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

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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

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Due to the incomplete penetrance and variable age of onset, identification of a BMPR2 mutation may have a complex and serious psychosocial impact on the family, often associated with guilt in the parent who has passed on mutations to the children. Genetic testing is most helpful when it is able to identify members of the family who are not at risk for PAH and therefore can forgo screening for PAH. The most common reason that individuals pursue genetic testing involves issues of informing their children of their hereditary predisposition or in making informed decisions about family planning. In the past, many patients have failed to pursue genetic testing due to anxiety regarding genetic discrimination. Recognition of these concerns has led a number of countries to introduce either voluntary or legal codes to protect individuals requesting genetic counselling and formal testing. For example, in the United States, the Genetic Information Non-Discrimination Act, passed in May 2008, provides protection from discrimination in coverage or cost of health insurance coverage to members of both individual and group health insurance plans and protects against discrimination in employment based upon a genetic predisposition. Genetic testing of children should be performed with caution due to the potentially significant psychological impact on a child, particularly in the face of overt anxiety for the future development of a potentially fatal disease without methods for effective disease prevention.

Perspectives

In spite of dramatic breakthroughs, advances in genetic and genomic understanding of PAH are in the very early stages. Opportunities exist to advance our understanding of the basic molecular pathogenesis of HPAH, to discover new genes and pathways that modify the pathobiology of PAH, and to identify genes responsible for variations in therapeutic response among PAH patients. In the future, collaborative studies of BMPR2 mutation carriers should enable identification of environmental modifiers, biomarkers for disease development and disease progression, and surrogate markers for efficacy endpoints in clinical drug development. With advances in genomic technology and with international collaborative efforts, genome-wide association studies may be conducted to identify genetic modifiers for BMPR2 penetrance and genetic susceptibility to PAH associated with other disorders.

What critical issues will the genetics and genomics subcommittee address at the 5th World Symposium on Pulmonary Hypertension?

The answer to this question remains speculative. Based upon goals set at the Dana Point meeting, the committee will undoubtedly examine new scientific observations arising from genetic association studies and confirmed by replication studies. Some key areas for investigation include: (1) understanding difference in gender-specific penetrance; ie, why are women with BMPR2 mutations more likely to develop PAH? Is testosterone protective? Does estrogen or progesterone increase susceptibility? Does autoimmunity play a role? What is the relationship to pregnancy and/or contraceptives?; (2) refined estimates of the penetrance of BMPR2 mutations (studies of familial PAH provide overestimates); and (3) identification of genes that are responsible for the development of other forms of PAH, eg, PAH associated with portal hypertension. ■

Diagnosis and Assessment of Pulmonary Arterial Hypertension: A Glance at the Output From the Dana Point Conference

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The ideas regarding definition, diagnosis, and assessment of pulmonary arterial hypertension (PAH) are evolving. The importance of objective evaluation of right ventricular (RV) function is now more emphasized. The progress in imaging techniques and biomarkers used to follow patients' responses to therapy and to screen populations at risk for development of PAH must be monitored and eventually translated into clinical routine. As early treatment becomes an essential target and new therapies are developed, screening, prompt diagnosis, and accurate assessment of disease severity become particularly important. The Dana Point meeting offered a possibility of updating evidence and reaching a consensus regarding its clinical implications in everyday practice.

Key Words—biomarkers, echocardiography, right heart catheterization, functional class, 6-minute walk

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Definition of Pulmonary Hypertension

After some discussion of the threshold of 20 mm Hg as a parameter to define pulmonary hypertension (PH), the consensus decision was to maintain resting mean pulmonary arterial pressure (mPAP) ≥25 mm Hg as a criterion required for the diagnosis of PH. Pulmonary occlusion (wedge) pressure <16 mm Hg at rest is still required before a diagnosis of PAH can be made.

However, based on the evidence provided by Professor Horst Olschewski's group from Graz (Austria), 2 important remarks were made: the upper limits of normal for mPAP, based on published data, is 20 mm Hg. However, because patients in the 20-24 range of mPAP have not been included in clinical trials, more data