Diagnosis, Assessment, and Treatment of Nonpulmonary Arterial Hypertension Pulmonary Hypertension: A Brief Summary From the 4th World Symposium on Pulmonary Hypertension

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The 4th World Symposium in Dana Point was the first among the world meetings on pulmonary hypertension (PH) that assigned a working group to address in detail the so-called nonpulmonary arterial hypertension (PAH) forms of PH; ie, those forms of PH that are seen in patients with chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), left heart disease, venous thromboembolism, and other conditions. The full manuscript from this symposium has been published in July 2009, and this short summary will provide a brief synopsis of the working group's recommendations.

Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is one of the most common conditions associated with PH. In patients with advanced COPD, PH, defined by a mean pulmonary artery (PA) pressure >20 mm Hg at rest, may be detectable in up to 90% of patients. However, in the vast majority of these cases, PH is relatively mild with mean PA pressures between 20 and 30 mm Hg and a normal cardiac output. Progression of PH is usually slow, especially when these patients are receiving long-term oxygen therapy. Affected patients may present with signs of diastolic right ventricular dysfunction, particularly elevated right ventricular filling pressures and edema. Right heart failure with low cardiac output as seen in PAH is exceedingly rare. Nevertheless, the presence of PH in COPD patients is an ominous prognostic sign since even mild PH is an independent risk factor of mortality in this patient population.

Several authors have described a small subgroup of COPD patients with so-called "out-of-proportion" PH; ie, severe PH with hemodynamic features resembling those seen in PAH. The prevalence of this form of PH ranges from 1% to 5% among COPD patients and there is no relationship between the severity of COPD and the severity of PH.

Few studies have addressed medical treatment of COPD-associated PH. Several years ago, calcium channel blockers and other vasodilators were tried, but these drugs had no beneficial effects and it was found that any vasodilator had the potential to worsen gas exchange in these patients. More recently, small pilot trials studied the effects of novel drugs that have been approved for PAH in COPD-associated PH. The results of these trials, however, were mostly negative. The endothelin receptor antagonist bosentan did not improve exercise capacity and the drug was even associated with a worsening in gas exchange and quality of life. Preliminary data with the phosphodiesterase-5 inhibitor sildenafil suggest the same. So far, no study has addressed the role of medical therapy in patients with "out-of-proportion" PH. All in all, it is obvious that the pathogenesis of COPD-associated PH differs from that of PAH so that the drugs used in PAH may not necessarily be effective in COPD-associated PH.

Pulmonary Hypertension in Interstitial Lung Disease

Pulmonary hypertension is a common complication of ILD and has been associated with clinical worsening as well as a poor prognosis in this patient population. As in COPD, it is unclear if patients with ILD-associated PH may benefit from PH-targeted medical therapy. Short-term improvements have been reported with sildenafil and inhaled iloprost but rigorous studies are lacking. So far there is no sufficient evidence regarding the safety and efficacy of PAH drugs in this patient population and no drug has been approved for the treatment of ILD-associated PH.

Recommendations for the Management of Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease and Interstitial Lung Disease

Echocardiography remains the most important initial diagnostic tool once PH is suspected in chronic lung disease. However, the limitations of echocardiography are well known and false positive as well as false negative findings have been reported. Biomarkers, especially brain natriuretic peptide (BNP), may also have a role in detecting PH in patients with underlying lung disease, but BNP lacks sensitivity (especially for milder forms of PH) and specificity since elevated levels may also reflect left heart disease. Thus, whenever medical therapy of PH is considered, confirmation by right heart catheterization should be sought. The same is true for patients entering clinical trials since it is of utmost importance to characterize those patients who may benefit from PH-targeted therapy.

Regarding medical therapy, the used of the so-called PAH drugs is not yet recommended in patients with COPD or ILD and

Key Words—interstitial lung disease, vasodilators, endothelin receptor antagonists, echocardiography, biomarkers

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PH as there are no robust data regarding safety and efficacy of any of these drugs in these patient populations. It is evident that some patients with severe PH may benefit from targeted therapy but for now this decision should be left to expert centers.

Chronic Thromboembolic Pulmonary Hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the most prevalent forms of PH. Chronic thromboembolic pulmonary hypertension differs from PAH by its major vessel involvement of the vascular remodeling process, which can be approached surgically by pulmonary endarterectomy (PEA) as the treatment of choice for this condition. However, small vessel arteriopathy is variably present in CTEPH and the extent of small vessel arteriopathy is an important determinant of the outcome after PEA.

Perfusion scanning remains the examination of choice for ruling out CTEPH. A normal or "low-probability" perfusion scan in a patient with PH effectively rules out CTEPH. Patients with at least 1 segmental or larger perfusion defect should undergo further imaging, including computed tomography of the chest. If PEA is considered, most centers will ask for a pulmonary angiogram, but this examination should be performed at the center where surgery would take place.

There is an ongoing debate whether or not the so-called PAH drugs are efficacious in patients with inoperable CTEPH. While several open-label studies with bosentan, sildenafil, and prostanoids have reported favorable results, the only randomized, controlled trial (BENEFIT, bosentan vs placebo) failed to show improvement in exercise capacity after 16 weeks of therapy. Thus, the working group called for additional studies and did not recommend the general usage of PAH drugs in CTEPH.

PH Associated With Left Heart Disease

Left sided heart disease is one of the most common causes of PH and it is seen in patients with systolic heart failure as well as diastolic heart failure. The pathogenesis of PH in left heart disease is complex. There is a passive (pulmonary venous) component in response to increased left atrial pressure. In some patients, a superimposed active component due to pulmonary arterial vasoconstriction and precapillary vascular remodeling may lead to further increase in pulmonary arterial pressure.

In some cases it can be difficult to distinguish between PH due to diastolic left ventricular (LV) dysfunction and PAH. Risk factors of LV dysfunction include an older age, hypertension, obesity, diabetes, and other conditions. Although echocardiography provides important information, invasive measurements of pulmonary capillary wedge pressure or LV end diastolic pressure (LVEDP) may be required to document the presence of elevated LV filling pressures. Occasionally, these pressures are normal at rest so that exercise or volume challenge may be required to unmask LV diastolic dysfunction.

When treating PH in patients with left heart disease the underlying substrate should be the focus of management. So far, there is no indication to use the so-called PAH drugs in this condition as none of these drugs has been thoroughly evaluated in patients with left heart disease.

Summary

All of the non-PAH forms of PH have various features that distinguish them from PAH. Differences are seen in the pathogenesis, clinical presentation, diagnostic approach, and response to medical therapy. Medical therapies that have proven effective in PAH have not been sufficiently studied in any other form of PH and further studies are needed to define the role of PH-targeted therapies in these patient populations.

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