

EDITORIAL

Pulmonary Hypertension: *Which drug for which patient?*

University Heart Journal 2017; 13(2): 38-39

Pulmonary hypertension (PH) is defined as an elevated mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at right heart catheterisation (RHC). One of the most used parameters is the estimated pulmonary arterial systolic pressure (PASP), derived from the tricuspid regurgitant jet velocity. As this estimates pulmonary artery systolic pressure, the threshold for detecting PH at echocardiography (ie PASP ≥ 40 mmHg) differs from the RHC-driven mean pulmonary artery pressure threshold used to definitively diagnose PH (ie mPAP ≥ 25 mmHg). Current classification is adapted from the Fifth World Symposium. PH is classified according to a shared underlying pathophysiology and approach to therapy. In general, only patients with PAH (group 1) and CTEPH (group 4) respond to PH-specific therapy and thus warrant referral to a specialist centre. PAH and CTEPH are uncommon diseases, with an annual incidence of 2.4–7.6 cases/million and 1.75 cases/million respectively.

One of the challenges in PH is that a definitive diagnosis cannot be made without resorting to RHC. The cardinal symptom of PH, exertional dyspnoea, is non-specific and common to many cardiopulmonary disorders. If routine cardiopulmonary investigations, such as echocardiography, lung function tests and computed tomography (CT), indicate an alternative explanation for a patient's breathlessness then a diagnosis of PAH or CTEPH need not be pursued. It is therefore important to consider the pre-test probability of treatable PH before embarking on testing. Several systemic diseases are associated with PAH and CTEPH and thus a higher index of suspicion and a lower threshold for investigation is required when these patients present with unexplained breathlessness. Breathlessness in PH is initially mild, but progressive over time. Dyspnoea is consistent, rather than variable, and not commonly associated with other symptoms such as cough or wheeze.

Initial (primary) therapy should be directed at the underlying cause of the PH. In addition, the need for diuretic, oxygen, and anticoagulant therapy should be assessed. For patients with fluid retention due to PH, we suggest diuretics. For patients with group 4 PH, anticoagulant therapy is indicated. For patients with

systemic sclerosis-associated PAH, we suggest that anticoagulant therapy not be administered. For patients with other forms of PAH, anticoagulation has largely fallen out of favor and we suggest administering it on a case-by-case-basis. For patients with group 3 PH and resting or exercise hypoxemia, we recommend supplemental oxygen. For patients with other types of PH, we suggest supplemental oxygen if resting, exercise, or nocturnal hypoxemia exists

Patients with persistent PH whose WHO functional class is II, III, or IV despite treatment of the underlying cause of the PH should be referred to a specialized center to be evaluated for advanced therapy. Advanced therapy is treatment that is directed at the PH itself, rather than the underlying cause of the PH.

Advanced therapy is widely accepted for many patients with group 1 PAH. In contrast, it must be considered on a case-by-case basis for patients with group 4 PH or group 5 PH, after carefully weighing the risks versus the benefits. Advanced therapy should NOT be administered to most patients with group 2 or group 3 PH.

Advanced therapy should not be administered until a diagnostic right heart catheterization (RHC) and extensive investigations for the etiology of PH have been performed. Additionally, most patients with group 1 pulmonary arterial hypertension (PAH), in particular, those with idiopathic PAH, heritable PAH, and anorexigen-induced PAH, should also undergo vasoreactivity testing during RHC which facilitates agent selection.

For patients who have a positive vasoreactivity test, we suggest a trial of calcium channel blocker (CCB) therapy with a dihydropyridine or diltiazem prior to the initiation of therapy with prostacyclin pathway agonists, endothelin receptor antagonists, or nitric oxide-cyclic guanosine monophosphate enhancers (cGMP). Patients who respond to such therapy should be reassessed after three to six months of treatment.

For patients with idiopathic pulmonary arterial hypertension (IPAH) who have a negative vasoreactivity test or fail CCB therapy with a dihydropyridine or

diltiazem, we recommend advanced therapy with a non-CCB agent. For patients with another type of group 1 PAH who have a negative vasoreactivity test or fail CCB therapy with a dihydropyridine or diltiazem, we suggest advanced therapy with a non-CCB agent.

For patients in whom a non-CCB agent is chosen, the preferred agent(s) depends on the functional severity of disease. Patients with WHO functional class I do not require therapy but should be monitored for disease progression and contributing causes of PH should be treated.

For patients who are WHO functional class II or III, oral agents rather than intravenous prostanoids are preferred.. Classes of suitable agents include oral endothelin receptor antagonists (ambrisentan, bosentan, or macitentan), oral phosphodiesterase inhibitors (sildenafil or tadalafil), oral guanylate cyclase stimulants (riociguat), and oral prostacyclin pathway agonists (selexipag). **In Bangladesh** sildenafil, tadalafil, bosentan and ambrisentan are available. Among the options, we suggest ambrisentan and tadalafil rather than other combinations or single agent therapy. For patients with functional class III who have rapid progression or other markers of poor clinical prognosis, some experts administer oral selexipag, intravenous epoprostenol, inhaled iloprost, intravenous treprostinil, or subcutaneous treprostinil.

For patients who are WHO functional class IV, we suggest intravenous epoprostenol, rather than any alternative agent. For patients with refractory disease, combination therapy with a second, and rarely third, agent of a different class is appropriate, with the exception of combining PDE5 inhibitors and guanylate cyclase stimulants, which is contraindicated due to an unfavorable safety profile.

PH is a progressive disease that may be fatal, if untreated. However, the rate of progression is highly variable and depends upon the type and severity of the PH. In general, patients with group 1 PAH who are not on therapy and patients with severe PH have a poor prognosis.

Survival rates among patients in group 1 PAH have been reported as 85 percent at one year, 68 percent at three years, 57 percent at five years, and 49 percent at seven years. PAH-directed therapy may improve mortality. Factors associated with poor prognosis include age older than 50 years, male gender, functional class III or IV, failure to improve functional class with therapy, indices of right ventricular failure, connective tissue disease-associated PAH, and others. Many patients die from circulatory collapse from right heart failure (44 to 50 percent). The prognosis of patients on group 2 through 5 likely varies with the prognosis of the underlying disease, severity of the PH, and response to therapy.

The term ‘pulmonary hypertension’ covers many conditions, of which only a small minority respond to PH-specific therapy. Identifying this cohort can be challenging and many patients go undiagnosed. Determining a ‘pre-test’ clinical level of suspicion can help when interpreting subsequent investigations and determining whether or not to make an onward referral. The use of a full range of cardiopulmonary investigations can also help in determining the relative contributions of left heart and/or lung disease, the presence of which generally precludes patients from receiving PH specific therapy.

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Refereces:

1. Suntharalingum J, Ross RM, Easaw J. Who should be referred to a specialist pulmonary hypertension centre -a referrer's guide. *Clinical Medicine* 2016 Vol 16.No.2:135-41
2. Hopkins W and Rubin LJ, Treatment of pulmonary hypertension in adults. <https://www.uptodate.com/contents/treatment-of-pulmonary-hypertension-in-adults> (accessed online on 22/06/2018)