Cardiac Catheterization a Must in PAH Diagnosis

BY NANCY WALSH
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NEW YORK — Any patient with suspected pulmonary hypertension must have a thorough work-up, including right heart catheterization, before initiating treatment, Dr. Roxana Sulica said at a meeting sponsored by the Pulmonary Hypertension Association and the University of Michigan.

Because the typical presenting symptoms of pulmonary arterial hypertension (PAH) are subtle and nonspecific, with dyspnea, fatigue, and syncope or near syncope being the most common, a high index of suspicion is needed or the diagnosis may not be made until the disease is advanced and the prognosis is poor, she said.

Risk factors for PAH include underlying connective tissue disease, especially limited scleroderma and mixed connective tissue disease, a family history of PAH, the presence of congenital heart disease, and environmental factors such as exposure to anorexigens.

Clinical assessment of patients with possible PAH includes an electrocardiogram, which may show changes in the right ventricle, including right axis deviation, right atrial enlargement, and right ventricular hypertrophy, Dr. Sulica said.

A chest x-ray may reveal prominent proximal pulmonary arteries, peripheral hypovascularity, and reduced retrosternal air space.

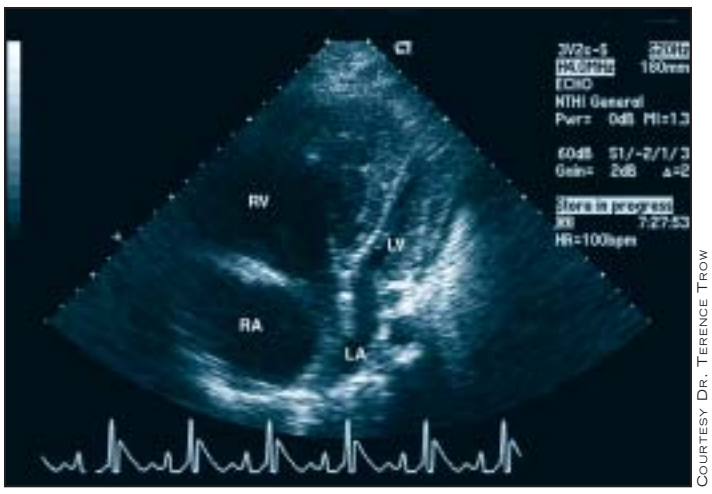
An echocardiogram should then be done, and typical—but not diagnostic—findings on the echocardiogram include right atrial and ventricular enlargement, right ventricular dysfunction, and intraventricular septal flattening.

The definitive diagnosis of PAH can be made only by cardiac catheterization, which can exclude congenital heart disease, measure wedge pressure, and establish the degree of hemodynamic impairment, according to Dr. Sulica, who is director of the pulmonary hypertension program, Beth Israel Medical Center, New York.

The hemodynamic definition of PAH is a mean pulmonary artery pressure greater than 25 mm Hg, with a pulmonary capillary wedge pressure less than 15 mm Hg and a calculated pulmonary vascular resistance greater than 3 Wood units.

Right heart catheterization also permits a determination of the pulmonary vasodilator reserve through vasodilator testing using inhaled nitric oxide, intravenous epoprostenol, or intravenous adenosine. A positive response is defined as a reduction in mean pulmonary artery pressure of 10 mm Hg or more to a mean of 40 mm Hg or less, with an unchanged or increased cardiac output. Only positive responders should be given treatment with calcium channel blockers, Dr. Sulica cautioned.

New guidelines from the American College of Chest Physicians stress the limited role of calcium channel blockers, which have been studied for PAH for 2 decades.



Courtesy Dr. Terence Trow

An echocardiogram shows right atrial and right ventricular enlargement that is impinging on the left side.

The guidelines point to a study of 557 patients with idiopathic PAH who underwent acute pulmonary vasodilator testing, with the 70 positive responders receiving long-term oral calcium channel blocker monotherapy. By 1 year, only 38 (6.8% of the total group) showed a favorable clinical response (Circulation 2005;111:3105-11).

Another recent study found that inappropriate—and potentially harmful—calcium channel blocker use remains common. In a registry that enrolled 1,360 PAH patients, 31% were on calcium channel blockers at the time of referral to a tertiary care center (Eur. Respir. J. 2007 Sept. 5 [Epub doi:10.1183/09031936.00042107]).

In patients who are not responders to vasodilation, the use of calcium channel blockers can decrease cardiac output and systemic vascular resistance, without improving pulmonary artery pressure or pulmonary vascular resistance. Routine vasodilator testing before treatment initiation could eliminate this inappropriate use of calcium channel blockers, Dr. Sulica said.

The prognosis for PAH is still fairly poor. Two-year survival among patients with scleroderma complicated by PAH is only 40%, compared with 80% among those without pulmonary complications (Respir. Care 2006;51:368-81).

The prognosis also is grim for patients in advanced functional classes and those with poor exercise endurance, as well as for those whose hemodynamic findings include elevated right atrial pressure and reduced cardiac index.

"Screening patients with scleroderma can lead to an earlier diagnosis of PAH. Soon we may see if early treatment can improve the long-term prognosis," Dr. Sulica said. ■

Pulmonary Arterial Hypertension Guidelines Reflect New Data

BY NANCY WALSH
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The American College of Chest Physicians has issued updated clinical practice guidelines for the medical management of pulmonary arterial hypertension that reflect findings from several recent clinical trials as well as the additional drugs that have been approved since the previous guidelines were issued in 2004.

The guidelines include an evidence-based, updated treatment algorithm intended to assist physicians in decision making, as "the paradigm for treatment of pulmonary arterial hypertension (PAH) continues to advance rapidly" (Chest 2007;131:1917-28).

Providing new data were two "important" studies that showed survival benefits in patients treated with bosentan, which binds to both endothelin receptors (ET_A and ET_B), according to lead author Dr. David B. Badesch of the University of Colorado Health Sciences Center, Denver.

In the first study, 169 patients (aged 13-80 years) with class III or IV PAH were treated with bosentan as first-line therapy. Survival was 96% at 12 months and 89% at 24 months, in contrast to predicted survival rates from the earlier National Institutes of Health registry of 69% and 57%, respectively (Eur. Respir. J. 2005;25:244-9).

In the second study, survival in 139 patients treated with bosentan was compared with historical data from 346 patients who had been treated with epoprostenol. Survival estimates after 1 and 2 years were 97% and 91%, respectively, in the bosentan-treated group, and 91% and 84% in the epoprostenol-treated group (Thorax 2005;60:1025-30).

The baseline characteristics of the patients suggested that the patients in the epoprostenol cohort had more severe disease. Nonetheless, Cox regression analyses adjusting for baseline factors showed a greater probability of death in the epoprostenol group, with a hazard ratio of 2.2.

Bosentan also has now been evaluated in children with PAH associated with congenital heart disease or connective tissue disease. In a retrospective study, 86 children were treated with bosentan with or without concomitant epoprostenol or treprostinil. WHO functional class improved in 46% of patients and was unchanged in 44%, and survival estimates at 1 and 2 years were 98% and 91% (J. Am. Coll. Cardiol. 2005;46:697-704).

Another recent study included 245 patients (aged 12-78 years) who received bosentan, placebo, or one of two doses of a selective ET_A endothelin receptor antagonist, sitaxsentan. At week 18, patients receiving the higher dose of sitaxsentan (100 mg/day) had significant improvements on a 6-minute walk test, compared with those receiving placebo. The incidence of elevated transaminases was 6% in the placebo group, 5% in the sitaxsentan low-dose (50 mg/day) group, 3% in the high-dose sitaxsentan group, and 11% in the bosentan group (J. Am. Coll. Cardiol. 2006;47:2049-56).

Sitaxsentan remains investigational in the United States, but has been approved for use in Europe and Canada.

A second selective ET_A endothelin receptor antagonist, ambrisentan, was evaluated in a double-blind, dose-ranging study that included 64 adult patients with PAH. They were randomized to receive 1 mg, 2.5 mg, 5 mg, or 10 mg of ambrisentan orally once daily for 12 weeks.

The 6-minute walk test improved significantly for all groups, with a mean increase from baseline of 36.1 m. Improvements also were seen in WHO functional class, Borg dyspnea index, and cardiac index (J. Am. Coll. Cardiol. 2005;46:529-35).

Adverse events were mild, with elevated serum aminotransferase exceeding three times the upper limit of normal seen in 3.1% of patients. This drug was recently approved for class II and class III PAH in the United States.

The phosphodiesterase inhibitor sildenafil also is now approved for the treatment of all classes of PAH in a dosage of 20 mg three times daily. The drug was evaluated in a double-blind study that randomized 278 patients (mean age 50 years) to placebo or 20, 40, or 80 mg three times daily for 12 weeks.

Improvements were seen in the 6-minute walk test in all groups, with placebo-corrected treatment effects being 13%, 13.3%, and 14.7% in the 20-, 40-, and 80-mg groups, respectively. The incidence of clinical worsening did not differ significantly between the placebo and sildenafil groups.

Side effects included flushing, dyspepsia, and diarrhea.

In summarizing the treatment options, the authors noted that for patients in functional class II, the only current recommended drugs are sildenafil and subcutaneous and intravenous treprostinil, and suggested that sildenafil may be the first choice for most patients because of ease of administration and relative efficacy.

For patients in functional class III, five drugs are available: bosentan, sildenafil, intravenous epoprostenol, inhaled iloprost, and subcutaneous or intravenous treprostinil. For those with early class III disease, oral bosentan or sildenafil may be used, with the choice reflecting relative toxicities. For patients with more advanced disease, prostanoid therapy may be needed.

All the available agents are approved for patients with class IV PAH. However, the authors wrote, "[we] strongly encourage IV epoprostenol as the treatment of choice for these most critically ill patients. IV epoprostenol has a rapid and predictable onset of action, and most experts are familiar with how to titrate this drug in the acute setting."

They also recommended that patients with PAH be referred to specialized centers because of the complex diagnostic and therapeutic considerations involved. ■