Top Ten List in Pulmonary Vascular Disease

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Key words: activin-receptor-like kinase; bone morphogenetic protein receptor II; high-altitude pulmonary hypertension; pulmonary arterial hypertension; pulmonary thromboembolism

Abbreviations: BMPR2 = bone morphogenetic protein receptor II; HAPH = high-altitude pulmonary hypertension; PAH = pulmonary arterial hypertension

PULMONARY ARTERIAL HYPERTENSION GUIDELINES


This statement of clinical guidelines, although at times subjective in its ratings of evidence, is valuable as an overview of the field of pulmonary hypertension and comprehensive in its review of the extant literature. Sections include diagnosis and management of pulmonary arterial hypertension (PAH); methodology and grading for pulmonary hypertension evidence review and guideline development; screening, early detection, and diagnosis of PAH; medical therapy for PAH; surgical treatments/interventions for PAH; PAH and sleep-disordered breathing; and prognosis of PAH.

GENETICS AND PATHOPHYSIOLOGY OF PULMONARY VASCULOPATHIES


Sixty-seven families with familial PAH were identified and studied over 20 years. The authors assessed some family members for mutations in the gene encoding bone morphogenetic protein receptor II (BMPR2), a known cause of familial PAH. They found that cases of seemingly sporadic PAH may, in fact, be familial. Also, relatives of those with PAH, who do not themselves exhibit PAH, may have a susceptibility to the disease that may be identified through BMPR2 testing. In this article, a proposed mechanism for how BMPR2 works is elucidated.


In this report, a patient with clinical pulmonary veno-occlusive disease is identified with a BMPR2 mutation. This mutation is also found in two of the patient’s family members. This finding suggests a genetic association between pulmonary veno-occlusive disease and PAH.


Five kindreds and one individual patient with hereditary hemorrhagic telangiectasia were evaluated, and 10 cases of PAH were identified among these. A region on chromosome 12q13 was identified that was implicated as a genetic linkage between these two disorders. On that chromosomal region of 12q13, activin receptor-like kinase 1 mutations were found in patients with PAH in association with hereditary hemorrhagic telangiectasia. The vasculopathic changes of dilatations and occlusions seen in
PAH and hereditary hemorrhagic telangiectasia are associated with the activin receptor-like kinase 1 mutations.

**High-Altitude Pulmonary Hypertension**


Of 741 Kyrgyz high-altitude-dwelling male subjects in the Tien-Shan and Pamir Mountains of Kyrgyzstan, 14% were found to have cor pulmonale on ECG. Of 136 Kyrgyz male highlanders with dyspnea, high-altitude pulmonary hypertension (HAPH) was found in 20% at right-heart catheterization (mean pulmonary artery pressures > 25 mm Hg). In addition, 26% of nonpulmonary hypertensive subjects had an exaggerated response to 11% oxygen and were labeled hyperresponsive to hypoxia. Ten years later, these hyperresponsive subjects had increases in their baseline pulmonary artery pressures. Most interestingly, a threefold increase in the frequency of a genetic polymorphism of the angiotensin-converting enzyme gene was found in highlanders with HAPH, compared to normal highlanders. The authors conclude that specific genotypes may determine propensity for development of HAPH and hyperresponsiveness to acute hypoxia.

**Treatment of PAH**


In this double-blind, placebo-controlled study (self-dubbed “BREATHE-1”), 69 patients received placebo and 144 patients received bosentan, the endothelin receptor antagonist, at either 125 mg bid or 250 mg bid daily. At week 16, patients treated with bosentan had an improved 6-min walking distance by 36 m, whereas those receiving placebo had a deterioration of 8 m. This study shows improvement in PAH using an oral drug. However, there is no evidence as of yet that there is any reversal of the vasculopathic remodeling lesions of PAH with bosentan; the improvement seen in this study may be explained on the basis of vasodilation alone.


The rats underwent left pneumonectomy on day 0 and were administered monocrotaline on day 7 with resultant pulmonary hypertension. The rats were classified into groups: those that received vehicle had much more severe pulmonary hypertension (pulmonary artery pressure, 53 mm Hg) than rats that received simvastatin on postoperative days 5 through 35 (pulmonary artery pressure, 27 mm Hg). Pulmonary vascular remodeling changes on pathologic examination were also much more severe in rats receiving vehicle (vascular occlusion score, 1.98) than those receiving simvastatin (vascular occlusion score, 0.59). Finally, lung endothelial nitric oxide synthase gene expression was decreased in vehicle-treated rats but restored toward normal levels in simvastatin-treated rats. In this model, simvastatin, a commonly used drug in patients, strongly attenuated PAH.

**Pulmonary Thromboembolism**


This huge, comprehensive, thoughtful article is an overview of the subject of major pulmonary embolism, a subject that has been evolving for some time and that clinically should be tackled within the first hour of presentation, the “golden hour.” The relative importance and the reasoning behind the use of echocardiography and spiral CT scanning are discussed. The role of right ventricular ischemia and decompensation is reviewed. Theory behind the use of thrombolytic therapy is outlined.


This prospective, randomized, double-blind study compared 138 patients treated with heparin plus placebo to 118 patients treated with heparin plus alteplase for pulmonary embolism and either pulmonary hypertension or right ventricular dysfunction, but without arterial hypotension or shock. Treatment with heparin plus placebo was associated with three times the risk of either death or clinical deterioration (eg, shock, worsening respiratory failure or right ventricular dysfunction, need for cardiopulmonary resuscitation, and emergency surgical treatment for embolism) compared to treatment with heparin plus alteplase.
Lung Transplantation


This important update from the International Society for Heart and Lung Transplantation is a compilation of all relevant statistics in this field. Important data are examined and graphed, including the numbers of heart-lung transplants reported by year, diagnoses in adult heart-lung transplants over 2 decades, unilateral vs bilateral lung transplantation data, actuarial survival data, and risk factors for mortality, among other data.

Sickle Cell Anemia and Pulmonary Hypertension


Jison ML, Gladwin MT. Hemolytic anemia-associated pulmonary hypertension of sickle cell disease and the nitric oxide/arginine pathway [editorial]. Am J Respir Crit Care Med 2003; 168:3–4

Arginase is an enzyme that competes with nitric oxide synthase for arginine substrate; nitric oxide synthase converts arginine to the powerful vasodilator nitric oxide. In this study, arginase activity was elevated almost twofold in patients with sickle cell disease and pulmonary hypertension, possibly limiting arginine bioavailability for conversion to nitric oxide. After 5 days of oral arginine therapy in 10 patients with sickle cell disease and steady, nonacute pulmonary hypertension, estimated systolic pulmonary artery pressures fell 15% (from 64 to 54 mm Hg). In study patients, levels of arginine, known to be deficient during sickle cell crises, tripled with treatment. Arginine is a promising new therapy for a disease with a high mortality rate and limited treatment options.