Medical *Education* Network

PRIORITY PRESS

American Heart Association 2011 Scientific Sessions

Orlando, Florida / November 12-16, 2011

Pulmonary Arterial Hypertension: Addressing the Challenge of Early Diagnosis and Treatment

Orlando - As initial symptoms are non-specific, early diagnosis of pulmonary arterial hypertension (PAH) is challenging. Echocardiography is the best screening tool but a definitive right heart catheterization should not be delayed as early diagnosis permits the use of oral treatments and is associated with the greatest likelihood of prolonged survival. Although there is often reluctance to move to an invasive study when patients are still in functional class I or II disease, this step may be critical in the effort to improve outcome. Early diagnosis means an opportunity to prevent structural damage and reduce progressive deterioration, making a watch-and-wait approach inappropriate when PAH remains a possibility in the differential diagnosis. Although measures are needed to increase suspicion of PAH, such as thorough screening for prominent risk factors, a willingness to refer quickly to right heart catheterization when concern persists may be life-saving.

Chief Medical Editor: Dr. Léna Coïc, Montréal, Quebec

Pulmonary arterial hypertension (PAH) cannot be cured but it can be effectively controlled with endothelin receptor antagonists, phosphodiesterase-5 (PDE-5) inhibitors and inhibitors of the prostacyclin pathway. In a relatively small subset, calcium channel blockers (CCBs) can also be effective, but they can also pose a risk for harm, so patient selection is critical. Late-stage disease generally requires intravenous (i.v.) prostacyclins, but PAH caught at an earlier stage can be managed effectively with well-tolerated oral agents, so that many patients can return to usual activities with a well-preserved quality of life. The key variable is catching right heart pathology at an early stage.

"In the [National Institutes of Health] NIH registry, which collected data between 1981 and 1985, the median time from symptom onset to diagnosis was 1.3 years. In the REVEAL Registry, which collected data in 2006 and 2007, the median time was 1.1 years despite multiple education efforts in between," reported Dr. Vallerie V. McLaughlin, University of Michigan, Ann Arbor. This modest reduction is disappointing because "if we can get to patients when they have less advanced PAH, we are more likely to be successful," she told AHA delegates.

Early Signs of Disease

The late signs of PAH, such as cardiomegaly, cool extremities and ascites, generally produce sufficient concern that diagnostic algorithms are pursued more aggressively, but the early signs, which include dyspnea and fatigue, are not as compelling. While dyspnea is reported in more than 60% of patients and fatigue in a substantial minority, syncope, the third most common early symptom, is only reported in about 20% of patients. Others, such as chest pain, palpitations and edema, develop in less than 10%. As a result, it is important to conduct a history that increases suspicion.

"Dyspnea can have a broad array of etiologies, but one clue is that dyspnea due to PAH does not wax and wane. It is not seasonal. Rather, it is typically progressive," explained Dr. Myung H. Park, University of Maryland, Baltimore. She noted that other useful signs are syncope on exertion, which is an uncommon symptom with other etiologies. There is no single symptom profile because the causes of PAH are so diverse. These include heritable forms of PAH, PAH that is drug- and toxin-induced or PAH as a complication of portal hypertension, congestive heart disease or chronic hematolytic anemia. Even when an echocardiogram confirms right side abnormalities, particularly in the right ventricle, right side catheterization is essential for a definitive diagnosis.

"It is essential to consider a right side catheterization when there is suspicion of PAH because the cost of a delayed diagnosis is very high. If treatment is started early, the outcome can be promising. In advanced disease, the options are more limited," noted Dr. Park. She cited data suggesting that average survival in functional class (FC) IV disease is only about 6 months vs. 5 or more years in FC I or II.

Improved Outcome with Early Treatment

Most of the trials with PAH therapies, including oral therapies, have been conducted either in late-stage disease or in a mixed population of patients in a range of FCs from mild to severe. However, a double-blind, placebo-controlled study that only enrolled patients in FC II did confirm that early treatment improved outcome.

In this study, 168 patients were randomized to the dual endothelin receptor antagonist bosentan or placebo. At the end of 6 months, the placebo patients, as expected, progressed on multiple measures, including increased mean vascular

resistance (107.5% of baseline value) and shorter 6-minute walk distance (-7.9 metres vs. baseline). Among those treated with bosentan, mean pulmonary vascular resistance was reduced to 83.2% of baseline value and the 6-minute walk improved by +11.2 metres. Both were statistically and clinically significant. Overall, active therapy was associated with a delay in clinical worsening. Syncope was more common on bosentan but was not significant (P=0.2098), but right ventricular failure was more common in the placebo group.

While a variety of end points have been used in the clinical trials with the available agents for the treatment of PAH, the 6-minute walk distance test is one of the most reliable and commonly used measures. Benefit on this end point in controlled trials has also been observed with the prostacyclin analogues, including i.v. epoprostenol, inhaled iloprost and i.v., subcutaneous and inhaled treprostinil in advanced disease. The major trials conducted with the PDE-5 inhibitors sildenafil and tadalafil, which are both oral agents, have also included but were not limited to patients with early disease. Although these did improve the 6-minute walk results, neither was effective in the delay of clinical worsening.

PAH Across a Variety of Presentations

Importantly, the presence of left ventricular dysfunction does not preclude the presence of right heart dysfunction and pulmonary hypertension. According to Dr. Mardi Gomberg-Maitland, University of Chicago, Illinois, a substantial proportion of patients eventually referred for a positive work-up of right heart dysfunction started with left heart disease. Characteristic of the need to think of PAH across a variety of presentations, Dr. Gomberg-Maitland also noted that scleroderma patients often have concomitant PAH and pulmonary venous hypertension. Like other experts, she emphasized the need for right heart catheterization, which has a low complication rate (1.1%), when PAH is suspected. However, treatment selection is also important.

"When you make the diagnosis of PAH and you initiate therapy, follow-up is critical to ensure that the intervention makes a difference. Some degree of a clinically meaningful response should be seen within 6 to 8 weeks of starting any treatment for PAH," Dr. Gomberg-Maitland suggested.

Treatment Choices

Of the available therapies, oral and inhaled treatments are preferred by patients. In the trials, both bosentan and the endothelin receptor antagonist ambrisentan, unlike the PDE-5 inhibitors, have been associated with a delay in clinical worsening. However, all of the oral agents have been associated with improvement in cardiopulmonary hemodynamics. The combination of oral drugs has not been studied, although Dr. Gomberg-Maitland acknowledged that patients not well controlled on 1 agent are often given a second oral or inhaled agent (not available in Canada) in an effort to circumvent or delay the use of an i.v. therapy.

In the small group of patients with a substantial vasodilator response and who maintain cardiac output when challenged with adenosine or nitric oxide, CCBs may be an appropriate choice. Dr. McLaughlin cautioned delegates that this is a minority, and a trial of CCBs without first testing vasodilator response is not appropriate. In addition to the negative inotropic effect of CCBs, vasodilation from this mechanism can exacerbate right heart dysfunction and cause harm in patients who do not meet selection criteria for these agents.

"For many of the decisions regarding PAH, it is appropriate to consult with specialists in this area, but it is important to think of PAH early in patients with a presentation that can fit with this disease," Dr. Park suggested.

Summary

Until late stages, the symptoms of PAH are non-specific, but the greatest benefits from therapy accrue when the diagnosis is made early. While the number of etiologies leading to PAH is broad, a high index of suspicion can help guide history-taking and screening with echocardiography. Although right heart catheterization is required for a definitive diagnosis of PAH, clinicians should not hesitate to refer patients to this examination rather than pursue a watch-and-wait approach when PAH is a significant possibility. Current therapies, including well-tolerated oral therapies, can improve function and delay clinical worsening. Although there is no cure for PAH, this disease can be effectively managed if caught before pathology has advanced. □

To view an electronic version of this publication along with related slides if available, please visit www.mednet.ca/2011/pp12-043e.

Medical Education Network Canada Inc. 132 chemin de l'Anse, Vaudreuil, Quebec J7V 8P3

PP12-043E DL