Are indexed values better for defining exercise pulmonary hypertension?

To the Editor:

Pulmonary hypertension (PH) is defined by resting mean pulmonary arterial pressure (mPAP) ≥25 mmHg [1]. Patients with pulmonary vascular disease (PVD) or left heart disease (LHD) may demonstrate abnormal haemodynamic responses to exercise even when resting mPAP is normal [2]. After the 4th World Symposium on PH in 2008, exercise PH, defined as mPAP >30 mmHg during exercise, was abandoned due to a lack of supportive evidence and the observation that mPAP frequently exceeds 30 mmHg in healthy individuals who attain high cardiac output (CO) [3, 4]. A disproportionate increase in mPAP relative to CO during exercise, however, reflects either an increase in pulmonary vascular resistance (PVR), as in PVD, or elevated left ventricular filling pressure in LHD. Therefore, attention to the mPAP/CO relationship, such as the mPAP/CO slope or the total pulmonary resistance (TPRmax) >3 Wood units (WU) at maximal exercise, could redefine the definition of an abnormal haemodynamic response to exercise in order to reduce false positive diagnoses [5-7]. Indeed, combining mPAP (mPAPmax) >30 mmHg and the TPRmax >3 WU at maximal exercise has been demonstrated to have high accuracy in discriminating patients with PVD or LHD and resting mPAP ≤20 mmHg from controls or healthy volunteers [7]. Furthermore, these criteria have superior diagnostic performance compared to either the mPAP/CO slope or change in mPAP/CO during exercise [8].

Cardiac index (CI) and pulmonary vascular resistance index, obtained by standardisation of cardiac output with body surface area (BSA), are sometimes reported in studies of exercise haemodynamics [9]. It is also conventional to normalise resting pulmonary vascular resistance for BSA in congenital heart disease and paediatric patients [1]. However, it is unknown whether standardising the maximal mPAP/CO for BSA (TPRImax) for the definition of exercise PH further improves discrimination between PVD or LHD and healthy adults with normal resting mPAP. Therefore, this current study aimed to compare the diagnostic performance of TPRmax, TPRImax, mPAP/CO slope and the mPAP/CI slope. Additionally, we tested the performance of two criteria for exercise PH: 1) mPAP/CO ratio at maximal exercise (i.e. the TPRmax) and mPAPmax >30 mmHg or 2) mPAP/CI ratio at maximal exercise (i.e. the TPRI max) and mPAPmax >30 mmHg.

A total of 209 individuals (control n=89, PVD n=54, LHD n=66) with resting mPAP ≤20 mmHg who underwent exercise haemodynamic testing with supine lower limb ergometry were included in this analysis. The identification of patients as controls, PVD or LHD were as described in HERVE et al. [7]. Maximal exercise measurements for mPAP and CO were defined as the values obtained during the final stage of an incremental work rate protocol. Exercise protocol details are as previously reported and participants exercised until exhaustion or development of limiting symptoms [7]. This study was approved by the ethics board of Université Paris-Sud (Le Kremlin-Bicêtre, France) and informed consent was obtained from all patients. Optimal cut-offs for TPRmax, TPRImax, mPAP/CO slope and mPAP/CI slope were obtained that maximised sensitivity and specificity. Receiver operating characteristic (ROC) analysis was performed to determine the area under the curve (AUC) for each variable, followed by analysis of TPRmax and TPRImax in combination with mPAP >30 mmHg. AUC values were compared using the method of HANLEY and McNEIL [10]. Statistical analyses were performed using Stata (version 13.1, StataCorp, College Station, TX, USA) with a p-value <0.05 considered significant.

Of the 209 individuals included in this analysis, 169 patients were reported in reference [7] and 40 patients were not previously reported. The baseline characteristics of patients in the current study were not significantly different from the previously reported cohort [7]. Mean age was 51±15 years, mean body

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mass index (BMI) was 25.4±5.9 kg·m⁻², mean BSA was 1.8±0.2 m² and 68 (32%) were male. Overall, 16% of patients were obese (BMI >30 kg·m⁻²) and 4% had a BMI >35 kg·m⁻². There were no differences in BMI or BSA between controls or patients with PVD or LHD, however patients with PVD and LHD were older (mean age 43±15, 55±13, 57±13 years for controls, PVD and LHD, respectively, p<0.001). For TPRmax, the optimal cut-off value was 3.0 WU (sensitivity 0.89, specificity 0.99, positive likelihood ratio (LR+) 79.4, negative likelihood ratio (LR–) 0.11) with AUC of 0.98 (95% CI 0.97–0.99) and for TPRImax the optimal cut-off was 4.6 WU·m² (sensitivity 0.96, specificity 0.80, LR+ 4.7, LR– 0.05) with AUC of 0.95 (95% CI 0.93–0.98). The optimal cut-off value for mPAP/CO slope was 2.7 mmHg·L⁻¹·min⁻¹ (sensitivity 0.78, specificity 0.90, LR+ 7.7, LR– 0.24) with AUC of 0.94 (95% CI 0.91–0.97) and for mPAP/CI slope it was 4.2 mmHg·L⁻¹·min⁻¹·m⁻² (sensitivity 0.88, specificity 0.81, LR+ 4.6, LR– 0.15) with AUC of 0.92 (95% CI 0.89–0.96). Comparison of AUCs determined that TPRmax had superior diagnostic performance than TPRImax, the mPAP/CO slope and the mPAP/CI slope (p=0.006) in discriminating PVD and LHD from healthy controls (figure 1). TPRmax (sensitivity 0.86, specificity 0.93) also remained superior to TPRImax (sensitivity 0.95, specificity 0.42) in the 33 patients with BMI >30 kg·m⁻² (AUC 0.95 versus 0.87, p=0.046). mPAP: mean pulmonary artery pressure; CO: cardiac output; CI: cardiac index; AUC: area under the curve; BMI: body mass index.

There is no consensus as to whether the use of indexed values in exercise haemodynamic studies is more appropriate and opposing arguments have been made. On one hand, the rationale for using cardiac index comes from the observation that increased body mass is associated with higher cardiac output and oxygen consumption as well as being a risk factor for LHD [11]. In otherwise healthy obese adults, increasing body mass correlates with higher CO and pulmonary artery wedge pressure at rest and at exercise, which will have opposing effects on the mPAP/CO relationship [12, 13]. On the other hand, it has been argued that indexing to BSA is unnecessary, since metabolic rate and oxygen demand are not proportional to BSA, particularly during non-weight-bearing exercise such as cycle ergometry [14]. Finally, it must be noted that the current definition of pulmonary arterial hypertension, based on resting haemodynamics, uses a pulmonary vascular resistance >3 WU, without normalisation for BSA [1]. Our current results demonstrate that the use of indexed values (the TPRImax or mPAP/CI slope) in the definition of exercise PH did not improve diagnostic accuracy and TPRmax remained significantly better than TPRImax in the subgroup of patients with BMI >30 kg·m⁻². However, it must be noted that indexed values were more sensitive in the overall population and in the subgroup of obese individuals, but at the cost of considerably lower specificity. The rate of false positives was particularly high in the 33 obese individuals when using the TPRmax or mPAP/CI slope cut-off points derived from the entire population. The optimal sensitivity and specificity for TPRImax among the obese subgroup was 5.9 WU·m² (sensitivity 81, specificity 83), which is higher than the optimal TPRmax cut-off point of 4.6 WU·m² derived from the total population.
Therefore, a high proportion of obese controls without disease (seven out of 12) were incorrectly classified using the TPRI_{max} threshold derived from the total population. This could be even more problematic in populations with a higher prevalence of obesity than in this study (16%). In clinical situations where higher sensitivity is more desirable, the use of indexed values could be advantageous. However, for rare diseases with expensive therapies associated with important side effects, minimising false-positive diagnoses is also important. We acknowledge a limitation in this study because of the effect of large respirophasic variations in mPAP and pulmonary arterial wedge pressure (PAWP) at peak exercise, which could have potentially misclassified some normal individuals as having LHD. As our approach did not consider the values of mPAP or PAWP at submaximal stages, where respirophasic swings may be less marked, useful data for classifying patients may have been omitted.

In conclusion, our study demonstrated that TPRI_{max} is superior to TPRI_{max} mPAP/CO slope and mPAP/CI slope in discriminating adult patients with PVD or LHD and resting mPAP ≤20 mmHg. Although indexed values were more sensitive, specificity was considerably lower and there was no advantage when using TPRI_{max} >4.6 U·m^{-2} versus TPRI_{max} >3 U in addition to mPAP >30 mmHg in the criteria for exercise PH in this adult population. Therefore, we continue to favour a definition of exercise PH as the presence of maximal exercise mPAP >30 mmHg and maximal exercise TPR >3 U, without adjustment for BSA in future studies.

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Received: Feb 02 2017 | Accepted after revision: June 02 2017

Support statement: J. Weatherald is the recipient of a joint European Respiratory Society/Canadian Thoracic Society Long-Term Research Fellowship (LTRF 2015–4780). Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

Acknowledgements: We would like to acknowledge Marie Line Goubet and Antoine Goineau from the Cardiac Catheterization Laboratory, Service de Pneumologie, Centre de Référence de l’Hypertension Pulmonaire Sévère, Hôpital de Bicêtre (Le Kremlin-Bicêtre, France) for their assistance in performing exercise haemodynamic testing.

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https://doi.org/10.1183/13993003.00240-2017