Editorial

Pulmonary Arterial Hypertension: The Mandatory Role of the Cardiologist

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Pulmonary arterial hypertension (PAH), once a lethal condition, is a rapidly evolving area of clinical and research interest.[1,2] The median life expectancy from the time of diagnosis in patients with idiopathic pulmonary hypertension used to be 2.8 years. In the past decade, however, we have made many advances in the treatment of this disease and it is important for cardiologists to understand this progress. After all, many patients are identified by echocardiogram and are therefore part of our practice.

The diagnostic evaluation of pulmonary hypertension can be quite challenging. It may take almost 3 years from the time of onset of symptoms until the patient is diagnosed.[3] Cardiologists need to have a working understanding of what this disease state is and a high index of suspicion in order to make the diagnosis promptly. The definition of PAH is a good old-fashioned haemodynamic one: it is the presence of a mean pulmonary artery pressure in excess of 25 mmHg at rest or at least 35 mmHg during exercise, while at the same time there is normal or near normal left-sided cardiac filling pressure.[4]

The symptoms are notoriously non-specific.[5] Most patients present with dyspnoea and at some point almost every patient has dyspnoea. Patients may also present with angina, syncope, Raynaud's syndrome, or even with oedema due to the failing right heart. It is important to take a very detailed history of risk factors and always to ask about a family history or a history of connective tissue disease or congenital heart disease.[6]

Physical examination remains the critical first step. The two most important and fairly easily elicited physical findings are the enhanced pulmonic component of the second heart sound and the right ventricular lift. Some simple tests may be used in diagnosing this disease before we move to the more advanced forms. The findings from the electrocardiogram reflect the right heart's response to chronic pressure overload; therefore, there must be significant pressure overload for a sufficiently long period of time. Right axis deviation with right atrial enlargement, right ventricular hypertrophy with strain, are all indications that the right ventricle is suffering under the constraints of pulmonary hypertension.[5,7] The X-ray is very helpful in diagnosing this disease. Typical findings are the prominent hilar arteries, the pruning of the distal arteries, and the right ventricle obliterating the retrosternal space on the lateral view.[5]

Echocardiography revolutionised the screening strategy for PAH. Cardiologists must have the ability to go beyond the surface of this test and give information that may not be readily apparent to non-cardiologists who are clinically active in this disease state. The accurate evaluation of the tricuspid insufficiency jet, the estima-

tion of the right atrial size and pericardial effusions, which have been reported as negative prognostic markers, could be potential sources of confusion in echocardiograms. Evidence of left-sided heart disease, such as an enlarged left atrium, should raise a red flag that the most likely cause of pulmonary hypertension is chronically elevated left-side filling pressures.[8] Tissue Doppler imaging is a rapidly evolving technique that assesses right ventricular strain and has impressive correlations with invasive haemodynamics.[9] More modern ways of looking into ventricles that are undergoing rapid improvement are 64-slice computed tomographic (CT) scanning and magnetic resonance imaging (MRI), which provide valuable information about structure and function.[10] One of the major causes we need to rule out is chronic thromboembolic disease, because surgery can be curative in those patients. If chronic thromboembolic disease is suspected we can evaluate this further with a lung scan, or with fancier methods, such as CT scan or MRI pulmonary angiography.

Right heart catheterisation is mandatory for the diagnosis of PAH but the willingness to perform it and the ability to interpret the results properly are often in question. There are three reasons why this haemodynamic assessment is obligatory: 1) the accuracy of pulmonary haemodynamics; 2) the measurement of the left-side cardiac filling pressures; and 3) the evaluation of cardiac output, which is a factor in the calculation of the pulmonary vascular resistance but also plays a critical role in our understanding of how aggressively the patient must be treated initially.

Vasodilator testing, which is performed at the time of the cardiac catheterisation, is important primarily to eliminate inappropriate use of calcium-channel blockers (CCB). The definition of a response is a 10 mmHg decrease in the mean pulmonary artery pressure to a value of less than 40 mmHg in the setting of an unchanged or an increased cardiac output. Patients who were responders and were treated with high doses of CCBs had 95% 5-year survival compared with 55% for non-responders. Notably, only approximately 10-15% of patients with PAH will meet the criteria for a positive response, and only half of those will receive sustained clinical and haemodynamic benefits.[11,12]

The next step is the treatment of the disease to a level that is commensurate with our knowledge and our interest. The full range of treatment options in this disease cannot be provided by everybody, but as newer, easier-to-use therapies–oral therapies specifically–come into our armamentarium, more of us can participate in the treatment. However, we need to be aware of our limits. Assessing dose response, monitoring clinical outcomes, switching agents and applying combination therapy (including different modalities) requires considerable experience to ensure optimal outcomes.

First, the patient's oxygenation at rest, on exertion and overnight must be recorded. Patients with PAH simply cannot afford reactive pulmonary vasoconstriction superimposed by hypoxia and should receive oxygen if arterial saturation goes below 90% at rest or, very importantly, with any exercise (Table 1). Second, diuretics must be provided cautiously in patients who have signs and symptoms of volume overload. A chronically pressure-overloaded right ventricle tends to be preload sensitive, and over-diuresis could lead to a falling cardiac output and clinical deterioration. Warfarin is generally recommended in patients with significant PAH.[13] The best data concerning anticoagulation come mainly from patients with idiopathic disease. Though controversial, digitalis can be useful for patients who manifest right heart failure.[14]

A response to vasodilator challenge determines

Table 1. Pulmonary arterial hypertension (PAH): treatment strategy.

- Confirm diagnosis - refer to experienced pulmonary vascular disease centre.
- Treat underlying disease if not primary.
- Treatment for all patients with PAH:
  - Oxygen if there is arterial saturation <90% at rest or desaturation with any exercise.
  - Diuretics.
  - Anticoagulation (warfarin) with international normalised ratio range 2-2.5.
  - Sodium/fluid restriction.
  - Inotropic agents (digoxin) if there is right heart failure.
  - Avoid potentially offending agents/conditions: contraceptives, anorexic agents, pregnancy, smoking.
- Patient and family education regarding the disease and treatment options.

which patients might benefit from a period of CCB therapy. If the patient is a responder and normalises pulmonary pressures, oral CCB should be started.[12] The CCBs predominantly used are nifedipine and diltiazem. Amlodipine is also effective and is increasingly used. If the response is sustained, treatment with CCB must be continued. If it is not, there are three categories of drugs that could be initiated: endothelin receptor antagonists, chronic intravenous prostaglandins, and new phosphodiesterase type 5 (PDE-5) inhibitors. Epoprostenol has been shown to improve exercise capacity and haemodynamic parameters. Interestingly, the initial haemodynamic response does not always dictate long-term response. Although long-term follow-up data exist with regard to the use of intravenous epoprostenol, in the present era this drug is no longer the first-choice agent because of the availability of newer oral agents that are usually tried first.[15] Significant improvements in exercise capacity, haemodynamics and clinical event rate were demonstrated by administration of prostacyclin analogues. Bosentan is an oral endothelin receptor (ETA and ETB) blocker that has been associated with an improvement in all clinical and haemodynamic efficacy measures and a reduction in the risk of clinical deterioration. Patients receiving treatment with bosentan require monitoring, including the possibility of elevated liver enzymes.[16,17] Sitaxsentan and ambrisentan are both selective ETA receptor antagonists, with favourable patient outcome.[18,19] Sildenafil is an oral PDE-5 inhibitor for which a dose-dependent drop in mean pulmonary artery pressure and an improvement in 6 minute walk test distances have been demonstrated.[20] Tadalafil, a newer PDE-5 inhibitor that acts longer than sildenafil, could also be useful in the treatment of PAH.[21]

For patients who present with evidence of right heart failure or right ventricular dysfunction, a parenteral agent (typically epoprostenol or a prostacyclin analogue) can be appropriate, but the initiation of an oral agent, which at present tends to be bosentan, should also be considered. Increasingly, many patients are hesitant to consider a parenteral agent in the face of available oral agents; however, no long-term data exist regarding the use of the oral agents in patients with severe right ventricular dysfunction.

Therapeutic efforts should be made to interfere with as many of these mechanisms as possible, even in patients whose symptoms respond to a single drug. Data supporting this concept are accumulating and consideration should be given to a combination therapy approach started early in the disease process.[22,23]

In checking the progress of a patient with PAH, reasonable treatment goals are certainly survival, preventing clinical deterioration and improving exercise tolerance as well as haemodynamics. It is also very important to note that these benefits should remain beyond the usual 12 to 16 weeks. Follow-up echocardiograms and catheterisations need to be performed at some point in order to ensure that the patient's condition has at least not become worse, and that a drop of at least 30% in total pulmonary resistance has been achieved. Some novel non-invasive biomarkers, such as brain natriuretic peptide or troponin, may be useful in the future, but those parameters certainly need to be studied further.[24,25] The suggested predictors of survival are the mean pulmonary artery pressure, the right atrial pressure and the cardiac index. Some of the important prognostic tests, which can easily be performed in clinics and correlate well with survival, are the 6-minute walk test and the peak systolic pressure.[26] In centres where a cardiopulmonary exercise test can be performed, patients with peak VO_2 $\leq$10.4 mL/kg/min and systolic blood pressure at peak exercise $\leq$120 mmHg (i.e. two risk factors) had poor survival rates at 12 months (23%), whereas patients with one or neither of these risk factors had better survival rates (79% and 97%, respectively). Of course, cardiologists should maintain vigilance in watching for superimposed non-PAH cardiovascular disease.

The diagnosis and management of PAH are optimal when cardiologists are actively involved. Aggressive efforts must be made to diagnose PAH and facilitate access to effective therapies. With the availability of multiple agents and the potential for combination therapy, the treatment of PAH is now entering a new era.

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