Task Force on Diagnosis and Assessment: Identifying the Most Useful Tools

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A diagnostic algorithm that is accepted among experienced centers (Pull-Out, next page) can guide the evaluation of pulmonary hypertension. Like all guidelines, the algorithm may be modified according to specific clinical circumstances. Most patients are diagnosed as the result of an evaluation of symptoms, while others are diagnosed during screening of asymptomatic populations at risk. Symptomatic patients should be managed with an aggressive therapeutic strategy to reduce symptoms, improve hemodynamics, and prolong survival. Asymptomatic or incidentally discovered subjects should be managed with conservative treatment (depending on the severity of the hemodynamic abnormality), identification of reversible underlying causes, and close monitoring for progression.

A high level of suspicion is of paramount importance for the diagnosis of pulmonary hypertension regardless of underlying cause. Once suspect, a methodical workup using commonly employed diagnostic interventions allows confirmation of the presence of pulmonary hypertension and elucidation of its etiology. Clarification of etiology is necessary to ensure that the proper therapeutic interventions are implemented.

In patients with a suspicion of, or risk of, pulmonary arterial hypertension (PAH), the physical examination should be performed to assist in directing further evaluation to more specific and efficient assessment for defining the presence, severity and substrate of PAH. In addition, an ECG should be performed to screen for a spectrum of cardiac and arrhythmic problems. Although an ECG lacks sufficient sensitivity to serve as an effective screening tool for PAH, it does contribute some prognostic information in patients with known idiopathic PAH. A chest X-ray should also be obtained to reveal features supportive of a diagnosis of PAH and lead to diagnoses of underlying diseases.

Doppler echocardiography should be performed as an appropriate and useful screening tool to detect clinically significant degrees of elevated pulmonary pressure, although in some patients it may be imprecise in determining actual pressures (compared with invasive evaluation). In patients with high-risk substrates, eg, systemic sclerosis, family history of idiopathic PAH, known genetic predisposition, Doppler echocardiography should be performed periodically, ie, every 1 to 3 years, to screen for possible development of clinically significant degrees of elevated pulmonary pressure. Doppler echocardiography should also be obtained in patients with suspected or documented pulmonary hypertension to look for left ventricular systolic and diastolic dysfunction, left-sided chamber enlargement, or valvular heart disease, any of which may cause or contribute to pulmonary hypertension and may be treatable. A contrast study during Doppler echocardiography is also useful to look for evidence of intracardiac shunting.

Screening for connective tissue disease and HIV infection by serologic testing (along with appropriate history and physical examination) should also be performed in patients with suspected or documented pulmonary hypertension. A ventilation-perfusion lung scan should be performed to rule out chronic thromboembolic pulmonary hypertension; a negative scan effectively excludes a diagnosis of chronic thromboembolic pulmonary hypertension. Contrast-enhanced computed chest tomography or magnetic resonance imaging can provide useful morphologic information, but should not be relied upon to unequivocally exclude chronic thromboembolic pulmonary hypertension. In patients with a V/Q scan suggestive of chronic thromboembolic pulmonary hypertension, pulmonary angiography is required for accurate diagnosis and best anatomic definition. Contrast enhanced computed chest tomography or magnetic resonance imaging can be obtained to provide complementary morphologic, functional and prognostic information.

Pulmonary function testing and arterial blood gas measurements should be performed to evaluate potentially contributory ventilatory factors and diffusion abnormalities. In patients with systemic sclerosis, pulmonary function testing should be performed periodically, ie, every 6 to 12 months, to detect deteriorating DLCO as a sign of progressive pulmonary vasculopathy.

Lung biopsy is not recommended because of the risk in patients with suspected or documented pulmonary hypertension, except under circumstances in which a specific question can be answered only by tissue examination. Finally, right heart catheterization is required in patients with suspected pulmonary hypertension to establish the diagnosis of pulmonary hypertension and document pulmonary hemodynamics. Furthermore, prior to initiation of medical therapy, assessment of vasodilating capacity (during the right heart catheterization) is required to determine the appropriate therapy for an individual patient.

Techniques that have recently been evaluated to predict disease severity include: assessment of right ventricular function, using Doppler echocardiographic semi-quantitative indices, functional class, exercise testing, ie, exercise endurance assessed by a 6-minute walk test and exercise tolerance assessed with cardiopulmonary exercise testing, and demographic and hemodynamic parameters. Neurohormone levels, such as BNP and ANP, have recently been demonstrated to correlate with survival, and norepinephrine and endothelin-1 levels also appear to be useful parameters of disease severity. In addition, uric acid levels have been reported to correlate with the severity of PAH.

Some of these modalities may provide prognostic information that is similar to that derived from invasive tests and may be more useful and convenient in assessing treatment efficacy

over time. These newer tools may also enhance predictive accuracy when used in combination with the "standard" testing modalities. Many of these variables have been shown to correlate with one another; thus, which parameters will prove to be the most useful in assessing disease severity requires further investigation. Importantly, all of the above studies evaluated idiopathic PAH patients but not patients with PAH related to connective tissue disease, congenital heart disease, anorexigens, HIV infection, or portal hypertension. Thus, these parameters must be applied cautiously to PAH patients in whom comorbid factors may contribute significantly to overall outcome, eg, in general, patients with PAH related to connective tissue disease have a worse prognosis than idiopathic PAH patients, whereas patients with PAH related to congenital heart disease have a much more slowly progressive course than do patients with idiopathic PAH.

In conclusion, PAH is diagnosed by following a careful series of investigations that include tests that are regarded as essential in making the diagnosis, as well as additional tests that may help clarify the category of pulmonary hypertension present. Disease severity can be evaluated by several modalities that are complementary and that together are useful in helping to choose therapy and evaluate the response to therapy. Close follow-up at a center specializing in pulmonary hypertension is recommended, with careful monitoring at frequent intervals of the course of the disease. ■

Overview of Genetics as presented at the PAH Symposium in Venice

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Medical scientists have achieved three major goals proposed by the 1998 Evian task force on the genetics of pulmonary hypertension. First, mutations in the gene that codes for bone morphogenetic protein receptor 2 (BMPR2) are linked to familial primary pulmonary hypertension. BMPR2 mutations are detectable in approximately half of the families affected by primary pulmonary hypertension. The gene that codes for BMPR2 is large (13 exons) and already more than 26 mutations are described. Second, many patients with apparently sporadic primary pulmonary hypertension have mutations of the gene that codes for BMPR2. This observation, combined with observations of common ancestors among patients with apparently sporadic primary pulmonary hypertension, indicates that an inherited basis underlies many cases of primary pulmonary hypertension. However, the relatively low penetrance of these mutations (only 15% to 20% of persons carrying a BMPR2 mutation develop clinically evident disease in their lifetime) makes identification of familial disease difficult. Third, BMPR2 mutations are rare in other classifications of pulmonary arterial hypertension, eg, pulmonary arterial hypertension associated with CREST, HIV infection, or fenfluramine exposure. Rare cases of pulmonary arterial hypertension with BMPR2 mutations and fenfluramine exposure raise the possibility of disease triggered by genetic predisposition and an environmental trigger.

The exact pathogenesis of familial primary pulmonary hypertension remains elusive in spite of the identification of BMPR2 mutations. The identification of abnormalities in other TGF beta receptors [ALK-1; TGF beta R2, and BMPR1A (ALK3)] suggests that dysfunctional TGF beta receptors are important in the pathogenesis of familial primary pulmonary hypertension. Indeed, TGFB represents a classic pleiotropic mediator to the vascular system by modifying growth, differentiation, and death of vascular cells. Nevertheless, other genes and/or environmental factors must also be important in order to explain the reduced penetrance of BMPR2 mutations. Genes that control nitric oxide synthesis, serotonin transport, or prostacyclin may prove important to the expression of disease. Animal models (eg, mice) allow study of genetic alterations of BMPR2 as well as other pathways, eg, serotonin. Inactivation of BMPR2 in mice leads to pre- and perinatal mortality because of abnormal mesoderm formation, illustrating the potential of BMPR2 mutations to cause vascular disease. To date, scientists have not been able to reproduce primary pulmonary hypertension in mouse models, but this remains an important goal for future research.

The discovery of mutations in the gene that codes for BMPR2 makes genetic testing and counseling possible. In the future such tests may corroborate diagnostic impressions and provide estimates of an individual's risk to develop primary pulmonary hypertension. The use of such tests requires an understanding of the meaning of the test results, as well as the risks and benefits of this knowledge to those who are tested and to other family members. Before and after the tests, education and counseling will be necessary, especially because the penetrance of known BMRP2 mutations is low and because the results may prove psychologically (eg, depression, anxiety) or socially (eg, employment barriers and effects on insurability) harmful.

For these reasons genetic testing for BMPR2 mutations will require adherence to basic rules. Informed consent is essential when a test can be linked to an individual. The consent should be voluntary, without coercion or intimidation; and patients should be assured that their care is unaffected by decisions to forego genetic tests. In addition confidentiality of results must be assured.

Genetic tests for mutations associated with primary pulmonary hypertension are not available in the United States. The BMPR2 gene is large, making tests expensive unless the test is directed at a known mutation. For these reasons the task force concluded that genetic testing needs development and is not ready for widespread implementation. ■