Evaluation of criteria for exercise-induced pulmonary hypertension in patients with resting pulmonary hypertension

To the Editor:

Owing to the lack of a suitable definition, exercise criteria for the diagnosis of pulmonary hypertension (PH) were removed from consensus guidelines following the 4th World Pulmonary Hypertension Symposium in 2008 [1] and have remained absent following the 5th World Symposium [2] and recent European Cardiology Society/European Respiratory Society guidelines [3]. Nonetheless, there remains significant interest in properly defining an abnormal pulmonary vascular response to exercise [4–6].

Two criteria incorporating the relationship between mean pulmonary artery pressure (mPAP) and cardiac output (CO) have been recently proposed: 1) the slope of multi-point mPAP–CO relationship >3 mmHg·min·L^{-1} during exercise [4] and 2) mPAP >30 mmHg and total pulmonary resistance (TPR) >3 WU at maximal exercise [6]. While these criteria have been shown to predict outcomes in patients with PH [7] and in systemic sclerosis patients without resting PH [8], studies directly comparing these two exercise-induced PH (EIPH) criteria are limited. Godinas *et al.* [9] retrospectively compared these criteria in a cohort of 169 patients with resting mPAP ⩽20 mmHg (68 healthy controls and 101 patients with some degree of pulmonary vascular pathology (n=49) or left heart (n=52) disease) and found concordant classification in 80.5% of patients (κ=0.61), indicating a discrepant classification in a substantial number of participants. However, it is not clear that the heterogeneous population in this study should necessarily all have pulmonary hypertension during exercise ($mPAP_{max}$ >30 mmHg and TPR_{max} >3 WU) and an abnormal pulmonary vascular response to exercise (mPAP–CO slope ⩽3 mmHg·min·L^{-1}). On the other hand, patients with resting PH should have both PH during exercise and an abnormal pulmonary vascular response to exercise and concordance between valid criteria in this population should be much stronger. Therefore, we aimed to evaluate exercise haemodynamics in patients with resting PH to determine the test characteristics of the two proposed EIPH criteria.

After institutional review board approval, we performed a retrospective, single-centre study of patients who underwent an exercise right heart catheterisation (RHC) between January 1, 2010, and February 1, 2017. All patients with pulmonary arterial hypertension (PAH) or with PH related to systemic sclerosis-associated interstitial lung disease (SScILD-PH) were included if resting haemodynamics demonstrated an mPAP ⩾25 mmHg, a pulmonary arterial wedge pressure (PAWP) ⩽15 mmHg and a pulmonary vascular resistance (PVR) >3 WU. 18 RHCs were performed as part of a prospective study evaluating mechanisms of right ventricular dysfunction in PAH, and 14 RHCs were performed as part of clinical care. As our standard, exercise was performed with a supine cycle ergometer using a staged protocol, beginning at 15 W and increasing by 10 W for every 2-min stage. Haemodynamic waveforms were measured at end-expiration at rest and averaged over the respiratory cycle during exercise [5]. CO measurements were made at rest and at the end of each stage of exercise by thermodilution (TDCO) and/or by direct Fick (DFCO). DFCO was measured as previously described [10]. In patients with both TDCO and DFCO measurements during exercise, DFCO was used for EIPH calculations. An average of 5.3 points per patient was used to define the mPAP–CO slopes. Comparisons between groups were performed using the Chi-squared test or Fisher's exact test, as appropriate, for categorical variables, and the t-test or

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Wilcoxon rank-sum test, as appropriate, for continuous variables. Results are presented as mean±SD unless otherwise noted. All statistical analyses were performed using Stata MP, Version 12.1 (Stata Statistical Software: Release 12; StataCorp, College Station, TX, USA).

Haemodynamic data from 32 patients were included: five idiopathic PAH (IPAH), 20 SSc-associated PAH (SSc-PAH) and seven SScILD-PH. 27 (84%) patients were female, 25 (78%) patients were white and 20 (74%) of SSc patients had limited SSc. Mean age was 60±12 years. Baseline haemodynamics were the following: heart rate (HR) 73±11 min^{-1}, right atrial pressure (RAP) 7±4 mmHg, mPAP 37±11 mmHg, PAWP 10±4 mmHg, CO 4.2±1.0 $L{\cdot}min^{-1}$, cardiac index (CI) 2.4±0.5 $L{\cdot}min^{-1}{\cdot}m^{-2}$ and PVR 7.3±4.3 WU.

All 32 patients met the criteria for EIPH defined by $mPAP_{max}$ >30 mmHg and TPR_{max} >3 WU. Notably, however, five out of 32 (16%) did not meet the criteria for EIPH as defined by mPAP–CO slope. Of the five RHC that did not meet the slope criteria, one was a follow-up RHC (IPAH) and four were diagnostic RHC (three had SSc-PAH, one had SScILD-PH). There was no suggestion of an association between diagnosis and failure to meet the mPAP–CO slope criteria (p=0.96), nor were there differences in mean age, sex or NYHA functional class. Similarly, there was no difference in resting mPAP (38±11 mmHg *versus* 34±15 mmHg, p=0.18), or other resting haemodynamic measures, including RAP, PAWP, CO, CI, PVR or HR.

Figure 1 shows mPAP *versus* CO at maximum exercise for all 32 patients, grouped by those that did and did not meet the mPAP–CO slope criteria. The five patients who did not meet slope criteria had a trend towards a lower $mPAP_{max}$ (49±14 mmHg *versus* 63±17 mmHg; p=0.06), and had a greater CO_{max} (11.52 ±1.80 $L{\cdot}min^{-1}$ *versus* 7.64±2.28 $L{\cdot}min^{-1}$; p=0.004) without any statistical difference in $PAWP_{max}$ (15 ±8 mmHg *versus* 17±9 mmHg; p=0.52) or maximum workload achieved during exercise (median (interquartile range) 45 (50) W *versus* 35 (30) W, p=0.35). The y-intercepts of the mPAP–CO relationship were substantially higher in those that did not meet the mPAP–CO slope criteria compared with those who did (29.5±15.4 mmHg *versus* 7.0±19.2 mmHg, p=0.03). Recalculating the mPAP–CO slope instead of using mPAP averaged over the respiratory cycle at rest did not significantly impact the slope values, nor did it reclassify the EIPH status of any patient. Four of the five patients who failed to meet the mPAP–CO slope criteria were taking calcium channel blockers (CCBs) at the time of RHC, although there was no difference in the proportion of patients taking CCBs between those who did and did not meet the mPAP–CO slope criteria (55.6% *versus* 80.0%; p=0.31). Of the four patients using CCBs, only one had IPAH with vasoresponsive disease where a CCB can be considered a true pulmonary vasodilator.

While it may not be surprising that patients with resting PH all had PH during exercise ($mPAP_{max}$>30 mmHg and TPR_{max}>3 WU), the fact that a substantial proportion of patients lacked an abnormal pulmonary vascular response with exercise (mPAP–CO slope $\leqslant$3 $mmHg{\cdot}min{\cdot}L^{-1}$) is an important finding. This suggests that the criterion based on a multi-point mPAP–CO slope may be less sensitive for diagnosing EIPH, consistent with Godinas *et al.* [9], where this criterion had a sensitivity of 0.67 (95% CI 0.52–0.80) for detecting EIPH. The population in their study consisted of patients without resting PH. That the slope criterion also lacks sensitivity in our distinct cohort with resting PH, all of whom should have an abnormal pulmonary vascular response to exercise, makes the mPAP–CO slope criteria for defining EIPH all the more concerning. Prior studies have noted high extrapolated pressure intercepts may be associated with a critical closing pressure that exceeds PAWP [11, 12]. Whether this

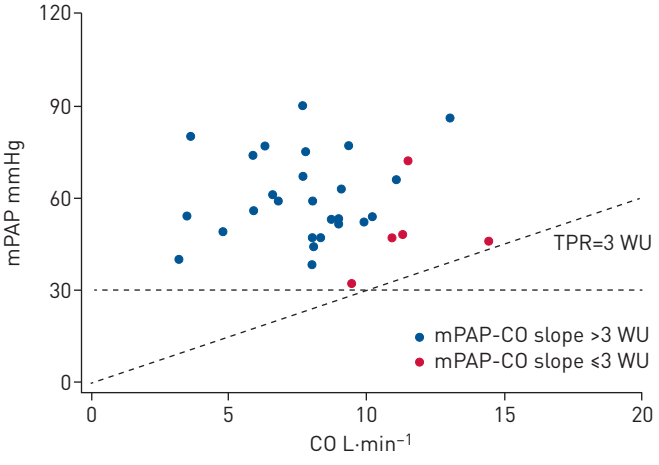

FIGURE 1 Mean pulmonary artery pressure *versus* cardiac output at maximum exercise for all 32 patients. Individuals with red markers had an mean pulmonary artery pressure (mPAP)–cardiac output (CO) slope ⩽3 WU, while the individuals with blue markers had an mPAP–CO slope >3 WU. The dashed lines represent the thresholds for one criterion for exercise-induced pulmonary hypertension (mPAP >30 mmHg and TPR >3 WU).

finding identifies a subset of patients with unique physiology with differential prognosis or response to treatment is unknown.

There are some potential limitations to our study. First, it is a relatively small, single-centre study, although the sample size is indicative of the scarcity of exercise hemodynamic data in those with resting PH. Second, the measurement of CO during exercise varied in our cohort. 17 (50%) had DFCO measurement during exercise, and the remaining 50% had TDCO measurements. Recent work by our group [10] has shown that TDCO underestimates DFCO during exercise, meaning that TDCO can overestimate the diagnosis of EIPH regardless of criteria used. If all patients had DFCO estimates, it is possible that even more patients than we reported would not meet either EIPH criteria. However, it would be unlikely that this would change the difference in sensitivity observed between the two criteria.

In summary, in this cohort of patients with resting PH, mPAP–CO slope >3 mmHg·min·L^{-1} with exercise was not observed in 16% of patients, whereas mPAP>30 mmHg and TPR >3 WU at maximal exercise was observed in all. Therefore, the latter criteria, proposed by Herve *et al.* [6], appear more sensitive to define EIPH. Correctly phenotyping these patients is a necessary precursor to understanding any homology that may exist between EIPH and pulmonary vascular disease detectable at rest.

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References

1 Badesch DB, Champion HC, Sanchez MA, *et al.* Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 54: Suppl., S55–S66.
2 Hoeper MM, Bogaard HJ, Condliffe R, *et al.* Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol;* 2013; 62: Suppl., D42–D50.
3 Galiè N, Humbert M, Vachiery J-L, *et al.* 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2015; 46: 903–975.
4 Naeije R, Vanderpool R, Dhakal BP, *et al.* Exercise-induced pulmonary hypertension: Physiological basis and methodological concerns. *Am J Respir Crit Care Med* 2013; 187: 576–583.
5 Lewis GD, Bossone E, Naeije R, *et al.* Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. *Circulation* 2013; 128: 1470–1479.
6 Herve P, Lau EM, Sitbon O, *et al.* Criteria for diagnosis of exercise pulmonary hypertension. *Eur Respir J* 2015; 46: 728–737.
7 Hasler ED, Müller-Mottet S, Furian M, *et al.* Pressure-flow during exercise catheterization predicts survival in pulmonary hypertension. *Chest* 2016; 150: 57–67.
8 Stamm A, Saxer S, Lichtblau M, *et al.* Exercise pulmonary haemodynamics predict outcome in patients with systemic sclerosis. *Eur Respir J* 2016; 48: 1658–1667.
9 Godinas L, Lau EM, Chemla D, *et al.* Diagnostic concordance of different criteria for exercise pulmonary hypertension in subjects with normal resting pulmonary artery pressure. *Eur Respir J* 2016; 48: 254–257.
10 Hsu S, Brusca SB, Rhodes PS, *et al.* Use of thermodilution cardiac output overestimates diagnoses of exercise-induced pulmonary hypertension. *Pulm Circ* 2017; 7: 253–255.
11 Janicki JS, Weber KT, Likoff MJ, *et al.* The pressure-flow response of the pulmonary circulation in patients with heart failure and pulmonary vascular disease. *Circulation* 1985; 72: 1270–1278.
12 Kafi SA, Mélot C, Vachiery JL, *et al.* Partitioning of pulmonary vascular resistance in primary pulmonary hypertension. *J Am Coll Cardiol* 1998; 31: 1372–1376.