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

regarding the natural history in these patients are needed. Importantly, evidence regarding a universal threshold for abnormal exercise mPAP, which would allow an earlier diagnosis of PH induced by a stress test, was considered not conclusive. Exercise hemodynamics were, therefore, removed from the definition of PH.

Noninvasive Definition of Pulmonary Hypertension?

Reliability of noninvasive estimation of pulmonary arterial pressure (PAP) and of PH diagnosis with echocardiography was discussed extensively. Doppler estimates of systolic and particularly mPAP are imprecise in individual patients, although this is despite tricuspid jet velocity (TJV) correlates strongly with systolic PAP and directly measured systolic PAP correlates with mean PAP. This is likely because of the intrinsic limitations of echocardiography and its operator dependency. While it appears reasonable to consider TJV >2.8 m/s and tricuspid insufficiency pressure gradient (TIPG) ≥31 mm Hg at rest as elevated (except in elderly and/or very obese patients), the formal diagnosis of PH and particularly of PAH requires right heart catheterization. Based on current evidence, echocardiography may be used in screening for PAH in mildly symptomatic patients with scleroderma or HIV infection, though relatively high numbers of false positive results and low diagnostic yield are discouraging. Exercise Doppler is not ready for clinical use to improve performance of such screening programs. Healthy volunteers too often display significant increases in TJV and the definition of abnormal echocardiographic response to exercise is still lacking. NT-proBNP (N-terminal pro-B-type natriuretic peptide) seems the most important new candidate for inclusion to echocardiographic screening programs, which should probably also use more comprehensive evaluation of the signs of RV overload instead of limiting measurements to TJVs.

Prognosis and Follow-up

The working group reviewed exciting evidence regarding prognostic markers, as well as the influence of currently available therapies on outcome. Since the meeting in Venice, significant amounts of information regarding humoral biomarkers have been gathered. Data on BNP and particularly on NT-proBNP were considered most convincing. A new prognostically relevant echocardiographic parameter has also been described. It is based on measurement of tricuspid annular plane systolic excursion (TAPSE) toward the apex and represents an easily measurable surrogate of RV ejection fraction. Although elevated NT-proBNP and abnormal TAPSE taken at baseline are predictors of worse survival, it is not clear whether their changes during treatment also have prognostic implications.

Indeed, the working group experts dedicated particular attention to the possibility of monitoring the patients on treatment and optimizing decisions when their treatment should be escalated. Two strategies were reviewed.

The "clinical" strategy is based on the signs and symptoms reported on clinical examination and selected laboratory tests. If functional class (FC) is considered satisfactory and no signs of right heart failure are detected, the therapy remains unchanged. Noninvasive examinations such as echocardiography, biomarkers, and 6-minute walk distance are performed but no prespecified criteria that would prompt a change or escalation of therapy are defined. Usually the intervals between consecutive patients' evaluations are 3 to 6 months, based on the results of landmark trials that showed poor prognostic significance of maintaining FC III or IV despite 3 months of therapy.

In contrast, the "goal-oriented" strategy of follow up has been proposed to make treatment decisions more objective. Parameters considered prognostically relevant should be kept within predefined "acceptable" limits. Treatment should be escalated until those thresholds are reached. While some encouraging examples from several centers were available, no consensus was reached regarding which parameters should be measured and whether noninvasive evaluation is sufficient in most cases.

Focus on the Right Ventricular Function and Coupling to Pulmonary Arterial System

When discussing parameters potentially useful for follow up, RV function in PAH was found of particular interest. In fact, the usual cause of death in PAH is RV failure. Both diastolic and systolic dysfunction are likely contributors to RV failure. A PAH treatment strategy based on measures that better reflect RV function may be interesting. Cardiac MRI offers an interesting perspective on RV morphology and function. It provides excellent spatial resolution and unrestricted access to any required cross-section of the heart. Cardiac MRI is currently a gold standard in the assessment of cardiac volumes, muscular mass, and ejection fraction of both ventricles. Precise flow measurements in the heart and great vessels can be made using velocity-encoded imaging.

As reported by a Dutch group, baseline RV stroke volume index >26 mL/m^2, RV end-diastolic volume <83 mL/m^2, and left ventricular (LV) end-diastolic volume >41 mL/m^2 indicated better survival and documented further dilatation of the RV. Decreases in LV diastolic volume and/or in RV stroke volume at 1-year follow-up were related to worse long-term outcomes despite treatment. Interobserver variability is low, which makes MRI a potentially useful tool for follow-up assessment; it will remain a research option as long as technical complexity makes it unsuitable for multiple serial testing, which is necessary in routine clinical follow-up of PAH patients.

I believe the best use of data collected from cardiovascular magnetic resonance (CMR) follow-up studies in PAH would involve selecting those parameters which are both indicated as prognostically significant by CMR and are possible to assess with echocardiography. Concentrating efforts on serial assessment of a few well-standardized measurements selected based on their CMR-proven prognostic implications should improve the value of echocardiography in therapeutic decision making in PAH.

Pulsatile hemodynamics represent a relatively unexplored area, accessible in the research setting by high fidelity pressure and flow recordings potentially by CMR, and in clinical practice (to a certain extent) by Doppler echocardiography. Measurements of timing and amplitude of the reflected pressure waves may influence our understanding of the coupling of RV to the pulmonary arterial bed and the efficacy of RV work. Cardiovascular magnetic resonance studies indicate that even the simplest pulsatile parameter such as RV stroke volume seems more prognostically relevant than an averaged cardiac output.

Looking Backward and Forward

I have mixed feelings about the work completed in the area of diagnosis and evaluation of PAH at the meeting in Dana Point. Just before this meeting, some PAH experts were advocating revolutionary changes in the definition of PH and PAH. Lowering the PH definition threshold to 20 mm Hg and creating a well-defined severity level based not only on pressure but also pulmonary vascular resistance had been suggested. After discussions, the work-

ing group supported the conservative positions and limited the changes to the removal of exercise criteria of PH, retaining the simple and universally recognized definition based on resting PAP ≥25 mm Hg. Another area that did not change much despite earlier expectations was the approach to echocardiographic diagnosis of PH. When compared with the Venice consensus, which offered an option of making an echocardiographic diagnosis of "mild PH," we may have even taken a step back. The current document limits the statement to a prudent: "it appears reasonable to consider TJV >2.8 m/s and TIPG ≥31 mm Hg at rest as elevated, except in elderly and/or very obese patients." In addition to collecting and digesting new evidence in PAH, the objective of future meetings must involve providing clearer indications about when to proceed to right heart catheterization and when to consider echocardiography as sufficient evidence of PH, particularly in the presence of clear causative factors such as lung or left heart disease. Professor Robert Naeije's suggestion to create and prospectively validate a noninvasive score assessing the "probability of PAH" and assisting in the decision whether to perform right heart catheterization seems very timely.

New evidence that could be useful in identification of an optimal set of goals to be achieved by PAH therapy would be most welcomed before the next world meeting, which should preferably be dedicated to the entirety of the pulmonary circulation rather than just PH. ■

Updated Evidence-Based Treatment Algorithm in Pulmonary Arterial Hypertension

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Ernst von Romberg, a German physician, described an autopsy in 1891 as "pulmonary vascular sclerosis"; however, only with the introduction of intravenous epoprostenol in 1995 have disease-specific targeted medical therapies for pulmonary arterial hypertension (PAH) become available. Furthermore, significant advances in the treatment of PAH have occurred during the past 15 years, with 8 medical therapies now approved. These agents target the prostacyclin pathway, the nitric oxide (NO) pathway, and the endothelin (ET-1) pathway. In addition, combination trials have demonstrated additive or synergistic benefit by targeting 2 or 3 of these pathways (**Figure 1**).

At the 4th World Symposium on Pulmonary Hypertension in Dana Point in early 2008, both uncontrolled and controlled clinical trials with different compounds and procedures were reviewed and compared to define

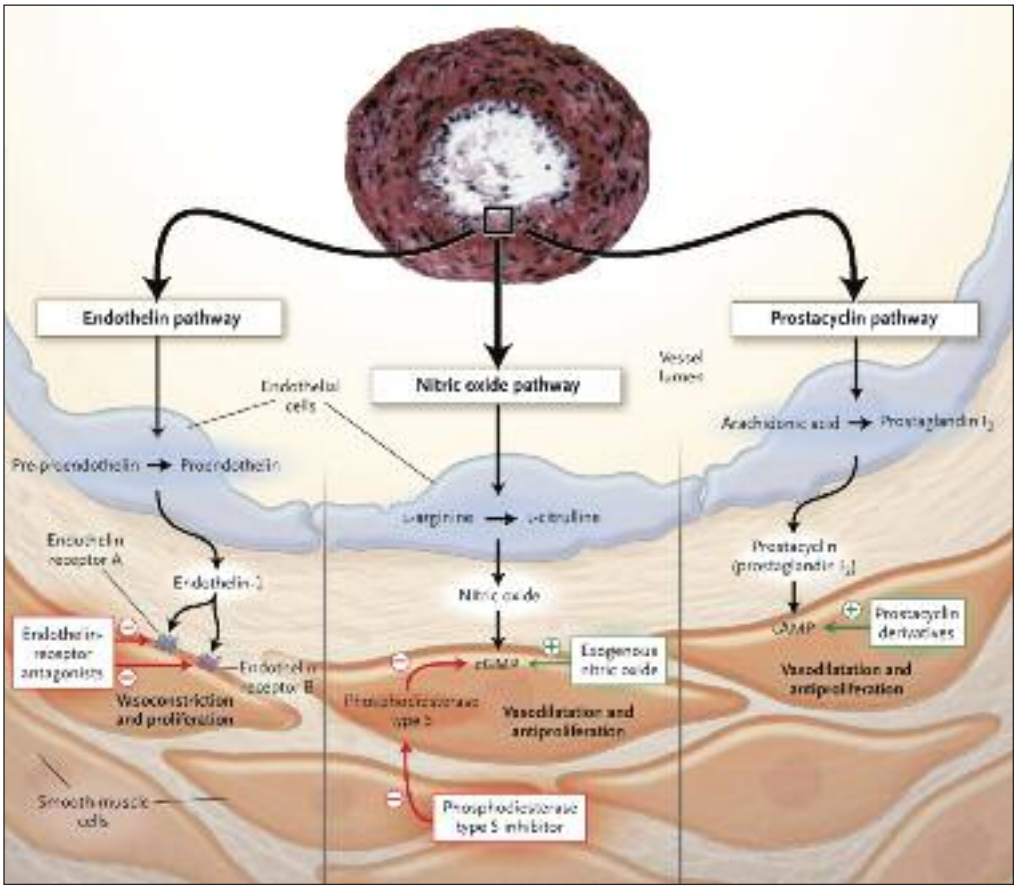

Figure 1. Pathways now defined for the treatment of PAH. (reprinted with permission from Humbert M, et al. *New Engl J Med*. 2004;351:1425-1436).

Key Words—idiopathic, calcium channel blockers, functional class, atrial septostomy, lung transplantation

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