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Exercise-Induced Pulmonary Arterial Hypertension

A New Addition to the Spectrum of Pulmonary Vascular Diseases

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Although the complex molecular mechanisms responsible for the vasculopathy of pulmonary artery hypertension (PAH) have only recently begun to be unraveled, it has been recognized for decades that the most significant determinant of both symptoms and survival in PAH is the degree of cardiac impairment that results from the increased right ventricular afterload.1 Exertional dyspnea, the most frequent presenting symptom of PAH,2–3 results from several physiological impairments that are measurable with cardiopulmonary exercise testing and are indicative of impaired right ventricular output during physical activity: (1) an inability to increase O2 transport to tissues during exercise, measured as a decrease in peak VO2 compared with normal; (2) premature lactic acidosis, measured as a decrease in the anaerobic threshold, increasing CO2 output and ventilatory drive; and (3) underperfusion of ventilated lung, measured as a high VE/VCO2 at the anaerobic threshold.4 Unfortunately, exertional dyspnea is a nonspecific complaint, and a definitive diagnosis of PAH is often delayed until signs and symptoms indicative of more advanced degrees of right heart functional impairment are present.

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In this issue of Circulation, Tolle and colleagues5 postulated that mild pulmonary vascular disease, when resting hemodynamics are not substantially abnormal, could be identified by unmasking the impairment in right ventricular function with exercise. They found that, although patients with evidence of PAH at rest had both severe hemodynamic abnormalities and impaired cardiopulmonary gas exchange during exercise, a population of patients with symptoms but relatively normal resting hemodynamics could be identified who manifested abnormalities with exercise whose severity fell between normal and resting PAH. Although the current hemodynamic definition of PAH encompasses abnormalities either at rest (mean pulmonary arterial pressure at rest >25 mm Hg) or with exercise (mean pulmonary arterial pressure during exercise >30 mm Hg),2 the evidence supporting this threshold as indicative of pulmonary vascular disease has been limited until now. The Tolle et al results support the notion that less severe degrees of pulmonary vascular disease, which they call exercise-induced pulmonary hypertension (EIPAH), are part of a continuum that can be associated with both symptoms and measurable impairment.

Tolle et al found that the 2 most common cardiopulmonary exercise testing diagnoses in their patients referred for exertional dyspnea were PAH and left ventricular diastolic dysfunction. They devised a strategy combining metabolic and invasive methodologies in their study, which underscores the importance of hemodynamic confirmation when pulmonary vascular disease is suspected. Failing to distinguish between these 2 abnormalities can lead to serious treatment errors. Previous studies have demonstrated that both overestimation and underestimation of pulmonary artery systolic pressure occur with echocardiography,6–8 particularly with exercise.9 In addition, echocardiography alone may be insufficient to include or exclude ventricular diastolic dysfunction.10 However, reliable invasive measurements during exercise are challenging to perform and interpret, in part because of the large swings in intrathoracic pressure associated with increased respiratory rate and tidal volume during exercise.11 In addition, a variable workload is likely to affect the hemodynamic response to exercise, thereby making it difficult to define a clear-cut threshold for normal. Nevertheless, the Tolle et al study provides insight into the degree of abnormality that suggests the presence of a disease state and suggests that any definition of “early” pulmonary hypertension should encompass both invasive and noninvasive parameters to provide a more thorough, global assessment of integrated cardiopulmonary function.

The development of “targeted therapy” for PAH12 has led to increased awareness of the condition. In an attempt to detect the problem at an earlier stage, guidelines have been developed for screening populations at risk for its development such as those with connective tissue diseases, HIV infection, or chronic liver disease with portal hypertension.13 The benefits of early diagnosis and intervention, particularly in those with milder disease, have recently been demonstrated by Galíè and colleagues14: In a 6-month prospective trial of 185 PAH patients with less severe symptoms (World Health Organization functional class II) randomized to receive the endothelin receptor antagonist bosentan or placebo, those receiving active treatment experienced a delay in time to clinical worsening compared with placebo over the 6-month study period.

Tolle et al found that VE/VCO2 at the anaerobic threshold was not significantly higher in the EIPAH group than in the normal group, suggesting that a single exercise parameter may not be sensitive enough to distinguish between EIPAH
and normal. However, they did find that those patients with PAH at rest had more severe hemodynamic abnormalities and more severely impaired cardiopulmonary gas exchange during exercise than patients with EIPAH. Importantly, only the patients with resting PAH displayed the characteristic abnormal ventilatory efficiency pattern with exercise seen in PAH patients (high Ve/VCO2 at the anaerobic threshold).

Although this study supports the notion that EIPAH may be part of the continuum from normal to severe pulmonary vascular disease, several questions remain unanswered. First, because 90% of the subjects in their study were referred for exercise intolerance, it is unclear whether cardiopulmonary exercise testing combined with invasive exercise hemodynamics can identify “preclinical” (asymptomatic) pulmonary vascular disease. Second, the mechanisms responsible for an increase in pulmonary artery pressure during exercise in the EIPAH group, which have implications for long-term management, are unclear. If, as the authors speculate, dynamic pulmonary vasoconstriction may be the cause, then such patients may be treatable with simple vasodilators such as calcium channel blockers, which are less expensive and less toxic than PAH-specific therapies. Future studies using potent, short-acting selective pulmonary vasodilators such as inhaled nitric oxide, which might blunt the increase in PAP during exercise, may help answer this question. Finally, the natural history of EIPAH and its long-term responsiveness to any type of therapy require further study.

The diagnosis and treatment of PAH are complex and evolving rapidly. Tolle and colleagues have made an important contribution to this field not only by characterizing a population with an abnormal pulmonary vascular response to exercise that warrants further attention but also, in this era of sophisticated technological advances, by highlighting the importance and timeliness of “classic” cardiopulmonary physiological testing in the approach to this disease.

Disclosures

Drs Oudiz and Rubin have served as investigators and consultants for Actelion.

References


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