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SCIENTIFIC EDITORIAL

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 PAP_{mean}. A $PAP_{mean} \geq 25$ 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 PAP_{syst} 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, PAP_{syst} closely correlates with PAP_{mean} at rest and in different states of activity [3,4]. A PAP_{syst} threshold of 36 mmHg is currently retained

Abbreviations: ESE, exercise stress echocardiography; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; PAP_{mean}, mean pulmonary artery pressure; PAP_{syst}, 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_{syst} at rest, dynamic exercise may unmask a large rise in PAP_{syst} 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_{syst} during exercise but head-to-head comparisons between Doppler derived PAP_{syst} 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_{syst} and cardiac output or workload are highly linear using ESE. When log PAP_{mean} 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_{syst} does not increase above 60 mmHg at low-level exercise [9]. Unlike resting PAP_{syst}, the rise in PAP_{syst} is largely influenced by age, and 50% of patients aged > 70 years have a $PAP_{syst} \geq 60$ 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_{syst} in a young patient should be considered as an abnormal response, interpretation of an increase in $PAP_{syst} \geq 60$ 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_{syst} 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_{syst}, 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 $PAP_{syst} > 60$ 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_{syst}, 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_{mean} often increases sharply during exercise, associated with a blunted increase in cardiac output [8] and a close correlation between PCWP and PAP_{mean} at each level of exercise [19]. Interestingly, some patients with heart failure and reduced LVEF may experience a decrease in PAP_{mean} during exercise [8]. Multiple intricate 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_{syst} 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 PVH 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 ($PAP_{syst} > 50$ 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-

cise oxygen saturation. These latter clinical characteristics are, in effect, similar to those of patients with HFpEF [24]. In patients with HFpEF, exercise intolerance is associated with a significant rise in PAP_{syst} during dynamic exercise and concomitantly with a fall in left ventricular systolic performance and eventually with the development or worsening of functional mitral regurgitation [25,26]. Using RHC, Borlaug et al. found that despite normal resting haemodynamic variables, a substantial number of dyspnoeic patients (65 ± 13 years) experienced a large exercise increase in PCWP, while controls (47 ± 17 years) did not [27]. Exercise PAP_{syst} did correlate tightly with exercise PCWP and ≥ 45 mmHg accurately predicted a haemodynamic-based HFpEF diagnosis [27]. Whether exercise PCWP rise is the sole mechanism of increased lung water and stiffness in patients with overt HFpEF remains uncertain. In addition, a precapillary component of pulmonary hypertension (vascular stiffness) is likely to further exacerbate exercise pulmonary hypertension in patients with HFpEF [28].

Pulmonary arterial hypertension

Unlike heart failure due to left ventricular systolic dysfunction, maximal exercise testing should be prohibited in PAH patients. In a landmark invasive study, Laskey et al. showed that in patients with PAH, PVR do not decrease during exercise and PAP increases sharply [29]. PAH is the most common cause of scleroderma-related deaths. Identifying the pulmonary vascular disease as early as possible is likely to offer the best management to improve haemodynamics and ultimately survival. Exercise-induced pulmonary hypertension may be a sensitive way to identify scleroderma patients with early PAH [30]. Moreover, Condliffe et al. found that 19% of patients with scleroderma who have exercise pulmonary hypertension develop resting pulmonary hypertension after 2.3 years [31]. Of note, sclerodermic patients may also exhibit exercise-induced PVH, suggesting underlying left ventricular dysfunction especially in older people [32]. In a large, multicentre, European cohort, the relatives of patients with idiopathic PAH had a higher proportion of pulmonary hypertension response during exercise compared with controls, especially those carrying *BMPR2* mutations [33]. The plateau pattern was found in patients without resting PAH and with $PAP_{mean} \geq 30$ mmHg at peak exercise, therefore suggesting an early stage of the disease [34]. The specificity of these plateau and takeoff patterns remains under debate, however [7]. Exercise pulmonary hypertension may also be evidenced in patients with chronic obstructive pulmonary disease, sickle cell disease or pulmonary fibrosis [35—38]. Hypoxic pulmonary vasoconstriction and reduced capillary bed contribute to elevations in PAP and exercise intolerance in these patients. Whether exercise testing refines the prognosis of these patients at risk of PAH remains uncertain. The 4th World Symposium on Pulmonary Hypertension decided that exercise-induced PH should be excluded from the diagnostic criteria for PAH; hence current recommendations do not recommend assessment of PAP during exercise in the management of PAH [39].

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_{syst} 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 somewhat with age. A large exercise increase in PAP_{syst} 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 requires cautious interpretation. Of note, the proportions of patients reaching a PAP_{syst} 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.

Conclusions

Preliminary experience suggests that exercise testing provides additional information over resting variables in the evaluation and management of pulmonary hypertension in various conditions. However, no confirmed consensus exists with regard to which PAP_{syst} threshold is diagnostically relevant for exercise pulmonary hypertension. Moreover, whether ESE and exercise RHC are interchangeable remains uncertain. How the stress is performed — whether supine or upright cycle ergometry or arm weight exercise — is another issue. Assessment of PAP_{syst} during ESE is feasible but still difficult even in expert hands (obesity, hyperinflated lungs, trivial tricuspid regurgitation, etc.). The role of right atrial pressure may be underestimated in ESE. The knowledge of the multiple intricate factors that may dramatically influence the level of PAP during exercise is a prerequisite safeguard to ensure that studying the dynamism of PAP during exercise effectively improves therapeutic strategies for and prognosis of our patients.

Disclosure of interest

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

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