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 (TPR_{max}) >3 Wood units (WU) at maximal exercise, could refine the definition of an abnormal haemodynamic response to exercise in order to reduce false positive diagnoses [5–7]. Indeed, combining mPAP ($mPAP_{max}$) >30 mmHg and the TPR_{max} >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 ($TPRI_{max}$) 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 TPR_{max}, $TPRI_{max}$, 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 TPR_{max}) and $mPAP_{max}$ >30 mmHg or 2) mPAP/CI ratio at maximal exercise (*i.e.* the $TPRI_{max}$) and $mPAP_{max}$ >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 Hervé *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 TPR_{max}, $TPRI_{max}$, 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 TPR_{max} and $TPRI_{max}$ 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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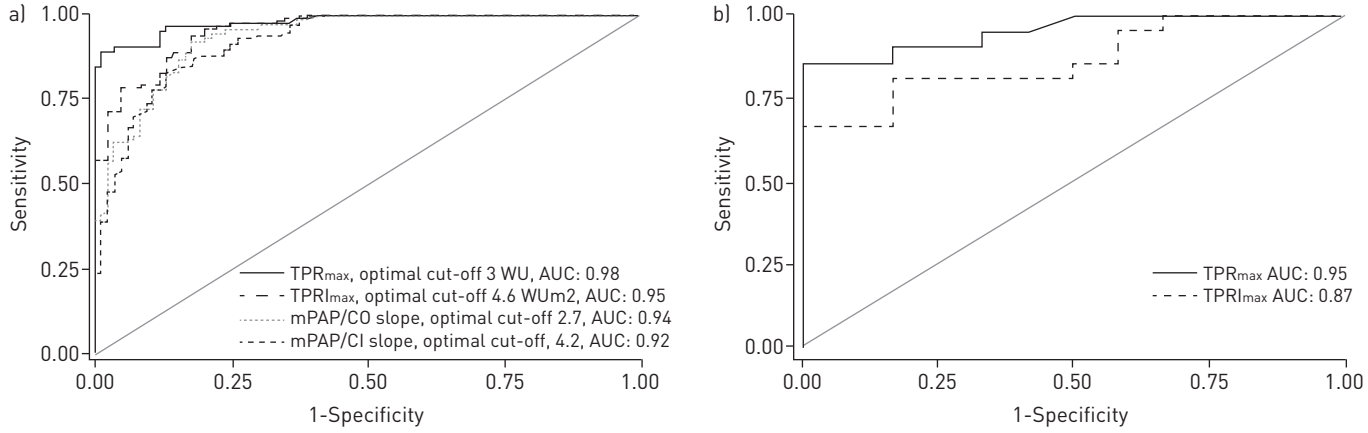

FIGURE 1 a) Receiver-operating characteristic curves and optimal cut-off values for maximal exercise total pulmonary resistance (TPR_{max}), total pulmonary resistance index ($TPRI_{max}$), mPAP/CO slope and mPAP/CI slope for discriminating patients with pulmonary vascular disease and left heart disease from controls. The AUC for TPR_{max} was higher than $TPRI_{max}$, mPAP/CO slope and mPAP/CI slope (p=0.006). b) TPR_{max} remained better than $TPRI_{max}$ in patients (n=33) 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.

mass index (BMI) was 25.4±5.9 kg·m^{-2}, mean BSA was 1.8±0.2 m^2 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 TPR_{max}, 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 $TPRI_{max}$ the optimal cut-off was 4.6 WU·m^2 (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 TPR_{max} had superior diagnostic performance than $TPRI_{max}$, the mPAP/CO slope and the mPAP/CI slope (p=0.006) in discriminating PVD and LHD from healthy controls (figure 1). TPR_{max} (sensitivity 0.86, specificity 0.93) also remained superior to $TPRI_{max}$ (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). We then compared the diagnostic accuracy of two combined criteria: 1) $mPAP_{max}$ >30 mmHg and TPR_{max} >3 WU *versus* 2) $mPAP_{max}$ >30 mmHg and $TPRI_{max}$ >4.6 WU·m^2 (n=209). Using the first criteria with TPR_{max} the sensitivity, specificity and accuracy were 90.9%, 100% and 94.8%, respectively. Using the second criteria with $TPRI_{max}$, the sensitivity, specificity and accuracy were 95.8%, 91.0% and 93.8%. There was no significant difference in the discriminating ability of these two criteria using ROC analysis (mPAP+TPR_{max} AUC 0.95 *versus* mPAP+$TPRI_{max}$ AUC 0.93, p=0.2).

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 $TPRI_{max}$ or mPAP/CI slope) in the definition of exercise PH did not improve diagnostic accuracy and TPR_{max} remained significantly better than $TPRI_{max}$ in the subgroup of patients with a 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 $TPRI_{max}$ or mPAP/CI slope cut-off points derived from the entire population. The optimal sensitivity and specificity for $TPRI_{max}$ among the obese subgroup was 5.9 WU·m^2 (sensitivity 81, specificity 83), which is higher than the optimal $TPRI_{max}$ cut-off point of 4.6 WU·m^2 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 TPR_{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 WU·m^2 *versus* TPR_{max} >3 WU 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 WU, without adjustment for BSA in future studies.

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