Criteria for diagnosis of exercise pulmonary hypertension

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ABSTRACT The previous definition of exercise pulmonary hypertension (PH) with a mean pulmonary artery pressure (mPAP) >30 mmHg was abandoned because healthy individuals can exceed this threshold at high cardiac output (CO). We hypothesised that incorporating assessment of the pressure–flow relationship using the mPAP/CO ratio, *i.e.* total pulmonary resistance (TPR), might enhance the accuracy of diagnosing an abnormal exercise haemodynamic response.

Exercise haemodynamics were evaluated in 169 consecutive subjects with normal resting mPAP ⩽20 mmHg. Subjects were classified into controls without heart or lung disease (n=68) *versus* patients with pulmonary vascular disease (PVD) (n=49) and left heart disease (LHD) (n=52).

TPR and mPAP at maximal exercise produced diagnostic accuracy with area under the receiver operating curve of 0.99 and 0.95, respectively, for discriminating controls *versus* patients with PVD and LHD. The old criterion of mPAP >30 mmHg had sensitivity of 0.98 but specificity of 0.77. Combining maximal mPAP >30 mmHg and TPR >3 mmHg·min·L^{-1} retained sensitivity at 0.93 but improved specificity to 1.0. The accuracy of the combined criteria was high across different age groups, sex, body mass index and diagnosis (PVD or LHD).

Combining mPAP >30 mmHg and TPR >3 mmHg·min·L^{-1} is superior to mPAP >30 mmHg alone for defining a pathological haemodynamic response of the pulmonary circulation during exercise.

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Introduction

The current haemodynamic definition of pulmonary hypertension (PH) is a mean pulmonary artery pressure (mPAP) ⩾25 mmHg at rest [1]. However, patients with a mild form of pulmonary vascular disease (PVD) or left heart disease (LHD) might fail to meet this resting diagnostic threshold, but develop haemodynamic derangement characteristic of PH only during exercise, together with effort dyspnoea [2, 3].

Following the 4th (2008) [4] and 5th (2013) [1] World Symposia on PH, the definition of exercise PH of mPAP >30 mmHg was abandoned because this threshold was not sufficiently supported by available evidence. Indeed, mPAP can exceed 30 mmHg in healthy subjects during maximal supine exercise at high cardiac outputs (COs) [5]. Thus, the PH scientific community has recommended that further research is required to delineate a robust definition for exercise PH, and to develop a standardised protocol for exercise haemodynamic testing of the pulmonary circulation [1].

Disproportionate increase in mPAP, induced by CO augmentation during exercise, reflects either increased pulmonary vascular resistance (PVR) to blood flow caused by pulmonary vascular remodelling in PVD or the upstream transmission of excessive left atrial pressure in LHD [6]. Thus, assessment of the pressure–flow relationship using the mPAP/CO ratio, *i.e.* total pulmonary resistance (TPR), at maximal exercise should be helpful for distinguishing the normal condition *versus* PVD or LHD.

Based on analysis of noninvasive and invasive haemodynamic data from the literature, both Naeije *et al.* [6] and Lewis *et al.* [7] have recently proposed that TPR should not exceed 3 mmHg·min·L^{-1} or Wood units (WU) during maximal supine exercise in healthy subjects. However, further clinical validation is required to determine the optimal haemodynamic criteria for diagnosing a pathological response of the pulmonary circulation during exercise.

Therefore, in the present study, we compared the haemodynamic response during dynamic supine exercise in three groups of subjects, all of whom had normal mPAP ⩽20 mmHg at rest [1]: 1) controls without heart and lung disease; 2) patients with PVD; and 3) patients with LHD. Our aim was to determine the respective diagnostic accuracies and optimal cut-offs of pulmonary haemodynamic variables (mPAP, PVR, TPR) during exercise for discriminating controls from patients with PVD or LHD. Part of this study has previously been presented at the American Thoracic Society (2012) in the form of an abstract [8].

Methods

Study population

This retrospective study was approved by the ethics board of the Université Paris-Sud (Le Kremlin-Bicêtre, France) (approval no. 9708) and informed consent was obtained from all patients. We extracted the cardiac catheter laboratory record of consecutive patients referred to the French National Reference Centre for Severe Pulmonary Hypertension (Le Kremlin-Bicêtre, France), who underwent exercise haemodynamic testing between January 2005 and November 2013. Amongst a total of 319 patients with exercise haemodynamic data, 169 patients had normal resting pulmonary haemodynamics (defined as mPAP ⩽20 mmHg and pulmonary artery wedge pressure (PAWP) <15 mmHg) [1] and were included in the present study.

Subjects with normal resting haemodynamics were classified into three groups according to diagnostic investigations and clinical information (fig. 1).

Control group

This group included 68 subjects undergoing right heart catheterisation (RHC) for investigation of dyspnoea of unknown origin, who otherwise had no apparent disease affecting the heart of lungs. Subjects in this group required fulfilment of 1) normal findings on lung function testing (forced expiratory volume in 1 s (FEV_1) >80%, forced vital capacity (FVC) >80% and total lung capacity (TLC) >80%) and cardiac echocardiography, no significant parenchymal lung disease on thoracic computed tomography scan, and normal ventilation-perfusion scintigraphy; 2) none of the following risk factors for PVD: connective tissue disorder, sickle cell disease, HIV infection, portal hypertension, chronic thromboembolic disease, or familial history of pulmonary arterial hypertension (PAH); and 3) PAWP <20 mmHg during maximal exercise [9].

PVD group

This group included 49 patients with proven PVD, normal resting haemodynamics and PAWP <20 mmHg during maximal exercise [9]. The diagnosis of PVD was confirmed by either 1) previous invasive confirmation of resting pre-capillary PH with haemodynamic amelioration following therapy (n=5); 2) evolution to resting pre-capillary PH during follow-up (n=5); 3) documentation of pulmonary chronic thromboembolic disease by positive ventilation–perfusion scintigraphy with vascular obstruction on

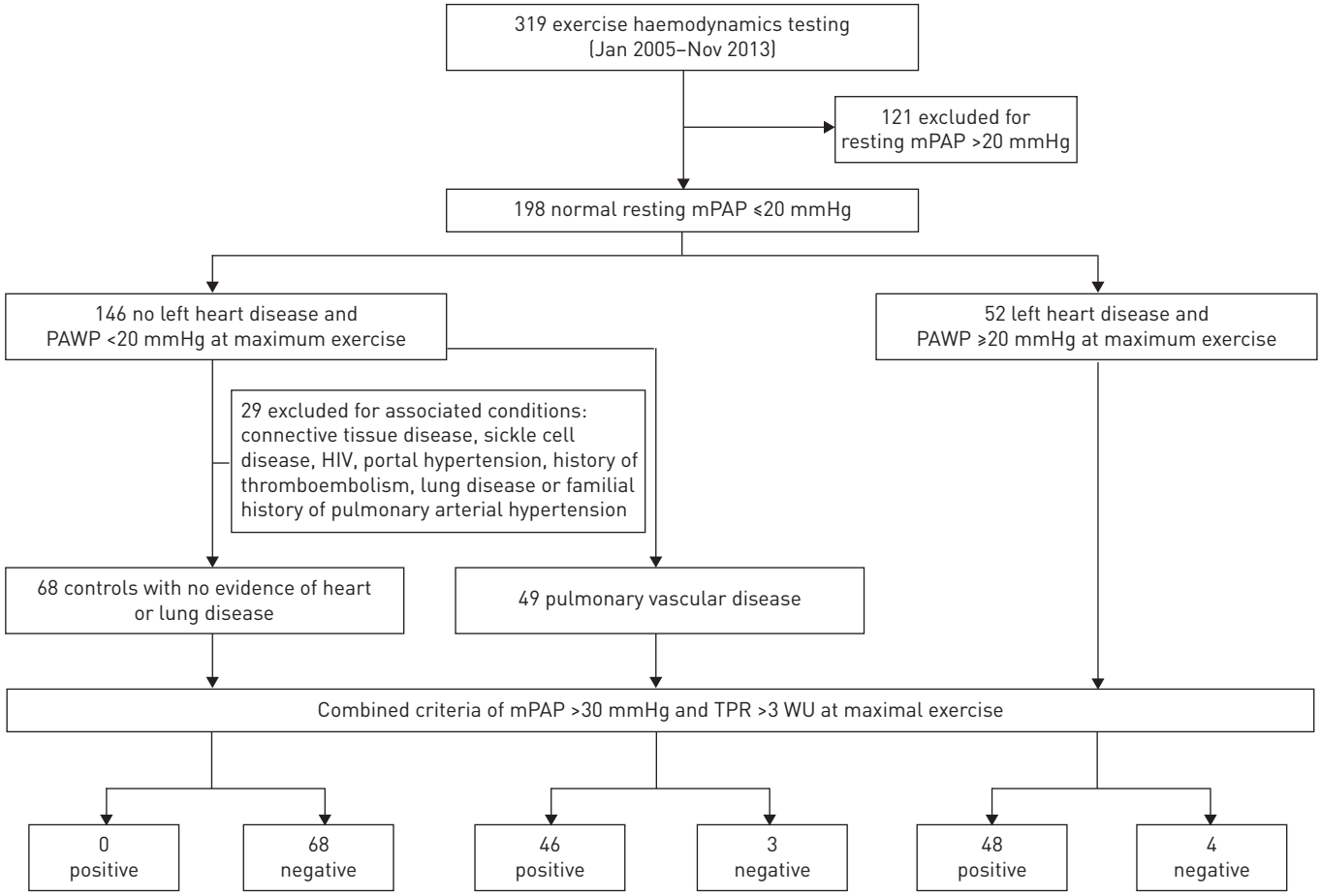

FIGURE 1 Flow diagram of patient population for study inclusion. mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; TPR: total pulmonary resistance.

pulmonary angiography (n=35); or 4) lung biopsy consistent with diagnosis of pulmonary venoocclusive disease (n=4).

LHD group

This group included 52 patients with normal resting haemodynamics and PAWP ⩾20 mmHg during maximal exercise [9]. Causes of LHD included heart failure with preserved ejection fraction (n=30), valvular disease (n=10) and connective tissue disease (n=12).

Historical healthy volunteers group

This group included 78 subjects from 15 studies [10–24]. From these studies, we analysed available data on mPAP and CO at rest and at maximal supine exercise.

Exercise haemodynamic protocol

Haemodynamic evaluation was carried out in supine position. The electrocardiogram and arterial oxygen saturation measured by pulse oximetry were monitored continuously. Systemic arterial pressure was measured by a cuff sphygmomanometer. Pulmonary haemodynamic measurements were obtained with a balloon-tipped, double-lumen, fluid-filled 7 Fr Swan Ganz catheter *via* either the brachial or jugular vein approach. Zero reference was set at the midchest level; [25] CO was measured using the thermodilution technique and three values differing by <10% were averaged.

Dynamic exercise was performed with subjects in supine position on an electronically braked lower limb cycle ergometer (Cycline 100; Tecmachine, Andrezieux-Boutheon, France) secured to the catheterisation table. Subjects were encouraged to cycle at a rate of 60 revolutions·min^{-1} until exhaustion or appearance of exercise-limiting symptoms. mPAP, PAWP and CO were measured at baseline and at the following stages: legs on cycle pedal, unloaded pedalling (0 W) and at constant workload increments of 10–30 W depending

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on estimated exercise capacity. Each exercise stage averaged 3–5 min and the number of work steps was determined for each individual to reach the maximum within 10–15 min of exercise. Pressure measurements were averaged over the respiratory cycle [26] and all measurements were obtained at steady state (*i.e.* stable mPAP and heart rate) during the last 1–2 min of each exercise step. Pulmonary vascular resistance (PVR) was calculated as (mPAP−PAWP)/CO and TPR as mPAP/CO. Pulmonary haemodynamics (mPAP, PAWP, CO, PVR and TPR) obtained at maximal exercise were defined as $mPAP_{max}$, $PAWP_{max}$, CO_{max}, PVR_{max} and TPR_{max}, respectively. Although our exercise protocol was developed before the recommendation [1, 4] to abandon the old criteria of exercise PH, all haemodynamics exercise tests were continued until exhaustion and none was terminated because mPAP was noted to be higher than 30 mmHg.

Statistical analysis

Data are presented as means±SD. Comparisons between controls, PVD and LHD patients for data at rest and at maximum exercise level were performed using ANOVA followed by a Newman–Keuls test. Receiver operating characteristic (ROC) analyses were performed to evaluate the diagnostic performance of mPAP, PVR and TPR values at rest or maximal exercise, to discriminate between controls or healthy volunteers and patients with PVD and/or LHD. The comparison of areas under the ROC curves (AUC) was performed using the method by HANLEY and MCNEIL [27]. From the ROC analysis, the best cut-off values for each variable were identified at the point where the sum of sensitivity and specificity was the highest according to the Youden index: (sensitivity+specificity)−1 [28]. Sensitivity, specificity, accuracy (number of correct assessments/number of all assessments) and positive and negative predictive values for each cut-off value for were calculated. Logistic regression analysis was performed to assess whether mPAP, TPR and PVR at maximal exercise independently provided diagnostic prediction. A p-value <0.05 was considered significant. All statistical analyses were performed using Statel (Ad Science, Paris, France). The study is reported according to the Standards for the Reporting of Diagnostic accuracy studies (STARD) criteria.

Results

Resting haemodynamics

Resting heart rate, right atrial and systemic arterial pressures were similar in control, LHD and PVD groups. CO was lower and mPAP higher in both PVD and LHD groups resulting in higher TPR and PVR than in control group. Upper limits (mean+2SD) of TPR and PVR in the control group were 3.5 WU and 2.2 WU, respectively (table 1).

TABLE 1 Demographics and haemodynamic variables at rest and maximal exercise

	Controls	PVD	LHD
Subjects n	68	49	52
Age years	46.1±14.5	55.8±13.9$^{\#}$	61.1±11$^{\#,\P}$
Female sex %	60	65	79
Body mass index kg·m^{-2}	25.8±5.0	23.6±3.8	26.6±5.2
Work max W	63.2±30.5	47.5±20.4$^{\#}$	45.1±26.4$^{\#}$
mPAP−CO points n	5.5±2.3	5.2±2.2	5.2±1.8
$mPAP_{rest}$ mmHg	14.7±3.3	17.9±2.0$^{\#}$	17.1±2.1$^{\#}$
$mPAP_{max}$ mmHg	26.8±5.2	37.3±5.0$^{\#}$	41.2±7.0$^{\#,\P}$
$PAWP_{rest}$ mmHg	6.9±3.3	5.7±3.1	8.2±3.1$^{\#,\P}$
$PAWP_{max}$ mmHg	11.2±3.9	11.2±3.5	27.4±4.6$^{\#,\P}$
$mPAP_{rest}$−$PAWP_{rest}$ mmHg	7.8±2.9	12.1±3.2$^{\#}$	9±3.2$^{\#,\P}$
$mPAP_{max}$−$PAWP_{max}$ mmHg	14.9±5	26.4±6.1$^{\#}$	13.8±6.6$^{\#,\P}$
CO_{rest} L·min^{-1}	6.7±1.3	5.3±1.2$^{\#}$	5.5±1.2$^{\#}$
CO_{max} L·min^{-1}	13.4±2.8	10.2±2.4$^{\#}$	9.7±2.4$^{\#}$
TPR_{rest} WU	2.3±0.6	3.5±0.8$^{\#}$	3.3±0.8$^{\#}$
TPR_{max} WU	2.1±0.5	3.8±0.9$^{\#}$	4.4±1.2$^{\#,\P}$
PVR_{rest} WU	1.2±0.5	2.4±0.8$^{\#}$	1.7±0.7$^{\#,\P}$
PVR_{max} WU	1.1±0.4	2.7±0.9$^{\#}$	1.5±0.7$^{\#,\P}$

Data are presented as mean±SD. PVD: pulmonary vascular disease; LHD: left heart disease; mPAP: mean pulmonary artery pressure; CO: cardiac output; $mPAP_{rest}$: mPAP at rest; $mPAP_{max}$: mPAP at maximal exercise; $PAWP_{rest}$: pulmonary artery wedge pressure at rest; $PAWP_{max}$: pulmonary artery wedge pressure at maximal exercise; CO_{rest}: CO at rest; CO_{max}: CO at maximal exercise; TPR_{rest}: total pulmonary resistance at rest; TPR_{max}: total pulmonary resistance at maximal exercise; PVR_{rest}: pulmonary vascular resistance at rest; PVR_{max}: pulmonary vascular resistance at maximal exercise. $^{\#}$: p<0.05 *versus* controls; ¶: p<0.05 *versus* PVD.

Exercise haemodynamics

In all patients, the exercise test was well tolerated and was terminated because of exhaustion. Responses in heart rate and systemic blood pressure were similar in the three groups. Peak workload and CO_{max} were higher in controls. Upper limits (mean+2SD) of $mPAP_{max}$ and $PAWP_{max}$ in the control group were 37 and 19 mmHg, respectively. $PAWP_{max}$ was similar in control and PVD but higher in LHD. Increase in $mPAP_{max}$ in PVD was intermediate between LHD and controls (table 1). In the control group, 18 (26%) of 68 subjects had a $mPAP_{max}$ exceeding 30 mmHg.

The upper limits of TPR_{max} and PVR_{max} in the control group were 3.1 and 1.9 WU, respectively. Individual mPAP and CO responses from rest to maximal exercise for control, PVD and LHD groups are shown in Figure s1 of the online supplementary material.

Diagnostic accuracy of haemodynamics variables for discriminating PVD and LHD from controls

Resting values of mPAP, PVR and TPR had low diagnostic specificity for differentiating PVD and LHD from controls. In contrast, TPR_{max} and $mPAP_{max}$ had high diagnostic accuracy with AUC values of 0.99 and 0.95, respectively, for differentiating PVD and LHD from controls (table 2, fig. 2). The ROC-derived optimal cut-off values for TPR_{max} and $mPAP_{max}$ were 2.97 WU, and 31 mmHg, respectively. The use of these cut-off values resulted in a sensitivity of 0.98 (95% CI 0.93–1.0) for $mPAP_{max}$ and a specificity of 0.99 (95% CI 0.92–1.0) for TPR_{max}. These findings were consistent with the distribution of the individual values of $mPAP_{max}$ as a function of CO_{max}. Both the mPAP line at 30 mmHg and the mPAP/CO line with a slope of 3 WU separated controls from those with PVD or LHD (fig. 3). Comparing the diagnostic performance of $mPAP_{max}$ and TPR_{max} for different subgroups, no significant differences in ROC AUCs were found for those with age $\leqslant$50 *versus* >50 years, females *versus* males, and PVD *versus* LHD (figure s2; and tables s1 and s2 in the online supplementary material).

In comparison with TPR_{max} and $mPAP_{max}$, the diagnostic accuracy of PVR_{max} was significantly lower, with an AUC of 0.81 (p-value <0.05 compared with both TPR_{max} and $mPAP_{max}$). However, when tested separately in only the PVD group, PVR_{max} had high accuracy (AUC 0.97; optimal cut-off, 2 WU; sensitivity 0.80 (95% CI 0.66–0.89); specificity 0.98 (95% CI 0.92–1.0)). The low diagnostic accuracy of PVR_{max} in LHD (AUC, 0.65) was likely related to the disproportionate increase in PAWP during maximal exercise, with a decrease in PVR in 57% of the patients. Indeed, there was a large overlap of the individual values of transpulmonary gradient (mPAP−PAWP) as a function of CO during exercise between the control and LHD groups (figure s3 in the online supplementary material).

Criteria for exercise PH

Stepwise multivariate logistic regression analysis using PVR_{max}, $mPAP_{max}$ and TPR_{max} showed that $mPAP_{max}$ and TPR_{max} were independent predictors for the diagnosis of PVD or LHD (table s3 in the online supplementary material). In order to propose a simple and unified definition of PH at exercise, we subsequently chose the criteria of 30 mmHg for $mPAP_{max}$ and 3 WU for TPR_{max}. A test was considered positive only if both $mPAP_{max}$ was >30 mmHg and TPR_{max} was >3 WU, and negative in any other circumstances. Using the combined criteria of $mPAP_{max}$ and TPR_{max}, we obtained high diagnostic accuracy with overall sensitivity of 0.93 (95% CI 0.86–0.96) and specificity of 1.0 (CI 95% 0.95–1.0). The diagnostic accuracy of the combined criteria remained robust across different sex, age, or diagnosis (PVD or LHD) (table 3). Diagnostic accuracy of the combined criteria was also high in the 35 patients with BMI>30 with sensitivity of 0.89 (95% CI 0.74–1.0) and specificity of 1.0 (CI 95% 0.82–1.0).

TABLE 2 Diagnostic performance of resting and exercise haemodynamic variables

	$mPAP_{rest}$ mmHg	PVR_{rest} WU	TPR_{rest} WU	$mPAP_{max}$ mmHg	PVR_{max} WU	TPR_{max} WU
AUC	0.76±0.04	0.81±0.03	0.88±0.03	0.95±0.02	0.81±0.03	0.99±0.01
Optimal cut-off	14	1.25	2.61	31	2.00	2.97
Sensitivity (95% CI)	0.92 (0.85–0.96)	0.86 (0.78–0.92)	0.84 (0.76–0.90)	0.98 (0.93–1.0)	0.48 (0.38–0.57)	0.94 (0.88–0.97)
Specificity (95% CI)	0.43 (0.32–0.54)	0.65 (0.53–0.75)	0.78 (0.67–0.86)	0.77 (0.65–0.85)	0.98 (0.92–1.0)	0.99 (0.92–1.0)

Data are presented as mean±SD, unless otherwise stated. $mPAP_{rest}$: mean pulmonary artery pressure at rest; PVR_{rest}: pulmonary vascular resistance at rest; TPR_{rest}: total pulmonary resistance at rest; $mPAP_{max}$: mean pulmonary artery at maximal exercise; PVR_{max}: pulmonary vascular resistance at maximal exercise; TPR_{max}: total pulmonary resistance at maximal exercise; AUC: area under the receiver operating curve.

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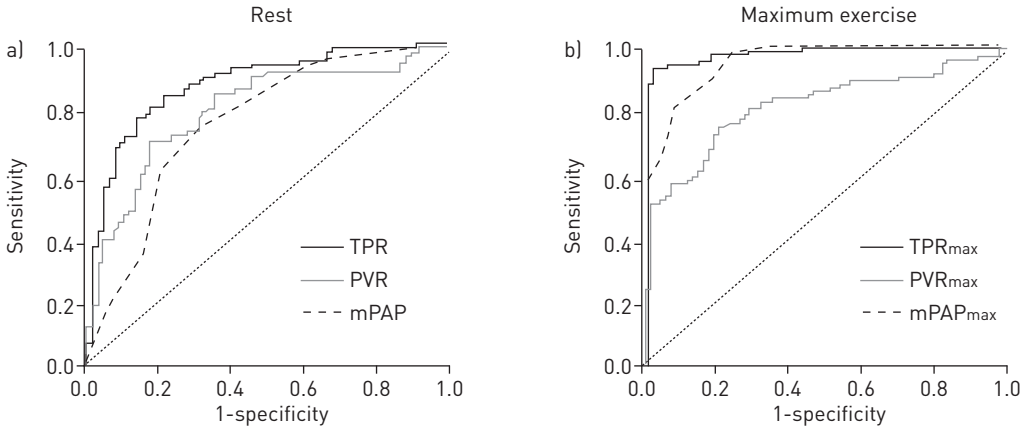

FIGURE 2 Receiver operating characteristic curves of pulmonary haemodynamic variables at rest and maximum exercise for discriminating controls *versus* disease group (pulmonary vascular disease and left heart disease). Overall, resting haemodynamic variables (a) performed poorly compared to exercise haemodynamic variables. For exercise haemodynamic variables (b), the performance of total pulmonary resistance (TPR) and mean pulmonary artery pressure (mPAP) obtained at maximal exercise (TPR_{max} and $mPAP_{max}$, respectively) were superior to pulmonary vascular resistance (PVR) at maximal exercise (PVR_{max}).

Submaximal versus *maximal exercise testing*

Because exercise elicited a steeper increment in the mPAP *versus* CO plot in LHD and PVD, the mPAP and TPR criteria of PH at exercise were met at submaximal exercise level (usually between 10 and 30 W) in 63% of patients. Moreover, all these LHD and PVD patients also fulfilled criteria at maximal exercise.

Validation of criteria for exercise PH with historical healthy volunteers

Comparing our control subjects with historical healthy volunteers, both groups had similar resting and exercise mPAP, CO and TPR (table 4). Using historical healthy volunteers as an independent validation cohort, both TPR_{max} and $mPAP_{max}$ had excellent diagnostic accuracies with AUC values of 0.99 and 0.96, respectively, for the diagnosis of PVD or LHD. Optimal cut-offs were also similar (30 mmHg for $mPAP_{max}$ and 2.97 WU for TPR_{max}). When the combined criteria of $mPAP_{max}$ >30 mmHg and TPR_{max} >3 WU were applied to differentiate historical healthy volunteers from PVD and LHD patients, sensitivity of 0.90 (95%CI 0.84–0.95) and a specificity of 1.0 (95% CI 0.95–1.0) were attained.

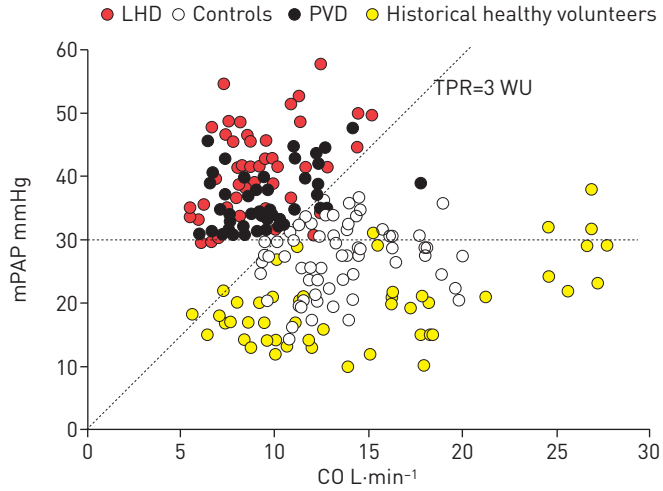

FIGURE 3 Relationship between exercise mean pulmonary artery pressure (mPAP) and cardiac output (CO). Individual data points represent mPAP and CO reached at maximal exercise stratified by subjects with pulmonary vascular disease (PVD), left heart disease (LHD), control subjects and historical healthy volunteers. It can be seen that the total pulmonary resistance (TPR) line with a slope of 3 Wood units (WU) differentiated the diseased (PVD and LHD) and non-diseased groups (controls and historical volunteers).

TABLE 3 Diagnostic accuracy of the association of the two criteria: $mPAP_{max}$ >30 mmHg and TPR_{max} >3 WU for entire study population and subgroups[#]

	n	Sensitivity (95% CI)	Specificity (95% CI)	NPV	PPV	Accuracy
All	169	0.93 (0.86–0.96)	1.0 (0.95–1.0)	0.91	1	0.96
Sex						
Male	55	0.82 (0.68–0.96)	1.0 (0.88–1.0)	0.84	1	0.90
Female	114	0.93 (0.87–0.99)	1.0 (0.91–1.0)	0.89	1	0.96
Age						
>50 years	95	0.94 (0.89–0.99)	1.0 (0.87–1.0)	0.87	1	0.96
⩽50 years	74	0.81 (0.67–0.95)	1.0 (0.92–1.0)	0.87	1	0.92
Diagnosis						
PVD	49	0.94 (0.84–0.98)	1.0 (0.95–1.0)	0.92	1	0.95
LHD	52	0.92 (0.82–0.97)	1.0 (0.95–1.0)	0.94	1	0.97

[#]: the test was considered positive only if both criteria $mPAP_{max}$ >30 mmHg and TPR_{max} >3 WU were satisfied. $mPAP_{max}$: mean pulmonary artery at maximal exercise; TPR_{max}: total pulmonary resistance at maximal exercise; NPV: negative predictive value; PPV: positive predictive value; PVD: pulmonary vascular disease; LHD: left heart disease.

Discussion

In the present study, we demonstrate that in subjects with strictly normal resting mPAP ⩽20 mmHg, the combined criteria of mPAP >30 mmHg and TPR >3 WU during supine dynamic exercise differentiated with high accuracy those with PVD or LHD from control subjects. Compared to the previous (abandoned)

TABLE 4 Haemodynamic variables in control patients from this study and in healthy volunteers from 15 historical studies

	Controls	Volunteers	p value
<50 years			
Subjects n	42	62	
$mPAP_{rest}$ mmHg	14.9±3.2	13.9±2.9	NS
CO_{rest} L·min^{-1}	6.9±1.3	7.1±1.9	NS
TPR_{rest} WU	2.2±0.6	2.05±0.6	NS
$mPAP_{max}$ mmHg	26.4±5.1	22.5±4.2	p<0.01
CO_{max} L·min^{-1}	13.8±2.7	14.9±3.1	NS
TPR_{max} WU	2.1±0.6	2.0±0.6	NS
51–70 years			
Subjects n	19	7	
$mPAP_{rest}$ mmHg	13.6±3.1	15.7±1.6	NS
CO_{rest} L·min^{-1}	6.3±1.3	5.9±1.4	NS
TPR_{rest} WU	2.1±0.5	2.8±0.8	p<0.01
$mPAP_{max}$ mmHg	26.3±5.1	26.5±7.8	NS
CO_{max} L·min^{-1}	13.8±2.7	12.2±2.2	NS
TPR_{max} WU	2.1±0.6	2.1±0.9	NS
>70 years			
Subjects n	7	9	
$mPAP_{rest}$ mmHg	17.3±2.8	15.4±2.5	p<0.05
CO_{rest} L·min^{-1}	6.3±1.0	5.6±0.6	NS
TPR_{rest} WU	2.8±0.6	2.7±0.6	NS
$mPAP_{max}$ mmHg	30.1±5.3	33.9±7.8	NS
CO_{max} L·min^{-1}	13.8±2.7	12.9±1.5	NS
TPR_{max} WU	2.5±0.4	2.6±0.5	NS

Data are presented as mean±SD, unless otherwise stated. $mPAP_{rest}$: mean pulmonary artery at rest; $mPAP_{max}$: mean pulmonary artery at maximal exercise; CO_{rest}: cardiac output at rest; CO_{max}: cardiac output at maximal exercise; TPR_{rest}: total pulmonary resistance at rest; TPR_{max}: total pulmonary resistance at maximal exercise; PVR_{rest}: pulmonary vascular resistance at rest; PVR_{max}: pulmonary vascular resistance at maximal exercise.

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definition of exercise PH which utilised a mPAP >30 mmHg as the sole criterion, the inclusion of TPR >3 WU significantly improved diagnostic specificity whilst maintaining adequate sensitivity.

Recently, NAEIJE *et al.* [6] and LEWIS *et al.* [7] analysed the main available non-invasive and invasive haemodynamic data in control subjects and both concluded that mPAP should not exceed 30 mmHg at a CO of less than 10 L·min^{-1} (or TPR >3 WU) in health. This analysis was based on a relatively small number of invasive measurements although both invasive and noninvasive data were in agreement. Thus, the strength and novelty of the present study should be viewed as the incorporation of a disease population with PVD and LHD, allowing the diagnostic performance of the criteria for exercise PH to be assessed and optimal cut-off values to be obtained. Furthermore, the use of exclusively invasive haemodynamic measurements in a relatively large number of subjects should also be viewed as a strength of the present study.

Optimal diagnostic cut-offs derived from the ROC analysis for differentiating PVD and LHD from controls were 31 mmHg for $mPAP_{max}$, *i.e.* the old criterion of exercise PH, and 3 WU for TPR_{max}, namely the upper limit of TPR in healthy subjects at maximal exercise reported from the literature [6, 7]. Because logistic regression analysis showed that $mPAP_{max}$ and TPR_{max} were independent variables contributing to diagnostic prediction, the combination of the two criteria may be used to define of PH at exercise. The present study extends the results of our preliminary study in PVD [8] to a larger number of patients including patients with LHD. Incorporation of TPR_{max} >3 WU into the diagnostic criteria overcame the lack of specificity suffered by the old exercise criterion, since healthy individuals can frequently exceed a mPAP of 30 mmHg at high COs, which was verified in 26% of our control subjects. Furthermore, the diagnostic accuracy of the combined criteria remained robust across different sex, age, BMI or diagnosis (PVD or LHD).

This disproportionate increase in mPAP in patients with mild forms of PVD or LHD is a reflection of either increased resistance to blood flow caused by pulmonary vascular remodelling in PVD or the upstream transmission of excessive left atrial pressure in LHD [6]. From a physiological perspective, the definition of exercise PH should therefore include not only a measure of pressure but also an assessment of the total resistance faced by the right ventricle to generate pulmonary blood flow. It is of interest to note that the combined criteria resulted in similarly high diagnostic accuracy for both the PVD and LHD groups, despite their distinct pathophysiology. Thus, it can be viewed that the unifying haemodynamic derangement of both disease groups is a steep pulmonary artery pressure–flow relationship during exercise, which is encapsulated by the mPAP and TPR thresholds at 30 mmHg and 3 WU, respectively.

Interestingly, the combined criteria were met at low workloads in most patients, an observation that enhances the feasibility of haemodynamic exercise testing. Thus, the test may be stopped at submaximal workload, if mPAP surpasses 30 mmHg at a CO of less than 10 L·min^{-1} (table 5). We suggest to exercise symptomatic patients with mPAP <25 mmHg including those with mPAP between 21 and 24 mmHg, because recent data indicate that the majority of these patients will display an abnormal pulmonary vascular response during exercise [29].

TABLE 5 Proposed standardised protocol of exercise haemodynamic testing

1. Include patients with resting mPAP<25 mmHg
2. Brachial or jugular vein approach
3. Dynamic exercise in supine position on bicycle
4. Number of work step and work increment to reach the maximum within 10–15 min
5. Successive stages: baseline supine, legs on cycle pedal, unloaded pedalling (0 W) and at constant workload increments of 10–30 W depending on estimated exercise capacity (usually 1–3 work load steps)
6. Measurement of mPAP and PAWP averaged over the respiratory cycle and CO in triplicate using thermodilution or direct Fick method
7. Measure mPAP, PAWP and CO at steady state at each step: *i.e.* unchanged mPAP and heart rate; usually during the last 2 min of each exercise step
8. Interpretations
   - If at submaximal workload, mPAP >30 mmHg with CO <10 L·min^{-1}: (TPR >3 WU) you can stop the test: exercise PH
   - If not, continue the test until maximum tolerable workload:
     - If TPR_{max} ⩽3 WU with mPAP >30 mmHg: no exercise PH
     - If TPR_{max} ⩽3 WU with mPAP ⩽30 mmHg: no exercise PH
     - If TPR_{max} >3 WU with mPAP ⩽30 mmHg: no exercise PH
     - If TPR_{max} >3 WU with mPAP >30 mmHg: exercise PH

mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; CO: cardiac output; TPR_{max}: total pulmonary resistance at maximal exercise; PH: pulmonary hypertension.

Study limitations

The study population consisted of symptomatic patients referred to a single specialised pulmonary vascular unit for investigation of either suspected PH or dyspnoea of unknown origin. However, we utilised strict clinical definitions for the disease and control groups. Each control subject underwent extensive investigations in order to eliminate heart or lung diseases. Moreover, our control group displayed similar resting and exercise hemodynamic values compared to historical healthy volunteers reported in the literature. Our control group was younger in age compared to the PVD and LHD groups, but diagnostic performance remained high when analysis was stratified by age groups.

For the LHD group, we utilised an exercise PAWP $\geqslant$20 mmHg as part of the case definition. We acknowledge that there remains no consensus regarding the age-dependent normal limits of exercise PAWP but a threshold of 20 mmHg has also been used by other authors in prior studies for the diagnosis of pulmonary venous hypertension during exercise [2, 9]. Exceeding a PAWP of 20 mmHg during exercise will increase the likelihood of reaching criteria for exercise PH, although this is not universal [9]. Finally, it must be kept in mind that measurement of PAWP during exercise can be technically challenging and pulmonary vascular pressure and flow measurements may inherently display some imprecision when measured by fluid-filled catheters and thermodilution technique, respectively [30]. For the PVD group, the majority of patients had chronic thromboembolic disease although subgroup analysis between those with and without thromboembolic disease did not demonstrate any significant differences in their haemodynamic response during exercise (data not presented).

In the present study, we excluded patients with lung disease where intrathoracic pressures may increase during exercise and influence pulmonary vascular pressure measurements [26]. Thus, our criteria require confirmation in patients with relevant lung disease. Relatively few elderly subjects >70 years were included in our study and the proposed criteria for exercise PH should be also used with caution in this population.

Finally, this was a retrospective, cross-sectional study designed to assess the diagnostic performances of different haemodynamic variables during exercise for discriminating controls *versus* those with PVD and LHD. Therefore, the proposed haemodynamic criteria require prospective validation in an independent cohort of patients.

Conclusions

In conclusion, a standardised haemodynamic protocol for evaluating the pulmonary vascular response during exercise can be proposed. In subjects with resting mPAP $\leqslant$20 mmHg, exercise haemodynamics showing maximal mPAP >30 mmHg and TPR >3 mmHg·min·L^{-1} has high sensitivity and specificity for discriminating controls *versus* patients with PVD and LHD. A physiologically rational and robust definition of exercise PH will facilitate the early identification of PVD and LHD, potentially improving future treatment outcomes in these conditions.

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