To assess exertional breathlessness you must exert the breathless

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This editorial refers to 'Impact of right ventricular reserve on exercise capacity and survival in patients with pulmonary hypertension’, by F.C. Blumberg et al., published in this issue on pages 771–775.

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are rare conditions associated with a poor prognosis, for which treatments are expensive and, at best, only moderately efficacious. Until the very latest stages of disease progression, symptoms occur almost exclusively with physical exertion, most probably reflecting insufficient oxygen delivery to peripheral muscles caused through limitations of right ventricular (RV) reserve relative to heightened pulmonary vascular afterload.1 Despite this, assessments are most frequently performed at rest. In this issue of the journal, Blumberg and colleagues2 remind us that resting measures may be an inadequate surrogate of the pathophysiology of pulmonary hypertension when assessed during exercise. They performed cardiopulmonary testing and cardiac catheterization at rest and during exercise in 21 PAH and 15 CTEPH patients, and observed a modest correlation between cardiac index during exercise and maximal oxygen uptake (peakVO2). This is not greatly surprising as cardiac output is known to explain the majority of variance in VO2 in health and disease3—put simply, if the blood cannot get to the muscles then it cannot be utilized. Of greater interest is the finding that the strongest predictors of survival were all obtained during exercise. Peak cardiac index and the pressure/flow relationship (analogous to the change in pulmonary vascular resistance) both predicted survival (61% at 5 years), while the strongest predictors were the non-invasively determined measures of peakVO2 and ventilatory efficiency (VE/VCO2).

These findings are consistent with previous experience. In a larger cohort, Wensel et al.4 demonstrated that peakVO2 was a strong predictor of survival in patients with PAH, especially when systolic blood pressure failed to increase during exercise. As compared with cardiopulmonary testing, a 6 min walk distance (6MWD) is a simpler measure of exercise capacity that may be nearly as accurate in predicting patient outcomes.5 Partly as a result of this simplicity, the 6MWD has been adopted as the primary endpoint for multiple clinical trials investigating the efficacy of various pulmonary vasodilators. This would seem reasonable given that 6MWD is a practical description of functional capacity (an important treatment goal) and the correlation between 6MWD and survival suggests utility as a surrogate of improved patient outcomes. However, recent analyses of pooled PAH patient data suggest that the 6MWD fails on both counts,6,7 leaving us to ask why. The agreement between 6MWD and peakVO2 is relatively poor,8 and perhaps the 6MWD is just too blunt a measure to detect meaningful differences in exercise capacity after only 3–4 months of therapy. Blumberg et al. did not assess 6MWD, but their data would suggest that well-performed exercise measures should not be dismissed. On the contrary, cardiopulmonary and haemodynamic measures were only of prognostic value when measured during exercise and thus we may conclude that the goal should be to sharpen our exercise measures further.

If surrogate measures are to be chosen as endpoints in PAH trials, then it is clearly desirable that they offer an insight into the pathophysiology of the condition and the mechanism of therapeutic effect.9 In this regard, the methodologies described by Blumberg et al.2 and Groepenhoff et al.10 enable some separation of pulmonary vs. systemic vascular vs. cardiac factors, and represent a clear advance on the 6MWD. However, significant limitations remain. Cardiopulmonary and thermodilution measures provide a very indirect summary of cardiac function which provides little insight into whether limitation is primarily due to RV or LV impairment of ventricular function during exercise has been a major challenge, but real-time cardiac magnetic resonance offers unprecedented accuracy in determining changes in cardiac volumes.11 and these techniques have been used by Holwerda et al. to describe elegantly the cardiac limitations of PAH patients1 (and exemplified in Figure 1). The quantification of ventricular volumes in combination with intracardiac pressure measures during exercise would provide the ultimate gold standard in which true appraisal of ventriculo-arterial interactions could be appraised.

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pulmonary vascular resistance and good RV function may have similar exercise pulmonary arterial pressures to those patients with high pulmonary vascular resistance and decompensated RV function. The distinction is important and can only be made if there is simultaneous assessment of both RV function and pressures.

Pulmonary arterial hypertension is rare, and the pathophysiologic implications of disease progression remain incompletely understood. The data of Blumberg et al. remind us of the importance of studying our patients during exercise, when symptoms and physiologic limitations are most appreciable. Their data challenge us to assess whether more accurate exercise measures will provide even greater insights into the pathophysiology of PAH and more specific measures against which treatment efficacy may be assessed.

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References


Figure 1  Real-time exercise cardiac magnetic resonance imaging demonstrating increasing right ventricular dilation and dysfunction during exercise in a patient with pulmonary hypertension. Short-axis images acquired at a mid-ventricular level in a subject with chronic thrombo-embolic pulmonary hypertension describing profound breathlessness and pre-syncpe with exertion. End-systolic images demonstrate a moderately dilated right ventricle with mild systolic dysfunction at rest (upper panel) becoming more dilated during near-maximal exercise (lower), resulting in filling impairment of the left ventricle and markedly attenuating increases in cardiac output. Thus, as compared with rest, the exercise pathophysiology better explains the severity of the symptoms.