The association between resting and mild-to-moderate exercise pulmonary artery pressure

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ABSTRACT: The mean pulmonary artery pressure ($\bar{P}_{pa}$) achieved on mild-to-moderate exercise is age related and its haemodynamic correlates remain to be documented in patients free of pulmonary hypertension (PH).

Our retrospective study involved patients free of PH investigated in our centre for possible pulmonary vascular disease between January 1, 2007 and October 31, 2009 who underwent right heart catheterisation at rest and during supine exercise up to 60 W. The 38 out of 99 patients aged <50 yrs were included and a $\bar{P}_{pa}$ of 30 mmHg was considered the upper limit of normal on exercise.

The 24 subjects who developed $\bar{P}_{pa} > 30$ mmHg on exercise had higher resting $\bar{P}_{pa}$ (19 ± 3 versus 15 ± 4 mmHg) and indexed pulmonary vascular resistance (PVRi; 3.4 ± 1.5 versus 2.2 ± 1.1 WU·m²; $p < 0.05$) than the remaining 14 subjects. Resting $\bar{P}_{pa} > 15$ mmHg predicted exercise $\bar{P}_{pa} > 30$ mmHg with 88% sensitivity and 57% specificity. The eight patients with resting $\bar{P}_{pa}$ 22–24 mmHg all had exercise $\bar{P}_{pa} > 30$ mmHg.

In subjects aged <50 yrs investigated for possible pulmonary vascular disease and free of PH, patients with mild-to-moderate exercise $\bar{P}_{pa} > 30$ mmHg had higher resting PVRi and higher resting $\bar{P}_{pa}$, although there was no resting $\bar{P}_{pa}$ threshold value that could predict normal response on mild-to-moderate exercise. The clinical relevance of such findings deserves further long-term follow-up studies.

KEYWORDS: Cardiac output, pulmonary hypertension, pulmonary vascular disease, right heart catheterisation

For the last 30 yrs, the diagnosis of pulmonary hypertension (PH) depended on either a resting mean pulmonary artery pressure ($\bar{P}_{pa}$) of >25 mmHg or an increase in $\bar{P}_{pa}$ on exercise to >30 mmHg, with the pulmonary capillary wedge pressure ≤ 15 mmHg in the subgroup of pre-capillary PH. Since the 4th World Conference on PH, new guidelines have recommended that the exercise criterion should be eliminated [1, 2], given both the marked age-dependency of “normal” $\bar{P}_{pa}$ threshold on exercise [3] and the paucity of robust data supporting its clinical relevance [1, 2]. The age-dependency of $\bar{P}_{pa}$ is much less at rest [3–7], such that a common 20.6 mmHg upper limit of normal (ULN) was suggested in supine healthy subjects [3]. Though a $\bar{P}_{pa}$ of ≥ 21 mmHg is beyond the normal range (mean +2 standard deviations) and may be

suspicious of pulmonary vascular disease, a small but significant proportion of apparently normal individuals will have a $\bar{P}_{pa} \geq 21$ mmHg and they will outnumber the previously documented proportion of patients with PH [3]. As a result, new guidelines have defined pulmonary hypertension by a $\bar{P}_{pa}$ at rest ≥ 25 mmHg (mean +3 standard deviations), and have also highlighted the fact that studies focusing on patients with resting $\bar{P}_{pa}$ of 21–24 mmHg are especially needed [1–3].

Numerous studies have documented the high percentage of patients at high risk for PH exhibiting elevation of $\bar{P}_{pa}$ on exercise >30 mmHg while their $\bar{P}_{pa}$ was normal at rest [8–16], and this may be considered as an early manifestation of pulmonary vasculopathy [12, 14, 17, 18]. Most of these studies

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had been carried out in middle-aged patients, at a time when normal $\bar{P}_{pa}$ values during exercise have not yet been defined. Recently, the review of the range of pulmonary haemodynamic responses to exercise in normal subjects by KOVACS *et al.* [3] was timely in alerting the community to the huge amount of available data supporting the “classical” definition of exercise induced PH in patients aged <50 yrs, while the ULN of 30 mmHg was not always supported by the available data in older patients. Thus, the precise relationship between resting $\bar{P}_{pa}$ and the age-related $\bar{P}_{pa}$ responses during mild-to-moderate exercise still deserve further studies in patients free of PH, and this may have implications for improving our understanding of PH pathophysiology.

The present study examined the range of haemodynamic responses in individuals aged <50 yrs with resting $\bar{P}_{pa}$ <25 mmHg being investigated for possible pulmonary vascular disease in our institution who underwent measurement of pulmonary haemodynamic responses to mild-to-moderate exercise while supine.

METHODS

This was a retrospective study. We extracted the catheter laboratory records of all patients who underwent diagnostic right heart catheterisation at the Centre National de Référence de l'Hypertension Pulmonaire Sévère, Hôpital Antoine Bécclère, Assistance Publique Hôpitaux de Paris, Université Paris-Sud, Paris, France over a 34-month period (January 1, 2007–October 31, 2009).

We included patients with a $\bar{P}_{pa}$ at rest of <25 mmHg and a pulmonary artery occlusion pressure (P_{pao}) ≤15 mmHg who

underwent progressive supine exercise test during the right heart catheterisation procedure. Patients with unexplained exertional dyspnoea or an abnormal screening echocardiogram $\bar{P}_{pa}$ were included, as well as patients with a history of probable or possible pulmonary thromboembolic disease being investigated for chronic thromboembolic pulmonary hypertension. As our aim was to examine a “real life” patient population undergoing diagnostic right heart catheterisation, we did not exclude patients with significant comorbidities, including diseases known to carry a risk of PH [1, 2]. We also excluded patients in whom acceptable quality P_{pao} could not be obtained. On exercise, P_{pao} >20 mmHg was considered as abnormal but the corresponding patients were not excluded *a posteriori*. The 6-min walking distance and respiratory and biological tests were obtained according to our routine protocol. Our retrospective study was compliant with requirements of the French Commission Nationale de l'Informatique et des Libertés (CNIL), and right heart catheterisation with exercise is part of the usual care at our institute.

Amongst the 99 eligible patients, only patients aged <50 yrs (n=38) were included in our final analysis and 30 mmHg was considered the ULN on mild-to-moderate exercise [3]. Patients aged ≥50 yrs were excluded, given that KOVACS *et al.* [3] have suggested that an upper limit of 30 mmHg could not be supported by the available data in such subjects. The main risk factors and comorbidities were a previous history of thromboembolic pulmonary disease (n=14, 37%), connective tissue disease (n=8, 21%; namely two lupus and six systemic sclerosis) and anorexigens intake (n=5, 13%) (table 1).

TABLE 1 Characteristics of the study population

	Overall population	$\bar{P}_{pa,ex} \leq 30$ mmHg	$\bar{P}_{pa,ex} > 30$ mmHg	p-value
Subjects n	38	14	24	
Demographic and clinical data				
Females	30 (80)	10 (71)	20 (83)	NS
Age yrs	40 ± 8	40 ± 8	40 ± 8	NS
BSA m ²	1.72 ± 0.22	1.86 ± 0.22	1.63 ± 0.18	<0.01
SAP mmHg	118 ± 17	123 ± 18	116 ± 16	NS
DAP mmHg	76 ± 10	77 ± 9	75 ± 10	NS
fc bpm	76 ± 11	74 ± 12	78 ± 10	NS
Haemoglobin g·dL ⁻¹	13.3 ± 2.0	13.7 ± 1.7	13.2 ± 2.1	NS
BNP pg·mL ⁻¹	31 ± 21	30 ± 8	32 ± 24	NS
6MWD m	505 ± 104	550 ± 100	478 ± 99	0.062
FEV ₁ % pred	86 ± 22	98 ± 20	81 ± 21	0.048
FVC % pred	85 ± 21	94 ± 19	80 ± 21	0.110
DL _{CO} % pred	62 ± 20	74 ± 18	56 ± 19	0.030
Risk factors and comorbidities n				
History of thromboembolic disease	14	6	8	
CTD	8	1	7	
Anorexigens	5	5	0	
Miscellaneous	7	1	6	
None	4	1	3	

Data are presented as n (%) or mean ± SD, unless otherwise stated. $\bar{P}_{pa,ex}$: exercising mean pulmonary arterial pressure; BSA: body surface area. SAP: systolic arterial pressure. DAP: diastolic arterial pressure; fc: cardiac frequency; BNP: brain natriuretic peptide; 6MWD: 6-min walking distance; FEV₁: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; DL_{CO}: diffusing capacity of the lung for carbon monoxide; CTD: connective tissue diseases; NS: not significant.

Patients had baseline haemodynamic measurements showing resting $\bar{P}_{pa} < 25$ mmHg and $P_{pao} \leq 15$ mmHg. They then carried out supine bicycle exercise ergometry [19, 20], including baseline measurements with feet in the pedals but no dynamic exercise followed by a stepwise increase of load. The number of steps and the pattern of increase in load were determined for each individual by the operator's judgement based on the patient's age, comorbidities and clinical response to initial load. As we have concentrated on examining the haemodynamic response at mild-to-moderate exercise, we examined the data obtained < 60 W [3]. As our standard protocol was developed before the new guidelines from the 4th World Conference on PH [1, 2], the exercise was terminated in cases where the $\bar{P}_{pa}$ was noted to be > 30 mmHg. In patients whose exercise was terminated prior to 60 W, either due to symptoms or reaching a $\bar{P}_{pa} > 30$ mmHg, we analysed their response at their highest workload.

Statistics

Data are presented as mean $\pm$ SD. Comparisons at baseline (rest) were performed by using one-way ANOVA followed by unpaired t-test. The haemodynamic effects of exercise were compared between patients with normal and abnormal $\bar{P}_{pa}$ on mild-to-moderate exercise by using a two-way ANOVA (group $\times$ time interaction). Correlations were tested by using the least squares method. Frequency distribution of both sex and $\bar{P}_{pa}$ responses between subgroups were compared using the Chi-squared test. Receiver operating characteristic (ROC) curves (with 95% confidence interval) were constructed for testing the ability of the resting $\bar{P}_{pa}$ to predict mild-to-moderate exercise $\bar{P}_{pa} > 30$ mmHg. A p-value < 0.05 was considered statistically significant. The statistical analysis was performed using StatView 512 software (Abacus concepts, Berkeley, CA, USA), except for ROC curves analysis which was performed by using MedCalc 8.1.0.0 software (Mariakerke, Belgium).

RESULTS

The study population ($n=38$) comprised 30 females and eight males (age $= 40 \pm 8$ yrs); their clinical characteristics are listed in table 1. Median workload was 40 W (mean $\pm$ SD 41 ± 16 W). Overall, 24 out of 38 (63%) of patients developed $\bar{P}_{pa} > 30$ mmHg on mild-to-moderate exercise. As compared with the remaining 14 subjects, the 24 patients who developed $\bar{P}_{pa} > 30$ mmHg on mild-to-moderate exercise had lower body surface area, lower forced expiratory volume in 1 s, and lower diffusing capacity of the lung for carbon monoxide (table 1). Differences in risk factors and comorbidities were also observed between the two groups (table 1). The two groups had similar sex ratio, age, systolic and diastolic arterial pressure, cardiac frequency and haemoglobin and brain natriuretic peptide blood content. The 6-min walking distance was 478 ± 99 m in the 24 patients who developed $\bar{P}_{pa} > 30$ mmHg and 550 ± 100 m in the remaining 14 patients ($p=0.062$) (table 1).

The haemodynamic characteristics of the study population are listed in table 2. Individual haemodynamic data are presented as online supplementary material. The 24 patients who developed $\bar{P}_{pa} > 30$ mmHg on mild-to-moderate exercise had higher resting $\bar{P}_{pa}$ (19 ± 3 versus 15 ± 4 mmHg; $p<0.01$) and higher indexed pulmonary vascular resistance (PVRi) at rest (3.4 ± 1.5 versus 2.2 ± 1.1 WU·m²; $p<0.05$) compared with the remaining 14 subjects, (table 2). They also had similar P_{pao} and cardiac index at

TABLE 2 Haemodynamics at rest and at mild-to-moderate exercise in the study population[#]

	Rest	Mild-to-moderate exercise [*]
P_{ra} mmHg	4 ± 3	Not recorded
$\bar{P}_{pa}$ mmHg	18 ± 4	31 ± 8
P_{pao} mmHg	8 ± 3	12 ± 5
TPG mmHg	10 ± 5	19 ± 7
CI L·min⁻¹·m⁻²	3.49 ± 0.54	6.34 ± 1.13
PVRi WU·m²	2.9 ± 1.5	$3.1 \pm 1.5^+$

Data are presented as mean $\pm$ SD. P_{ra} : right atrial pressure; $\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{pao} : pulmonary arterial occlusion pressure; TPG: transpulmonary pressure gradient; CI: cardiac index; PVRi: pulmonary vascular resistance index. [#]: $n=38$; ^{*}: $p<0.001$ in each case except where indicated; ⁺: not significant. $n=38$.

rest (table 2), and similar right atrial pressure at rest (4 ± 3 versus 5 ± 3 mmHg; $p=NS$).

In the overall study population, there was a weak positive relationship between resting $\bar{P}_{pa}$ and mild-to-moderate exercise $\bar{P}_{pa}$ ($r^2=0.44$; $p<0.001$) (fig. 1). There was no relationship between age and either resting $\bar{P}_{pa}$ or mild-to-moderate exercise $\bar{P}_{pa}$.

Haemodynamic responses to mild-to-moderate exercise in the two subgroups are detailed in table 3 and individual $\bar{P}_{pa}$, P_{pao} and cardiac index values are presented as online supplementary material. Cardiac index increased in a similar way and PVRi remained unchanged in the two subgroups (table 3). Mild-to-moderate differences in P_{pao} changes ($p=0.047$) were documented between the two subgroups. On exercising, two patients had $P_{pao} > 20$ mmHg (25 and 21 mmHg, see online supplementary material) with > 12 mmHg transpulmonary pressure gradient (24 and 13 mmHg, respectively), and both had $\bar{P}_{pa} > 30$ mmHg.

Exercising $\bar{P}_{pa}$ exceeded 30 mmHg in 15 out of 27 (55%) of the patients with resting $\bar{P}_{pa} < 21$ mmHg and in nine out of 11 (82%) of the patients with resting $\bar{P}_{pa}$ between 21 and 24 mmHg ($p=NS$) (table 4). The eight patients with resting $\bar{P}_{pa}$ 22–24 mmHg all had

FIGURE 1. Linear relationship between mean pulmonary arterial pressure whilst exercising ($\bar{P}_{pa,ex}$) and at rest ($\bar{P}_{pa,rest}$). $n=38$; $r^2=0.44$; $p<0.001$.

TABLE 3	Haemodynamic data at rest and while exercising according to the normal/abnormal response of mean pulmonary arterial pressure on mild-to-moderate exercise ($\bar{P}_{pa,ex}$)				
	$\bar{P}_{pa,ex} \leq 30$ mmHg		$\bar{P}_{pa,ex} > 30$ mmHg		Two-way ANOVA p-value
	Rest	Exercise	Rest	Exercise	
Subjects n	14		24		
$\bar{P}_{pa}$ mmHg	15±4	23±5	19±3**	36±5	0.0001
P_{pao} mmHg	8±4	10±4	8±3#	13±5	0.047
TPG mmHg	8±4	13±5	11±4*	22±6	0.0001
CI L·min ⁻¹ ·m ⁻²	3.62±0.56	6.26±1.24	3.41±0.52#	6.38±1.09	0.30
PVRI WU·m ²	2.2±1.1	2.1±1.0	3.4±1.5*	3.7±1.5	0.25

Data are presented as mean±SD, unless otherwise stated. $\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{pao} : pulmonary arterial occlusion pressure; TPG: transpulmonary pressure gradient; CI: cardiac index; PVRI: pulmonary vascular resistance index. #: not significant. *: p<0.05; **: p<0.01 versus resting values in the $\bar{P}_{pa,ex} \leq 30$ mmHg subgroup.

an exercising $\bar{P}_{pa} > 30$ mmHg. ROC curve analysis (fig. 2) indicated that a resting $\bar{P}_{pa} > 15$ mmHg predicted an exercising $\bar{P}_{pa} > 30$ mmHg with 88% sensitivity (95% CI 68–97%) and 57% specificity (95% CI 29–82%).

DISCUSSION

Our retrospective study was performed in 38 patients aged <50 yrs, free of PH (resting $\bar{P}_{pa} < 25$ mmHg), being investigated in our centre for possible vascular disease between January 1, 2007 and October 31, 2009. The main results were as follows: 1) patients with mild-to-moderate exercise $\bar{P}_{pa} > 30$ mmHg had higher resting PVRI and higher resting $\bar{P}_{pa}$; 2) it was not possible to reliably set a lower limit of resting $\bar{P}_{pa}$ that guarantees normal $\bar{P}_{pa}$ at mild-to-moderate exercise loads; and 3) all eight patients with resting $\bar{P}_{pa}$ 22–24 mmHg had exercising $\bar{P}_{pa} > 30$ mmHg. The clinical relevance of such findings deserves further long-term follow-up studies.

The present study was undertaken following recent articles and editorials that stressed the necessity of further research in the area of haemodynamics in patients with pulmonary vascular diseases, with special focus on the potential link between resting and exercising pulmonary haemodynamics and on the significance of resting $\bar{P}_{pa}$ 21–24 mmHg [1–3, 12, 17, 18]. Numerous studies [8–16] have documented the so-called “exercise-induced pulmonary hypertension” [12, 13, 15, 17] frequently observed in various populations carrying a high risk of PH while their $\bar{P}_{pa}$ was normal at rest. To the best of our knowledge, our study is

the first to take into account the recent recommendations made by KOVACS *et al.* [3], namely that the 30 mmHg ULN for the $\bar{P}_{pa}$ achieved on mild-to-moderate exercise fairly applies only in patients aged <50 yrs. Thus elderly patients (61 out of 99) were not included in our final analysis, given that an ULN of 30 mmHg could not be supported by the available data in such patients [3].

Our study focused on mild-to-moderate exercise only, and this was based on the following rationale. First, the literature review made it possible to define reliable ULN for $\bar{P}_{pa}$ during mild-to-moderate exercise [3, 5]. Secondly, reliable and consistent $\bar{P}_{pa}$, P_{pao} and cardiac output data have been published during mild-to-moderate exercise [4, 5, 21], thus allowing pathophysiological interpretation of our data. Finally, light exercise may reflect the daily life physiological stress put on the pulmonary circulation and right ventricle more accurately than maximal exercise [1, 2].

In healthy subjects aged <50 yrs, the resting $\bar{P}_{pa}$ is ~14 mmHg on average [1–3], and the haemodynamic changes on mild-to-

FIGURE 2. Receiver operating characteristic curve showing mean pulmonary arterial pressure at rest ($\bar{P}_{pa,rest}$) >15 mmHg and predicted exercise $\bar{P}_{pa} > 30$ mmHg with 88% sensitivity (95% CI 68–97%) and 57% specificity (95% CI 29–82%).

TABLE 4	Summary of resting mean pulmonary arterial pressure ($\bar{P}_{pa,rest}$) versus exercising $\bar{P}_{pa}$ ($\bar{P}_{pa,ex}$) in the 38 patients		
	$\bar{P}_{pa,ex}$	$\bar{P}_{pa,rest} < 21$ mmHg	$\bar{P}_{pa,rest} 21\text{--}24$ mmHg
≤ 30 mmHg		12	2
> 30 mmHg		15	9
Total		27	11

Data are presented as n.

moderate exercise while supine slightly differ according to the research team, with either unchanged PVR [5, 22], or slightly decreased PVR [23]. Pulmonary capillary pressure may increase slightly [3, 5, 6, 24], although other studies and reference textbooks often indicate unchanged pulmonary capillary pressure during exercise. The 18 mmHg resting $\bar{P}_{pa}$ value documented in our study (table 2) is consistent with that previously reported in populations similar to ours [12–15] and reflects the fact that patients were investigated in our centre for possible vascular disease. It has been suggested that age, sex and resting systolic blood pressure significantly influence $\bar{P}_{pa}$ responses to exercise, but all were similar in the two groups (table 1). The underlying risk factors and comorbidities (table 1) may contribute, at least in part, to explaining the high percentage (24 out of 38; 63%) of patients exhibiting abnormal $\bar{P}_{pa}$ responses [8–16].

The stress put on the right ventricle is minimal at rest and this may in part explain why resting pulmonary haemodynamics do not correlate highly with exercise pulmonary haemodynamics in patients with established PH [6, 8, 12, 19, 20, 25, 26]. In our patients at risk for PH and exhibiting normal $\bar{P}_{pa}$ at rest, ROC curve analysis indicated that resting $\bar{P}_{pa} > 15$ mmHg predicted exercise $\bar{P}_{pa} > 30$ mmHg with 88% sensitivity and 57% specificity. Interestingly, SAGGAR *et al.* [15] have suggested that resting $\bar{P}_{pa} \geq 14$ mmHg was associated with abnormal $\bar{P}_{pa}$ responses on exercise in patients with systemic sclerosis. However, in our study, it was not possible to reliably set a lower limit of resting $\bar{P}_{pa}$ that guarantees normal $\bar{P}_{pa}$ at mild-to-moderate exercise loads.

As far as the upper limit that guarantees abnormal $\bar{P}_{pa}$ at mild-to-moderate exercise loads is concerned, it may be expected that the closer the resting $\bar{P}_{pa}$ lies to the ULN on exercise (30 mmHg) the more likely the exercise $\bar{P}_{pa}$ threshold is to be breached. Resting $\bar{P}_{pa}$ was consistently higher in the 24 patients who developed $\bar{P}_{pa} > 30$ mmHg on mild-to-moderate exercise, and this was explained by the 55% higher levels for resting PVRi as compared with the remaining 14 patients who did not develop $\bar{P}_{pa} > 30$ mmHg on mild-to-moderate exercise (table 3). This could also explain why exercise $\bar{P}_{pa}$ was > 30 mmHg in 82% (nine out of 11) of the patients with resting $\bar{P}_{pa}$ 21–24 mmHg and in all eight patients with resting $\bar{P}_{pa}$ of 22–24 mmHg.

Significant differences in P_{pao} changes were also documented and contributed to explaining differences in exercising $\bar{P}_{pa}$ in the two subgroups (table 3). Amongst the 24 patients with $\bar{P}_{pa} > 30$ mmHg on exercise, two (8%) had an exercising P_{pao} of > 20 mmHg (see online supplementary material), thus confirming that acute left ventricular dysfunction could also contribute to the rise in $\bar{P}_{pa}$, *e.g.* diastolic dysfunction [27, 28]. Conversely, similar cardiac output responses on exercise were documented in the two subgroups and gave similar PVRi responses (table 3). In summary, in patients aged < 50 yrs and free of PH, the increased PVRi at rest resulting in higher resting $\bar{P}_{pa}$ was the main factor likely to explain abnormally high $\bar{P}_{pa}$ on mild-to-moderate exercise. Additionally, further exercise-related increases in capillary wedge pressure also played a role.

Our study did not involve healthy subjects, but patients with symptoms and a certain risk of PH. Accordingly, the results cannot be used to create novel thresholds of physiological changes during exercise and may not be compared with studies

examining healthy individuals. The clinical heterogeneity of the study group reflects the current “real-life” experience of a reference PH centre. Other limitations include the retrospective study design and the lack of extensive assessment of left ventricular function at rest (*e.g.* detailed echocardiography to detect diastolic and/or systolic dysfunction). The intrinsic limitations related to the exercise protocol must also be discussed. We have examined $\bar{P}_{pa}$ responses on mild-to-moderate exercise as best as we could, with the understanding that we do not measure oxygen consumption during our right heart studies. We could not determine the slope and pressure axis intercept of the $\bar{P}_{pa}$ –cardiac output relationship, as the number of data points and pattern of exercise varied between individuals. The determination of multipoint $\bar{P}_{pa}$ –cardiac output plots provides a more accurate insight into the nature of PVR than the single-point PVR, as the intercept may be higher than pulmonary capillary pressure [6, 7, 19, 20, 29, 30]. Thus, the observed pattern of increased transpulmonary pressure gradient and increased cardiac output together with unchanged or decreased single-point PVR does not necessarily reflect unchanged or decreased resistive properties of the pulmonary circulation [7, 20, 29, 30]. Similarly, we cannot exclude the possibility that our results reflect averaging patients with various patterns of $\bar{P}_{pa}$ –cardiac output relationship on exercise [20]. The two patients with exercise $P_{pao} > 20$ mmHg were included in our final analysis as our aim was to study the relationship between resting and mild-to-moderate exercise $\bar{P}_{pa}$ in patients at risk of PH but free of PH at rest ($\bar{P}_{pa} < 25$ mmHg) and with normal filling pressure at rest ($P_{pao} \leq 15$ mmHg). Finally, elderly subjects could not be studied for the above-mentioned reasons and further studies focusing on this population are thus needed.

The implications of our study must be carefully considered. First of all, we wish to emphasise the fact that our study did not intend to challenge the 4th World Conference proposal that exercise testing must be abandoned in the definition of PH [1, 2]. However, we remain concerned by the fact that the new consensus does sometimes leave clinicians faced with a patients that have symptoms suggestive of pulmonary vascular disease but with resting $\bar{P}_{pa} < 25$ mmHg [12, 14, 18]. Interestingly, our study pointed to a major redundancy between resting and mild-to-moderate exercise $\bar{P}_{pa}$ values in the subgroup of patients < 50 yrs with a resting $\bar{P}_{pa}$ of 22–24 mmHg. The 22–24 mmHg range of resting $\bar{P}_{pa}$ may help clinicians to recognise patterns consistent with abnormal haemodynamic responses on mild-to-moderate exercise. Elsewhere, our study demonstrates a lack of tight correlation between resting and exercise haemodynamics in non-PH patients. In other words, our data would suggest that it is not possible to reliably set a lower limit of resting $\bar{P}_{pa}$ that guarantees that pulmonary haemodynamic responses to exercise will be normal at mild-to-moderate exercise loads in patients < 50 yrs.

In conclusion, in subjects aged < 50 yrs and free of PH, patients with mild-to-moderate exercise $\bar{P}_{pa} > 30$ mmHg had higher resting PVRi and higher resting $\bar{P}_{pa}$. Although all patients with resting $\bar{P}_{pa}$ 22–24 mmHg had an exercising $\bar{P}_{pa} > 30$ mmHg, there was no resting $\bar{P}_{pa}$ threshold value that could reasonably predict normal/abnormal response on mild-to-moderate exercise. The clinical relevance of such findings deserves further long-term follow-up studies.

STATEMENT OF INTEREST

Statements of interest for K. Whyte, S. Hoette, D. Montani, L. Savale, D.S. O'Callaghan, G. Garcia, O. Sitbon, G. Simonneau and M. Humbert can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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