Epidemiology and Classification of Pulmonary Hypertension

Ivan M. Robbins, MD
Vanderbilt University School of Medicine

During the 4th World Symposium on Pulmonary Hypertension held last year in Dana Point, California, the consensus agreement of experts worldwide was to maintain the general philosophy and organization of the previous Evian and Venice classifications. However, a majority of experts felt that modification of the Venice classification was required in order to accurately reflect new information published over the past 5 years and to clarify some areas that were unclear. Important changes included in the Dana Point classification are summarized here. These changes should more accurately reflect the disease processes and allow for better communication among investigators.

Group 1: Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) has been the focus of the categorization of pulmonary hypertension (PH) since the first classification in 1973. A number of modifications of the subgroups of PAH were made in the Dana Point classification.

When PAH occurs in a familial context, germline mutations in the bone morphogenetic protein receptor 2 (BMPR2) gene, a member of the transforming growth factor beta signalling family, can be detected in about 70% of cases. BMPR2 mutations have also been detected in 11% to 40% of apparently idiopathic cases without any family history. Thus, the distinction between idiopathic and familial BMPR2 mutations is artificial as all patients with a BMPR2 mutation have heritable disease whether the patient is the first identified case, possibly with a *de novo* mutation, or whether other family members were previously diagnosed with PAH. In addition, no BMPR2 mutation has been identified in up to 20% of families with PAH. Thus, it was decided to abandon the term "familial PAH" in the new classification and replacing it with the term "heritable."

Additional changes in group 1 were also implemented in the Dana Point classification. The classification of PAH associated with congenital heart disease was modified to better define each condition. Hemolytic anemias, either inherited or acquired, have been reclassified as their own subcategory of PAH, based in large part upon growing awareness of PH in patients with sickle cell disease. Finally, schistosomiasis has been moved from the thromboembolic group to a subgroup of PAH.

Key Words—familial, idiopathic, persistent pulmonary hypertension of the newborn, left heart valvular disease, sarcoidosis

Address for reprints and other correspondence: ivan.robbins@vanderbilt.edu

Risk Factors for the Development of Pulmonary Arterial Hypertension

Two important changes regarding risk factors for PAH were discussed. First, based primarily on a large single-center case-control study, methamphetamine use appears to be a likely risk factor for the development of PAH. Second, although no increased risk of developing PAH with the use of selective serotonin reuptake inhibitors (SSRIs) was found in a multicenter epidemiological study, use of SSRIs in pregnant women was reported to increase the risk (OR 6.1) in the offspring of developing persistent pulmonary hypertension of the newborn (PPHN). Therefore, SSRI use in pregnancy is a potential risk factor for PPHN.

Group 2: Pulmonary Hypertension Owing to Left Heart Disease

This group has been modified to reflect the growing importance of left ventricular diastolic dysfunction as a cause of pulmonary venous hypertension. Subcategories in the new classification are: left heart systolic dysfunction, left heart diastolic dysfunction, and left heart valvular disease. No formal recommendations were made concerning patients with left heart disease and "out-of-proportion" PH, and there are currently no clinical trials that have shown benefit with PAH-approved medications in this group of patients.

Group 3: Pulmonary Hypertension Owing to Lung Diseases and/or Hypoxia

The primary modification within this group was to add another category of lung disease characterized by a mixed obstructive and restrictive pattern. This is a newly reported syndrome, characterized by the combination of pulmonary fibrosis (mainly of the lower zones of the lung) and emphysema (mainly of the upper zones of the lung) and has a reported prevalence of PH of almost 50%.

Group 4: Chronic Thromboembolic Pulmonary Hypertension

This group has been simplified to include only chronic thromboembolic PH (CTEPH). Other rare forms of obstruction of the pulmonary vasculature, such as pulmonary artery sarcoma, have

been reclassified into Group 5. In addition, the distinction between proximal and distal disease has been removed as this may be quite difficult to determine and is often dependent upon the experience of each individual center. Presently there is no consensus among experts regarding the distinction between proximal and distal CTEPH. It is strongly recommended that patients with suspected or confirmed CTEPH should be referred to a center with expertise in the management of CTEPH to consider feasibility of pulmonary thromboendarterectomy.

Group 5: Pulmonary Hypertension With Unclear or Multifactorial Etiologies

This group has been reorganized from the Venice classification and includes several subgroups that were previously classified elsewhere. This includes hematological disorders such as myeloproliferative disorders, systemic disorders such as sarcoidosis, metabolic disorders such as Gaucher's disease, and lastly, a miscellaneous group of conditions including such disorders as mediastinal fibrosis and end-stage renal disease with chronic hemodialysis. ■

Summary of Pulmonary Hypertension Genetics and Genomics

Greg Elliott, MD
University of Utah School of Medicine

The 4th World Symposium on Pulmonary Hypertension convened a group of investigators to define the current state of knowledge with respect to the genetics and genomics of pulmonary arterial hypertension (PAH), and to provide suggestions for future investigations. The consensus statement appears in a supplement to the *Journal of the American College of Cardiology* (Machado, 2009;54:S32-S42). In this communication, I will summarize several of the key clinical points made in the consensus statement, provide my perspective, and speculate with regard to future directions.

We now know that the majority of PAH patients with more than 1 affected family member have a mutation in the gene BMPR2, which codes for bone morphogenic receptor protein 2, a cell surface receptor of the transforming growth factor (TGF-β) superfamily. Rarely, familial PAH cases may be caused by mutations in genes that code for 2 other cell surface receptors of the TGF-β superfamily, activin-like kinase-type I (ALK-1) and endoglin (ENG), which are associated with hereditary hemorrhagic telangiectasia. There may be other genes, as yet unidentified, that cause PAH.

We also know that BMPR2 mutations can be identified in approximately 1 of every 5 individuals diagnosed with idiopathic PAH. In some instances, these mutations are *de novo* (spontaneous), and in other cases a parent carried the mutation (obligate carrier) without developing PAH (incomplete penetrance). The presence of mutations that cause disease in individuals diagnosed with idiopathic PAH (IPAH) necessitated a change in diagnostic nomenclature. Heritable PAH (HPAH) includes individuals with disease-causing mutations (BMPR2, ALK-1, ENG) and individuals with other family members diagnosed with PAH. The rationale for this change in nomenclature is the fact that either the presence of a disease-causing mutation or a clear family history of PAH identifies an increased risk for other family members to develop PAH.

At the time of the 4th World Symposium, investigators had described 298 BMPR2 mutations. The consensus summary lists the BMPR2 mutations that have been associated with PAH, most of which are unique to each family and are presumed to result in loss of BMPR2 function. Mutations associated with PAH alone are insufficient to cause PAH, as evidenced by mutation carriers unaffected by PAH. The uneven gender ratio of at least 1.7 women affected for every affected man suggests that hormonal factors (genetic and/or environmental) may influence disease penetrance.

Heritable and idiopathic pulmonary arterial hypertension have a similar clinical course, although HPAH may be associated with a younger age at disease onset and more severe hemodynamic impairment at diagnosis. Patients with PAH and disease-causing BMPR2 mutations are less likely to respond to acute vasodilator testing during right heart catheterization and are unlikely to benefit from calcium channel blocker monotherapy. This observation fits the known role of TGF-β receptors such as cytokine growth factors, which control proliferation, migration, differentiation, apoptosis, and extracellular matrix deposition and the concept that dysregulated cellular proliferation underlies HPAH.

Clinical genetic testing is available for BMPR2, ALK-1, and ENG mutations. Genetic testing may be offered to any individual with a family history of PAH or IPAH (without other known affected family members) with the current cost of testing ranging from approximately $1000 to $3000 USD to analyze the affected individual. Testing family members of a patient affected with PAH for whom the exact mutation is known costs approximately $300 to $500 USD. Genetic testing should involve pre-and post-test counselling by a genetic counsellor who understands heritable pulmonary hypertension and the potential psychosocial impacts of genetic test results.

Key Words—familial, idiopathic, hereditary hemorrhagic telangiectasia, right heart catheterization, genetic testing

Address for reprints and other correspondence: greg.elliott_MD@imail.org