Assessment of pulmonary hypertension during exercise: Ready for clinical prime time?

Évaluation de l’hypertension pulmonaire à l’exercice : prêt pour le « prime time » clinique?

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Background

The development of pulmonary hypertension at rest in patients with heart failure, chronic obstructive pulmonary disease, interstitial lung disease, thrombo-embolic disease, connective tissue disease, sleep apnoea disorders or cardiac valve disease often signals progression of the disease and poor outcome [1,2]. According to Ohm’s law, pulmonary arterial blood flow (cardiac output), PCWP and PVR primarily determine the P APmean. A P APmean ≥ 25 mmHg currently defines pulmonary hypertension; coexisting PCWP (or left atrial pressure or left ventricular end diastolic pressure) ≤ 15 mmHg indicates pulmonary arterial hypertension (PAH), whereas elevated PCWP indicates at least some degree of PVH. RHC remains the gold standard for pulmonary hypertension diagnosis. It also enables the evaluation of pulmonary vasoreactivity and oxygen saturation measurements. Because of its noninvasive nature, Doppler echocardiography is the screening tool of choice in patients who are suspected of having pulmonary hypertension. By adding the estimated right atrial pressure, the P APsyst may be estimated from the tricuspid regurgitant jet. In the absence of tricuspid regurgitation, pulmonary regurgitation may be used to derive PAP. In patients with healthy and diseased pulmonary circulations, PAPsyst closely correlates with PAPmean at rest and in different states of activity [3,4]. A PAPsyst threshold of 36 mmHg is currently retained

Abbreviations: ESE, exercise stress echocardiography; HFpEF, heart failure with preserved ejection fraction; LV EF, left ventricular ejection fraction; PAPmean, mean pulmonary artery pressure; PAPsyst, pulmonary arterial systolic pressure; PCWP, pulmonary capillary wedge pressure; PVH, pulmonary venous hypertension; PVR, pulmonary vascular resistances; RHC, right-sided heart catheterization.

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for the screening of pulmonary hypertension. Agreement between catheter and Doppler assessment of PAP highly depends on accurate recording of the tricuspid regurgitant jet and operator skill.

Pulmonary pressures are intrinsically dynamic with exercise, sleep, load conditions, high altitude, right ventricular performance or therapeutic interventions. Despite normal or near-normal PAP at rest, dynamic exercise may unmask a large rise in PAP that may be considered as a latent stage of pulmonary hypertension. Early therapeutic interventions at this stage might result in a more favourable outcome. Although challenging, ESE allows the noninvasive assessment of PAP during exercise but head-to-head comparisons between Doppler derived PAP and catheter measurements have seldom been performed [5]. Besides the difficulty in analysing tricuspid regurgitant velocity signals during ESE, the right atrial pressure based on inferior vena cava imaging has never been validated during exercise, when venous compliance is known to decrease [6]. It is worth noting that owing to the rapid return of PAP to baseline, Doppler measurements during recovery appear unreliable [7].

Healthy individuals

Physiologically, during dynamic exercise the high vascular compliance of the pulmonary circulation is such that a several-fold increase in pulmonary blood flow may be accommodated with small rise in PAP and fall in PVR [8]. Moreover, the relationships between PAP and cardiac output or workload are highly linear using ESE. When log PAP is plotted as a function of log cardiac output, both takeoff and plateau patterns may be identified in healthy subjects [7]. In healthy individuals of various ages, Mahjoub et al. demonstrated that PAP does not increase above 60 mmHg at low-level exercise [9]. Unlike resting PAP, the rise in PAP is largely influenced by age, and 50% of patients aged > 70 years have a PAP ≥ 60 mmHg at maximal workload. Both age-related vascular stiffening and reduced compliance of left ventricular (LV) filling, which is reflected back on the pulmonary vascular bed, are likely to account for the pulmonary pressure response during exercise [10]. Thus, whereas a large exercise-induced rise in PAP in a young patient should be considered as an abnormal response, interpretation of an increase in PAP ≥ 60 mmHg at peak exercise in elderly patients with exertional dyspnoea or fatigue requires caution. It is noteworthy that well-trained athletes may experience a large increase in PAP at high workload (tricuspid regurgitant maximal velocity ranging from 3.10 to 3.72 m/s in athletes vs 1.95 to 2.58 m/s in non-athletes) [11]. A large increase in blood flow probably influences the exercise PAP response in athletes [11]. Finally, using either RHC or ESE, age and workload achieved are key determinants of exercise PAP, making it difficult to define normal PAP values during exercise [12].

Cardiac valvular disease

The usefulness of ESE in the management of cardiac valvular disease has been recently reviewed [13,14]. In patients with asymptomatic organic mitral regurgitation, Magne et al. found that peak PAP > 60 mmHg is frequent (46%) during ESE and is mainly related to an exercise-induced increase in mitral regurgitation severity [15]. Importantly, exercise pulmonary hypertension (with a threshold of 56 mmHg) was a stronger predictor of 2-year symptom-free survival than resting PAP, which is close to the 60 mmHg recommended by the American College of Cardiology/American Heart Association guidelines [16]. Despite the lack of prospective prognostic data, a threshold of 60 mmHg during exercise is also recommended by current guidelines in mitral stenosis; decreased mitral valve compliance during exercise correlates with exercise-induced pulmonary hypertension in this setting [17]. The significance of exercise-induced pulmonary hypertension in patients with asymptomatic aortic stenosis or regurgitation has not been specifically addressed. Last, owing to abnormal left ventricular function or residual pathology of the pulmonary vascular bed, exercise pulmonary hypertension should be considered when there is no significant relief of symptoms after valve replacement [18].

Systolic heart failure

Pulmonary hypertension is a frequent complication of both systolic and diastolic left ventricular dysfunction. In patients with heart failure and reduced LVEF, PAP often increases sharply during exercise, associated with a blunted increase in cardiac output [8] and a close correlation between PCWP and PAP at each level of exercise [19]. Interestingly, some patients with heart failure and reduced LVEF may experience a decrease in PAP during exercise [8]. Multiple intrinsic factors, including larger rise in functional mitral regurgitation volume during exercise, myocardial dyssynchrony or absence of left ventricular contractile reserve bolster exercise-induced pulmonary hypertension, while right ventricular failure hinders exercise-induced pulmonary hypertension [20,21]. A positive relationship between exercise pulmonary hypertension and adverse outcome has been found in patients with left ventricular systolic dysfunction and coronary artery disease [22], whereas a decrease in PAP during exercise might identify a subset of heart failure patients with worse prognosis [23]. A multivariable approach, including assessment of right ventricular functional performance, is needed for a comprehensive interpretation of exercise PAP alteration in heart failure patients.

Heart failure with preserved ejection fraction

In clinical practice, significant exercise-induced PH may be observed in the case of inducible ischaemia in patients with preserved LVEF at rest and exertional dyspnoea. In a large, heterogeneous population of patients with preserved LVEF referred for ‘diastolic’ ESE, exercise-induced pulmonary hypertension (PAP > 50 mmHg at 50 W) has been associated with increased left ventricular filling pressure at rest, older age, female sex, increased systolic blood pressure at rest, shorter exercise duration and lower exer-
Exercise pulmonary hypertension

The authors have not supplied their declaration of conflict of interest.

Clinical implications

Comprehensive interpretation of PAP during exercise is required. Most studies reported PAP measurements only at peak exercise, thereby complicating the interpretation of an exercise-induced increase in PAP. A large increase in PAP at low workload or high workload may not have the same clinical significance. The impact of ageing on exercise-induced pulmonary hypertension is key, as vascular compliance tends to decrease with age. A large exercise increase in PAP in a 50-year-old patient with severe asymptomatic mitral regurgitation is likely to convey a poor outcome without surgery; the same finding in a 75-year-old patient with mild mitral regurgitation may require caution. Of note, the proportions of patients reaching a PAP of 60 mmHg at peak exercise were similar in the studies by Majhoub et al. and Magne et al., involving healthy controls and patients with organic mitral regurgitation, respectively; however, the workload achieved was lower in patients with mitral regurgitation [9,15]. The usefulness of exercise testing in systolic heart failure patients for assessing right ventricular performance and PAP prior to left ventricular assistance device might be tested. Testing of whether increased PAP during exercise is related to an increase in flow or in resistance using the ratio of pressure (tricuspid regurgitant velocity) to flow (time-velocity integral in the right ventricular outflow tract) is limited and deserves further investigation [40]. Last, whether ESE may help in the HFpEF working diagnosis deserves further studies, as noninvasive assessment of pulmonary venous pressure and PVR remains challenging.

Disclosures

The authors have not supplied their declaration of conflict of interest.
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