAH, accounting for about 15% of all cases in the French registry.[20] The prognosis of these patients remains worse compared with other forms of PAH.[21,22] Recently, it has been suggested that implementation of a systematic screening program that allows the use of specific therapies in a less symptomatic phase of the disease might result in better long-term outcomes for this subgroup of PAH patients.[23]

Patients with HIV are another group with increased risk of developing PAH. The prevalence of PAH in such group is estimated at 0.5%, with clinical and

Table 3. Updated Clinical Classification of Pulmonary Arterial Hypertension Associated With Congenital Heart Disease*

| |
|---|
| **1. Eisenmenger syndrome**<br>**Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of pulmonary vascular resistance (PVR) and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis and multiple organ involvement are usually present.** |
| **2. Left-to-right shunts**<br>**• Correctable†**<br>**• Noncorrectable**<br>**Include moderate to large defects; PVR is mildly to moderately increased systemic-to-pulmonary shunting is still prevalent, whereas cyanosis is not a feature.** |
| **3. Pulmonary arterial hypertension (PAH) with coincidental congenital heart disease**<br>**Marked elevation in PVR in the presence of small cardiac defects, which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. To close the defects in contraindicated.** |
| **4. Post-operative PAH**<br>**Congenital heart disease is repaired but PAH either persists immediately after surgery or recurs/develops months or years after surgery in the absence of significant postoperative hemodynamic lesions. The clinical phenotype is often aggressive.** |

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hemodynamic presentation very similar to IPAH.[24,25] Prognosis of this particular subgroup of PAH has improved in recent years; in the REVEAL registry, the mortality of HIV-PAH patients was 93% and 75% at 1 and 3 years, respectively.[26]

PAH associated with portal hypertension is another important subgroup of PAH patients, since about 6% of patients with portal hypertension might develop PAH[27] independently of the severity of the liver disease; nevertheless, long-term prognosis of these patients is determined by both the severity of PH and of liver disease.[28] Portopulmonary hypertension (POPH) represents an important problem for liver transplantation programs since its presence is related to increased mortality during the procedure.[29] The prognosis in POPH is worse than in IPAH; recent reported data suggest a 3-year survival of 40%.[30]

Due to the improvement in the management of congenital heart diseases (CHD), more children survive to adulthood and about 10% of these adults develop PAH.[31] According to findings from the last world symposium, patients with CHD-PAH (except those with more complex congenital heart defects) should be subclassified into 4 different subgroups (Table 3) to facilitate disease management. Nevertheless, absolute criteria to determine whenever a small cardiac defect is a cause or just a concomitant factor as the operability criteria for such defects are still missing, with most of the therapeutic approach based on expert consensus.[4]

Schistosomiasis is an infectious disease affecting more than 200 million people worldwide. PAH represents one of the most severe complications of chronic schistosomiasis,[32] with a 4.6% prevalence among patients diagnosed with hepatosplenic schistosomiasis mansoni.[33] Schistosomiasis-associated PAH has a clinical profile similar to IPAH and a similar targeted treatment response,[34] but with better clinical course (3-year mortality of about 15%).[35]

One of the key changes in the current classification is related to chronic hemolytic anemia. Previously classified into Group 1, it was shifted to Group 5 for a number of reasons. Recent cohorts on PH might be present in up to 10% of patients with hemolytic anemias. The hemodynamic profile of this patient is quite peculiar as a consequence of high cardiac output, with elevated pulmonary pressures and low pulmonary vascular resistance.[36–38] Also, available data on the pathological findings were inconsistent with the presence of many confounding factors.[39] Together with the absence of robust data regarding the use of targeted therapies in this particular subform of PH, it was changed to Group 5 until more evidence to support otherwise is generated.

Another important step in the current classification was related to pediatric PH. During the last world symposium it was determined that a single classification should be used for children and adults to facilitate the transition of children now surviving to adulthood from pediatric to adult medical services. To make this possible, a number of pediatric disorders/specificities were highlighted in the single classification, as the separation of persistence of PH of the newborn from Group 1 and the addition of left heart inflow and outflow obstruction in Group 2.[40]

It is important to emphasize that since the 5-group classification of PH was established, a number of benefits resulted: clinical trials were designed in less heterogeneous subgroups, allowing the registration of all available therapies; pathophysiological studies were also carried out according to the known subgroups, gathering more knowledge about each of the subforms of PH. While the system seems to remain robust, it does carry some important limitations. The main one might be related to the prevalence of the different forms of PH. Much of the focus has been on PAH, although PH due to left heart disease (Group 2), lung disease (Group 3), or chronic thromboembolic disease (Group 4) might be much more prevalent. Perhaps future classification should also reflect the importance of each one of the groups and subgroups of PH, also taking their prevalence into account.

In summary, the current classification

of PH parallels the improved understanding about PH gleaned in the last decades. Its concept is intended to provide pathophysiological and prognostic information as diagnosis and management guidelines: hence the importance of revisiting its structure occasionally, according to the best available knowledge about all forms of PH.

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