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Haemodynamic responses to exercise in patients with COPD

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ABSTRACT: The present study aimed to explore the prevalence of pre-capillary pulmonary hypertension (PH) and characterise haemodynamic vascular responses to physical exercise in chronic obstructive pulmonary disease (COPD) outpatients, where left ventricular dysfunction and comorbidities were excluded.

98 patients with COPD underwent right heart catheterisation at rest and during supine exercise. Mean pulmonary artery pressure (P_{pa}), pulmonary capillary wedge pressure (P_{pcw}) and cardiac output (CO) were measured at rest and during exercise. Exercise-induced increase in mean P_{pa} was interpreted relative to increase in blood flow, mean P_{pa}/CO, workload (W) and mean P_{pa}/W. Pulmonary vascular resistance (PVR) and pulmonary artery compliance (PAC) were calculated. PH at rest was defined as mean P_{pa} at rest $\geqslant$25 mmHg and P_{pcw} at rest $<$15 mmHg.

Prevalence of PH was 5%, 27% and 53% in Global Initiative for Chronic Obstructive Lung Disease stages II, III and IV, respectively. The absolute exercise-induced rise in mean P_{pa} did not differ between subjects with and without PH. Patients without PH showed similar abnormal haemodynamic responses to exercise as the PH group, with increased PVR, reduced PAC and steeper slopes for mean P_{pa}/CO and mean P_{pa}/W.

Exercise revealed abnormal physiological haemodynamic responses in the majority of the COPD patients. The future definition of PH on exercise in COPD should rely on the slope of mean P_{pa} related to cardiac output and workload rather than the absolute values of mean P_{pa}.

KEYWORDS: Pre-capillary, prevalence, pulmonary circulation, right heart catheterisation

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Pulmonary hypertension (PH) is a serious complication of chronic obstructive pulmonary disease (COPD). An increase in mean pulmonary artery pressure (P_{pa}) at rest of 10 mmHg is associated with a more than fourfold increase in mortality [1]. The actual prevalence of PH in COPD classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) is not well known [2].

Increased pulmonary artery stiffness is demonstrated early in the course of PH, even in patients where PH is detectable only during exercise [3]. The resistance and elasticity of the pulmonary artery play an important role in facilitating the transition from right ventricular pulsatile flow to nearly steady state flow at the capillary level. There is, however, little knowledge of how the pulmonary haemodynamics, measured by right heart catheterisation (RHC), are affected during exercise in stable COPD patients.

Accordingly, the present study aimed to explore the prevalence of pre-capillary PH in a cohort of stable COPD patients, where left ventricular (LV) disease and comorbidities were systematically excluded. Furthermore, and based on the fact that alternation of the elastic properties of pulmonary artery is observed even in patients without established PH, we hypothesised that abnormal haemodynamic vascular responses to exercise are also present in COPD patients without PH.

METHODS

Study population

The present cross-sectional study was performed at Oslo University Hospital, Oslo, Norway, between 2006 and 2010. 98 consecutive COPD patients were prospectively enrolled from our pulmonary outpatient clinic. Prior to inclusion all the participants were assessed by one of three pulmonary physicians (I. Skjørten, M.N. Melsom or S. Humerfelt) and classified by severity of airway obstruction according to GOLD. COPD medical therapy was standardised according to the GOLD statement [2]. None of the subjects had

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noninvasive positive-pressure ventilation support. Long-term treatment with oxygen was administered in eight patients and ambulatory oxygen support in four patients. 15% of the patients had chronic respiratory failure and, of those, four had hypercapnic respiratory insufficiency. The study was approved by the Local Research Ethics Committee, and all subjects gave written, informed consent. The study complies with the Declaration of Helsinki.

Inclusion and exclusion criteria

Norwegian Caucasian subjects, aged 40–75 years, with spirometrically confirmed COPD in GOLD stages II–IV, all either current or former smokers, with a smoking history of at least 10 pack-years, were included. They had to have been free of COPD exacerbations during the last 2 months prior to inclusion. All participants underwent pre-inclusion screening, including resting ECG and an exercise test on cycle ergometer to screen for potential ischaemic heart disease. In addition, all subjects were screened by echocardiography at rest and during exercise, and moderate or severe tricuspid regurgitation jets were not observed. Patients with the following: LV disease, treated arterial hypertension with blood pressure >160/90 mmHg, arrhythmias, intracardiac shunts, sleep apnoea syndrome, previous pulmonary embolism, other chronic pulmonary disease (pulmonary fibrosis or combined fibrosis/emphysema), malignancy, metabolic conditions (except metabolically stable diabetes), hyperthyroidism, systemic inflammatory diseases or renal failure with estimated glomerular filtration rate <60 mL·min^{-1}, were excluded. Patients using β-blockers, warfarin or clopidogrel or who could not perform bicycle-exercise testing or the 6-min walk test for any reason, were also excluded.

Physical and pulmonary function testing

Standardised 6-min walk distance (6MWD) without supplemental oxygen was obtained. Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were determined by spirometry in accordance with international guidelines [4]. FEV_1 and FVC predicted values were calculated [5]. GOLD classification was performed according to their best spirometric values and arterial oxygen tension (P_{aO_2}) and arterial carbon dioxide tension (P_{aCO_2}) on the test day after administration of their regular COPD medication. P_{aO_2} and P_{aCO_2} were obtained from the radial artery at rest and at maximal exercise breathing room air. Static lung volumes and diffusing capacity of the lung for carbon monoxide were measured [4, 6]. Patients performed a standardised incremental maximal exercise test (the cardiopulmonary exercise test (CPET)), which involved 4 min of unloaded pedalling and 4 min of pedalling with 25 W workload (W), followed by a progressive increase of 10 W every 2 min until exhaustion. The ratio of cardiac output (CO) to oxygen uptake (V'_{O_2}) was calculated as the change in CO from rest to exercise divided by the change in V'_{O_2}. All patients underwent high-resolution computed tomography (HRCT) to evaluate the presence of emphysema. Pulmonary function measurements, HRCT and CPET were obtained within 1 day of the haemodynamic measurements.

RHC and haemodynamic measurements

A balloon-tipped 7 F Swan–Ganz catheter was inserted into the antecubital or femoral vein and advanced into the pulmonary artery during short-time fluoroscopy (ArcoScope; Siemens, Munich, Germany). In the supine position, the pressures were zeroed at the mid-axillary line at the right atrial level, and automatic calibration was performed prior to pressure measurements. CO was measured by the thermodilution technique, averaging three or five output determinations. One CO measurement was performed at maximum workload. Mean P_{pa} and pulmonary capillary wedge pressure (P_{pcw}) were measured at rest and during the last minute of each exercise level, and right atrial pressure (P_{ra}) at rest and at peak exercise, while right ventricular pressures were measured only at rest. Pressures were measured during temporary breathhold at end-expiration and verified by flat respiration curve. Post-processing analyses were performed on pressure curves at end-expiration at rest and during exercise by manually corrected region of interest if necessary. Computer-generated algorithmic of mean pressures (mean P_{pa}, mean P_{ra} and mean P_{pcw}) were used, and were averaged over three to six cardiac cycles. The ECG was monitored continuously.

The following haemodynamic variables were used: transpulmonary gradient (TPG)=mean P_{pa}-P_{pcw}; pulse pressure (PP)=systolic P_{pa}-diastolic P_{pa} (mmHg); stroke volume (SV)=(CO/cardiac frequency (fC))×1000 (mL·beat^{-1}); pulmonary artery compliance (PAC)=SV/PP (mL·mmHg^{-1}); pulmonary vascular resistance (PVR)=(mean P_{pa}-P_{pcw})/CO (Wood units) and total pulmonary vascular resistance (TPR)=mean P_{pa}/CO (Wood units). Exercise-induced increase in mean P_{pa} was interpreted relative to the increase in blood flow (mean P_{pa}/CO) and workload (mean P_{pa}/W).

Dynamic supine leg exercise using a cycle ergometer (ERGOMED 840L; Siemens) was performed. A steady-state resting period was followed by a stepwise increment in workload, starting with a 4-min period of unloaded exercise (0 W) at 60 rpm, followed by 20 W for 4 min, and then a 10-W increment every 2 min until exhaustion while breathing room air.

As unloaded exercise at 0 W results in energy expenditure and augmentation in V'_{O_2} and CO with increase in mean P_{pa}, this ''internal work'' was added to the performed external work [7]. A correction factor was thus applied in all 98 participants, based on the known relationship between the increment in V'_{O_2} and workload during incremental exercise (10 mL·W^{-1}) [8, 9]. Thus, V'_{O_2} was calculated for the workload of 0 W. The increment in V'_{O_2} (mL·min^{-1}) from rest to 0 W was then used to calculate the ''internal workload'' and added to their external work during exercise, denoted as corrected workload [7]. The baseline and exercise pressure signals, respiration curves and the ECGs were digitally recorded using a Mac-Lab application (GE Healthcare Medical Systems, Milwaukee, WI, USA).

Definition of haemodynamic groups

Patients were divided into the following two main groups according to resting pressures: 1) non-PH, where mean P_{pa} was <25 mmHg and $P_{pcw\ was}$ ⩽15 mmHg; and 2) established pre-capillary PH, where mean P_{pa} was ⩾25 mmHg and P_{pcw} was ⩽15 mmHg [10]. A PVR >1.5 Wood units at rest (corresponding to upper limit of the 95% confidence interval for healthy controls (mean±1.96 SD)) was considered elevated in subjects aged >50 years [11].

Statistical analysis

The results of continuous variables are reported as mean±SD or mean±SEM. Categorical variables are expressed as frequencies or percentages. An independent t-test was used to compare the mean of two different groups, and a paired t-test used to compare mean differences between rest and exercise within the same group. A p-value <0.05 were considered statistically significant. For categorical variables, the Chi-squared test was used. Non-normally distributed data were log-transformed (N-terminal pro-brain natriureteric peptide (NT-proBNP)). Multivariate linear regression was used to determine whether higher resting mean P_{pa} and exercise PVR were associated with a shorter 6MWD, independent of potential confounders. The statistical analyses were performed using SPSS version 15 (SPSS Inc., Chicago, IL, USA) and SigmaPlot version 12.0 (Systat Software, Inc., London, UK).

RESULTS

Demographic characteristics

Demographic and pulmonary function characteristics are listed in table 1. 33 (34%) patients of the study population were treated for essential systemic hypertension. No differences in systolic or diastolic blood pressure were observed between those treated for and those without hypertension. Emphysema was diagnosed in all except three patients. These three did not differ from the rest with respect to haemodynamic data; however, the group was too small to make any conclusion. Respiratory failure (defined as P_{aO_2} <8 kPa) was observed in eight patients, all in GOLD stage IV and on chronic oxygen treatment. Four patients were on ambulatory oxygen, two each in GOLD stage III and IV, respectively. The oxygen-treated group comprised seven patients with PH (mean P_{pa} at rest 30±5, range 25–40 mmHg and P_{aO_2} 7.5±1.8 kPa), and five without (mean P_{pa} at rest 22±1, range 20–23 mmHg and P_{aO_2} 7.9±0.7 kPa).

Haemodynamic profile at rest

The haemodynamic variables and arterial blood gas profile in the two groups are summarised in table 2. The prevalence of PH was 27% (26 patients) and of non-PH was 73% (72 patients). Distribution of mean P_{pa} related to GOLD stages is shown in figure 1. PVR was elevated at rest in all patients with PH and in 50 (69%) patients in the non-PH group. PAC was significantly reduced in the PH group (p<0.01) compared with the non-PH group (table 2). Right ventricular function was normal at rest in both groups according to CO and P_{ra} (table 2), and none had elevated P_{pcw}.

Haemodynamic profile at peak exercise

The relationship between CO and workload is illustrated in figure 2. A CO increase of 68% and 100% in the PH and non-PH groups was associated with a 66% and 105% increase in mean P_{pa}, respectively. There was no significant difference in the absolute mean P_{pa} increase in response to maximal exercise between the groups (fig. 3).

PVR increased significantly by 11% in the PH group during exercise (p=0.04). In the non-PH group, a nonsignificant increase of 5% in PVR was observed (p=0.08). However, considering percentage change in PVR from rest to exercise, adjusted for changes in CO, a similar increase in PVR of 6.3% in non-PH group as in PH group (6.9%) was observed (p=0.9).

TABLE 1 Demographic and pulmonary function data in 98 chronic obstructive pulmonary disease patients according to mean pulmonary artery pressure at rest

Variables	Non-PH	PH
Subjects	72	26
Age years	64±6	62±8
Males %	53	42
BMI kg·m^{-2}	24±5	25±6
BSA m^2	1.8±0.2	1.8±0.3
SBP mmHg	139±22	140±18
DBP mmHg	69±12	68±13
*f*C beats·min^{-1}	74±12	84±13*
GFR mL·min^{-1}	90±35	109±45
NT-proBNP$^{\#}$ pmol·L^{-1}	13±12	16±17
Diabetes	5	4
Systemic hypertension	22	11
Former/current smokers %	68/32	69/31
Pack-years	41±19	39±20
Haemoglobin g·dL^{-1}	14.5	14.2
CO-Hb %	2.4±1.2	2.6±1.4
GOLD stages II/III/IV	35/23/14	2/8/16*
Respiratory failure	6	9
FEV_1 % pred	46±15	32±12*
FVC % pred	76±20	61±16*
FEV_1/FVC %	49±11	43±13*
D_{LCO}[¶] % pred	57±19	36±20*
TLC % pred	119±29	128±36
RV/TLC %	59±11	67±9
RV % pred	192±59	241±60*
Normoxaemia/hypoxaemia^{+} %	50/40/10	15/50/35
6MWD m	489±113	343±149*
Presence of emphysema[§]	69 (96)	26 (100)

Values are presented as n, mean±SD or n (%), unless otherwise stated. PH: pulmonary hypertension; BMI: body mass index; BSA: body surface area; SBP: systolic blood pressure; DBP: diastolic blood pressure; *f*C: cardiac frequency; GFR: glomerular filtration rate; NT-proBNP: N-terminal pro-brain natriuretic peptide; CO-Hb: carboxyhaemoglobin; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; TLC: total lung capacity; RV: residual volume; 6MWD: 6-min walk distance. $^{\#}$: log-transformed data; [¶]: D_{LCO} was not measured in 11%; $^{+}$: normoxic arterial oxygen tension (P_{aO_2})>10.0 kPa, mildly hypoxic P_{aO_2} 8.1–10.0 kPa and moderately hypoxic P_{aO_2} <8.0 kPa; [§]: by high-resolution computed tomography. *: p<0.05 *versus* non-PH (p<0.05).

For both groups, TPR was significantly increased from rest to exercise (p<0.01 for both); however, there were no differences in TPR increases between the groups (p>0.8) (fig. 4).

The increase in PP from rest to exercise exceeded the increase in SV. Hence, PAC decreased in response to exercise by 47% and 44% in PH and non-PH, respectively (table 3). However, the increase in PVR was accompanied by a relatively larger drop in PAC in the non-PH group compared with the PH group (PVR/PAC ratio 0.6±0.4 *versus* 1.5±1.4, respectively;

TABLE 2 Haemodynamic, arterial blood gas profile and cardiopulmonary exercise testing parameters at rest and during exercise in 98 chronic obstructive pulmonary disease patients with or without pulmonary hypertension (PH)

Variable	Non-PH		PH	
	Rest	Exercise	Rest	Exercise
Subjects n	72		26	
Mean P_{pa} mmHg	18±3	37±8	29±4#	48±7¶
sP_{pa} mmHg	28±4	55±11	41±8#	68±10¶
dP_{pa} mmHg	9±4	20±7	17±6#	28±7¶
TPG mmHg	10±3	20±6	18±6#	31±7¶
P_{pcw} mmHg	9±3	17±4	11±3#	17±4
P_{ra} mmHg	5±3	9±3	7±3#	11±3
PP mmHg	18±5	35±9	24±9#	39±9
TPR Wood units	3.6±0.9	3.8±1.4	5.3±1.5#	5.5±1.8¶
PVR Wood units	2.0±0.9	2.1±1.0	3.3±1.4#	3.7±1.6¶
PAC mL·mmHg^{-1}	4.1±1.3	2.3±0.7	3.2±1.5#	1.7±0.6¶
CO L·min^{-1}	5.2±1.0	10.4±2.5	5.6±1.2	9.4±2.8
edPRV mmHg	7±4		10±4#	
f_C beats·min^{-1}	74±12	108±13	84±13#	110±15
MPf_C %		69±9		69±10
W_C W		74±25		50±20¶
P_{aO_2} kPa	9.8±1.2	9.4±1.6	8.2±1.6#	7.3±1.9¶
P_{aCO_2} kPa	5.3±0.6	5.6±0.8	5.7±0.8#	6.2±1.1¶
S_{aO_2} %	96±2	94±4	92±5#	85±9¶
CO/V'_{O_2}		6.2±4.1		6.3±2.7
Maximum Borg 10 dyspnoea score		9.3±1.4		9.2±1.7
f_R breaths·min^{-1}	20±4	35±7	23±6#	33±8
Respiratory quotient		1.0±0.1		0.9±0.1
V'_{Emax} L·min^{-1}		46±15		38±13¶
V'_E/MVV %		90±23		105±22¶

Data are presented as mean±SD, unless otherwise indicated. P_{pa}: pulmonary artery pressure; sP_{pa}: systolic P_{pa}; dP_{pa}: diastolic P_{pa}; TPG: transpulmonary pressure gradient; P_{pcw}: pulmonary capillary wedge pressure; P_{ra}: right atrial pressure; PP; pulse pressure; TPR: total pulmonary vascular resistance; PVR: pulmonary vascular resistance; PAC: pulmonary arterial compliance; CO: cardiac output; edPRV: right ventricle end-diastolic pressure; f_C: cardiac frequency; MPf_C: maximum predicted f_C; W_C: corrected workload; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; S_{aO_2}: arterial oxygen saturation; V'_{O_2}: oxygen uptake; f_R: respiratory frequency; V'_{Emax}: maximum minute ventilation; MVV: maximal voluntary ventilation. #: $p<0.05$, significantly different from non-PH for resting values; ¶: $p<0.05$, significantly different from non-PH for exercise values. For all right heart catheterisation variables, except PVR in the non-PH group, there was a significant difference between rest and exercise values for haemodynamic variables. Workload obtained in cardiopulmonary exercise testing was similar to workload from right heart catheterisation.

$p<0.01$). Adjusted for workload, P_{pcw} showed a similar increase in response to exercise in both groups. 14 patients (four and 10 in the PH and non-PH groups, respectively) showed a more pronounced P_{pcw} response to exercise than the rest (average maximal P_{pcw} 23±2, range 21–26 mmHg). In table 3, the slopes related to workload and CO for haemodynamic parameters are summarised. Figure 5 illustrates how all 98 change (Δ) in mean P_{pa}/ΔCO slopes are related to mean P_{pa} at rest in non-PH and PH groups. There was only a weak correlation between mean P_{pa} at rest and Δmean P_{pa}/ΔCO ($r=0.2$; $p<0.05$).

Contribution of P_{pcw} and TPG to increase in mean P_{pa} by exercise

The $\Delta P_{pcw}/\Delta TPG$ ratio in the PH group was 0.5, and 0.8 in the non-PH group, reflecting a larger contribution of TPG than P_{pcw} to mean P_{pa} by exercise. The relative changes in mean P_{pa}, P_{pcw}, TPG, PVR and TPR from rest to exercise are shown in figure 4, and the slopes are presented in table 3.

Changes in blood gases by exercise and their relationship with haemodynamics

From rest to peak exercise a decline in relative arterial oxygen saturation (S_{aO_2}) of 2±3 and 8±7% was observed in non-PH and PH groups, respectively ($p<0.01$). The relative S_{aO_2} decline was significantly lower for the non-PH group (0.06±0.1 % per W) than for the PH group (0.3±0.4 % per W; $p<0.01$), which showed a fivefold larger decline in S_{aO_2} when related to maximum workload. During peak exercise, mean P_{pa} was negatively correlated to maximal P_{aO_2} ($r=-0.5$; $p<0.01$) in the entire cohort. The non-PH group, however, showed only a weak negative correlation between mean maximal P_{pa} and maximal P_{aO_2} ($r=-0.4$; $p<0.01$), while the PH group did not correlate at all ($r=0.2$; nonsignificant). PVR rest did not correlate with P_{aO_2} at

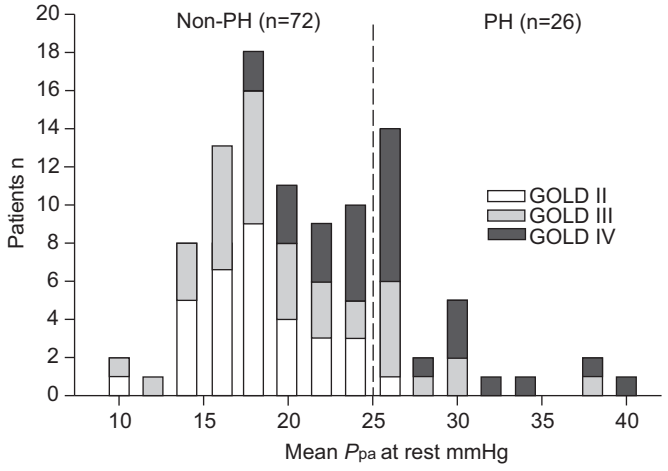

FIGURE 1. Distribution of mean pulmonary artery pressure (P_{pa}) in an outpatient cohort of 98 chronic obstructive pulmonary disease (COPD) patients in GOLD (Gobal Initiative for Chronic Lung Disease) severity stages II, III and IV. 72 patients had normal pulmonary artery pressure (nonpulmonary hypertension (non-PH)) and 26 had PH. The number of patients diagnosed with PH according to GOLD stage II, III and IV were 2, 8 and 16, respectively. The dotted line represents the current guideline definition of PH.

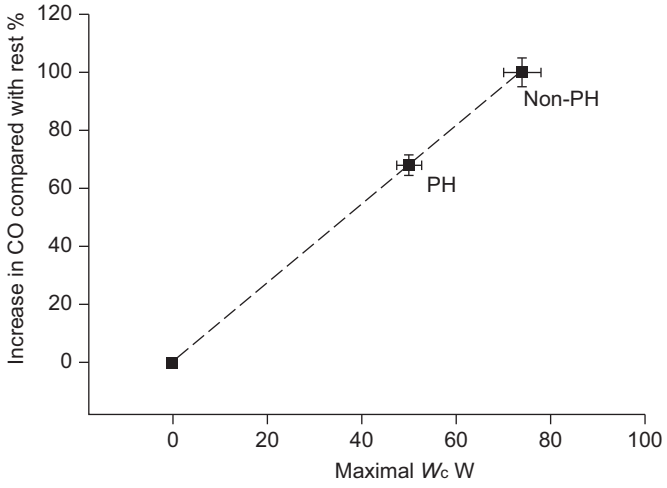

FIGURE 2. Relationship between the corrected workload (W_c) and percentage increase in cardiac output (CO) in chronic obstructive pulmonary disease patients. Average increase in workload in the pulmonary hypertension (PH) group was 68% of the increase in the non-PH group, corresponding to an increase in CO of 68% and 100% in the PH and non-PH group, respectively. Data are presented as mean±SEM.

rest in the non-PH group, while in the PH group, a strong negative correlation between PVR at rest and P_{aO_2} at rest (r= -0.6; p<0.01) was observed. PVR during peak load did correlate with maximal P_{aO_2} in both groups (r= -0.5; p<0.01).

Functional outcomes

Adjusted for age, sex, height, weight, FEV1 and P_{pcw}, mean P_{pa} at rest was negatively associated with 6MWD (r= -0.55; p<0.01). A 9.5-m decline in 6MWD for every 1-mmHg increase in mean P_{pa} (95% CI -14.3– -4.5 m; p<0.01) was observed. Adjusted for the same confounding variables in addition to S_{aO_2} measured by pulse oximetry, PVR was inversely related to 6MWD (r= -0.6; p<0.01). This multivariable linear regression model with 6MWD as dependent variable showed that for every Wood unit increase in PVR at peak exercise, the 6MWD dropped by 29.5 m (95% CI -48.9– -10.1 m; p<0.01). Furthermore, maximal workload was strongly correlated to PVR and PAC at peak workload (r= -0.7 and r=0.5, respectively; p<0.01 for both).

30 COPD patients showed a Δmean $P_{pa}/\Delta CO$ <3 mmHg·L^{-1}·min^{-1} (2.1±0.6, range 1.05–2.92 mmHg·L^{-1}·min^{-1}), representing ''true circulatory normal'' (fig. 6).

DISCUSSION

In the present cohort of COPD patients, recruited from an outpatient population where LV dysfunction, comorbidities and exacerbations were thoroughly excluded, a prevalence of pre-capillary PH of 27% was found. The prevalence related to GOLD stage II, III and IV was 5%, 27% and 53%, respectively. As expected, abnormal exercise-induced haemodynamic responses were observed in the PH group. However, similar and comparable haemodynamic responses to exercise were also demonstrated in non-PH subjects. Based on these results and previous findings in healthy subjects, we consider the responses to exercise in non-PH subjects as abnormal.

Mean P_{pa} at rest

The majority of prevalence data are based on patients with severe to very severe COPD disease, *i.e.* awaiting lung transplantation, where RHC is a part of routine clinical evaluation. Previous studies have reported prevalence of PH in COPD patients to vary between 30% and 90% [15–19]. The inconsistency in prevalence of PH associated with COPD is based mainly upon dissimilarities in definition of PH, methods used to determine mean P_{pa}, the physiological characteristics of the underlying lung disease and patient population examined [20]. In the present study, great effort was made to ensure inclusion of COPD patients who were clinically stable and optimally treated and without evidence of LV dysfunction either at rest or during exercise. Our prospectively collected data showed a lower prevalence of pre-capillary PH than in the majority of previous studies. Only 27% of our patients met the current definition of PH (mean P_{pa} $\geqslant$25 mmHg) [10]. This lower prevalence compared with published estimates of PH reflects the present study's more restrictive definition and, secondly, a very strict selection process to avoid including comorbidities (*i.e.* both post- and other pre-capillary diseases) that could contribute to a rise in mean P_{pa}. Using the previous definitions of PH (mean P_{pa} >20 mmHg), the prevalence of pre-capillary PH would have been 46% [19]. The average 18 mmHg resting mean P_{pa} value in the non-PH group in the present study is higher than that reported for healthy subjects [13], but in accordance with the study in 1999 by KESSLER *et al*. [21] on stable outpatients with COPD.

Mean P_{pa} response to increased W and CO

Workload and CO had a similar impact on the pressure increase of mean P_{pa}. The absolute increase in mean P_{pa} by exercise was also similar in those with and without PH. However, there was a larger increase in mean P_{pa} in the PH compared with non-PH group, which was related to the

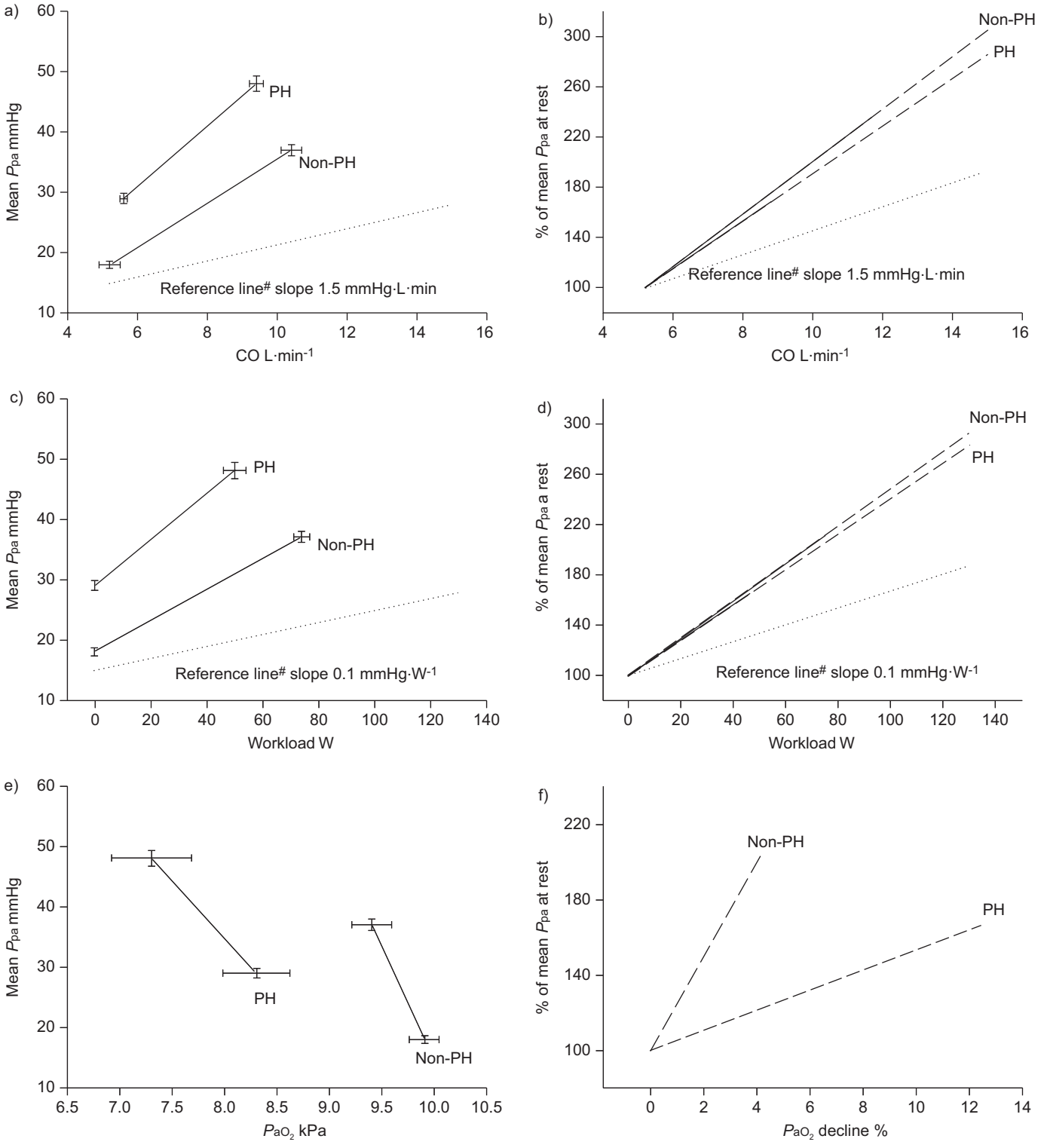

FIGURE 3. Measurements at rest and during maximal exercise in patients with chronic obstructive pulmonary disease categorised as pulmonary hypertension (PH) and non-PH are shown. a) Shows changes in mean pulmonary artery pressure (P_{pa}) relative to changes in cardiac output (CO), c) shows changes in workload and e) shows changes in arterial oxygen tension (P_{aO_2}). b, d and f) illustrate the relative change in mean P_{pa} from rest (resting mean P_{pa}=100%) to peak exercise (unbroken lines) in relation to the increase of CO, workload and P_{aO_2} decline in non-PH and PH, respectively; the broken lines are extrapolations of the relative mean P_{pa} increase until 15 L·min^{-1} (CO) and 140 W (workload) in both groups. Despite of a relatively minor decline in P_{aO_2} in the non-PH group, exaggerated responses in mean P_{pa} were observed. #: reference lines (dotted) are based on previously published mean values on healthy controls [7, 12].

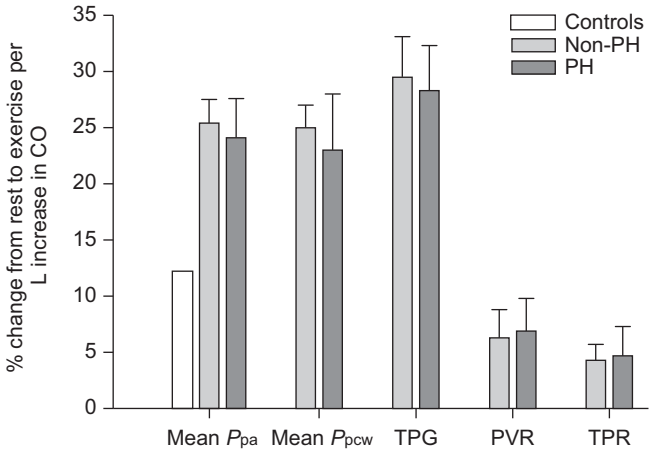

FIGURE 4. Percentage change from rest to peak exercise per litre change in cardiac output (CO) for five haemodynamic variables in pulmonary hypertension (PH) and non-PH; reference values are for historical controls of >50 years adapted from KOVACS and co-workers [11, 13]. P_{pa}: pulmonary artery pressure; P_{pcw}: pulmonary capillary wedge pressure; TPG: transpulmonary gradient; PVR: pulmonary vascular resistance; TPR: total pulmonary vascular resistance. Data are presented as mean±SEM.

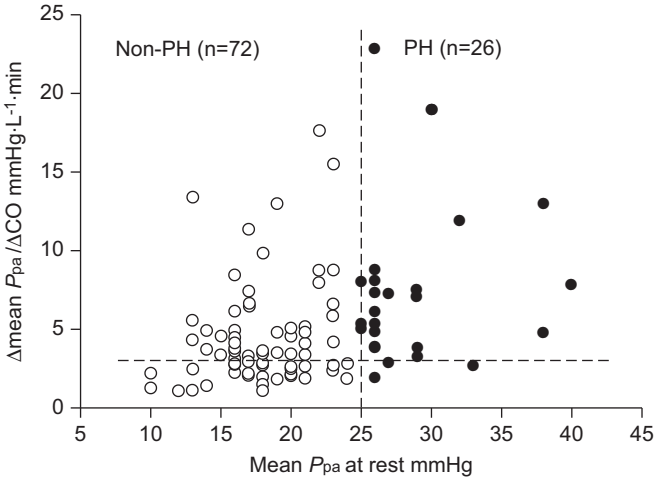

FIGURE 5. The relationship between change (Δ) in mean pulmonary artery pressure (P_{pa})/Δ in cardiac output (CO) slopes and mean P_{pa} at rest in 98 chronic obstructive pulmonary disease patients either with (PH) or without pulmonary hypertension (non-PH). The vertical dotted line is the current cut-off value for PH and the horizontal dotted line represents the slope cut-off (3 mmHg·L^{-1}·min as suggested by LEWIS [14]). 58% of the patients in the non-PH group had Δmean P_{pa}/ΔCO slopes >3 mmHg·L^{-1}·min.

increase in workload and CO. Thus, our results clearly support that exercise-induced rise in mean P_{pa} should be interpreted relative to increase in workload or increase in CO, rather than by evaluating a single threshold or an absolute peak exercise value of mean P_{pa}, as highlighted by SAGGAR *et al.* [22]. In this context, we are in agreement with the decision of the Working Group on Diagnosis and Assessment of Pulmonary Arterial Hypertension that, in 2008, withdrew exercise mean P_{pa} >30 mmHg as a diagnostic criteria for PH.

Comparable haemodynamic data in healthy controls are limited due to ethical reasons, but some data have been reported, albeit with small numbers of subjects in all studies [7, 12, 13]. LEWIS *et al.* [7] reported a Δmean P_{pa}/ΔCO slope of 1.4 mmHg·L^{-1}·min (age 60±12 years), and in a slightly younger cohort (age 41±4.8 years); DEGRE *et al.* [12] demonstrated 1.5 mmHg·L^{-1}. In a study by KOVACS *et al.* [13] on healthy controls aged >50 years, a Δmean P_{pa}/ΔCO of 2.8 mmHg·L^{-1}·min was demonstrated, and in a study of healthy older males (age 71±6 years), GRANATH *et al.* [23] reported a slope of 2.5±0.8 mmHg·L^{-1}·min. In the present study, we have shown slopes of 7.2 and 4.6 mmHg·L^{-1}·min in PH and non-PH groups, respectively. Compared with the

TABLE 3 Haemodynamic parameters in absolute change from rest to exercise and related to change in workload (W) and cardiac output (CO)

Variables	Non-PH			PH		
	Change	Slope *W*	Slope CO	Change	Slope *W*	Slope CO
Subjects n		72			26	
Mean P_{pa} mmHg	19±6	0.29±0.15	4.55±3.33	19±8	0.42±0.17*	7.17±4.88*
sP_{pa} mmHg	28±9	0.43±0.24	6.65±4.94	28±11	0.61±0.28*	9.59±6.64*
dP_{pa} mmHg	10±6	0.16±0.12	2.56±2.18	12±8	0.32±0.25*	5.69±7.37*
TPG mmHg	10±6	0.16±0.10	2.57±2.43	14±7*	0.29±0.17*	4.71±3.83*
P_{pcw} mmHg	9±3	0.13±0.08	1.98±1.51	7±3*	0.13±0.10	2.12±1.97
P_{ra} mmHg	4±3	0.07±0.07	1.98±1.51	4±3	0.08±0.08	2.12±1.99
PP mmHg	17±8	0.27±0.20	4.13±4.06	6±8	0.34±0.19	4.69±2.06
TPR mmHg	0.17±1.09	0.00±0.02	0.16±0.46	0.21±1.06	0.01±0.03	0.27±0.83
PVR Wood units	0.16±0.79	0.003±0.013	0.09±0.34	0.37±0.84	0.008±0.023	0.23±0.61
PAC mL·mmHg^{-1}	-1.19±1.21	0.02±0.02	0.32±0.50	-0.92±1.05	0.02±0.02	0.23±0.24

Data are presented as mean±SD, unless otherwise stated. PH: pulmonary hypertension; P_{pa}: pulmonary artery pressure; sP_{pa}: systolic pulmonary artery pressure; dP_{pa}: diastolic pulmonary artery pressure; TPG: transpulmonary pressure gradient; P_{pcw}: pulmonary capillary wedge pressure; P_{ra}: right atrial pressure; TPR: total pulmonary resistance; PVR: pulmonary vascular resistance; PAC: pulmonary arterial compliance. *: $p<0.05$ *versus* non-PH.

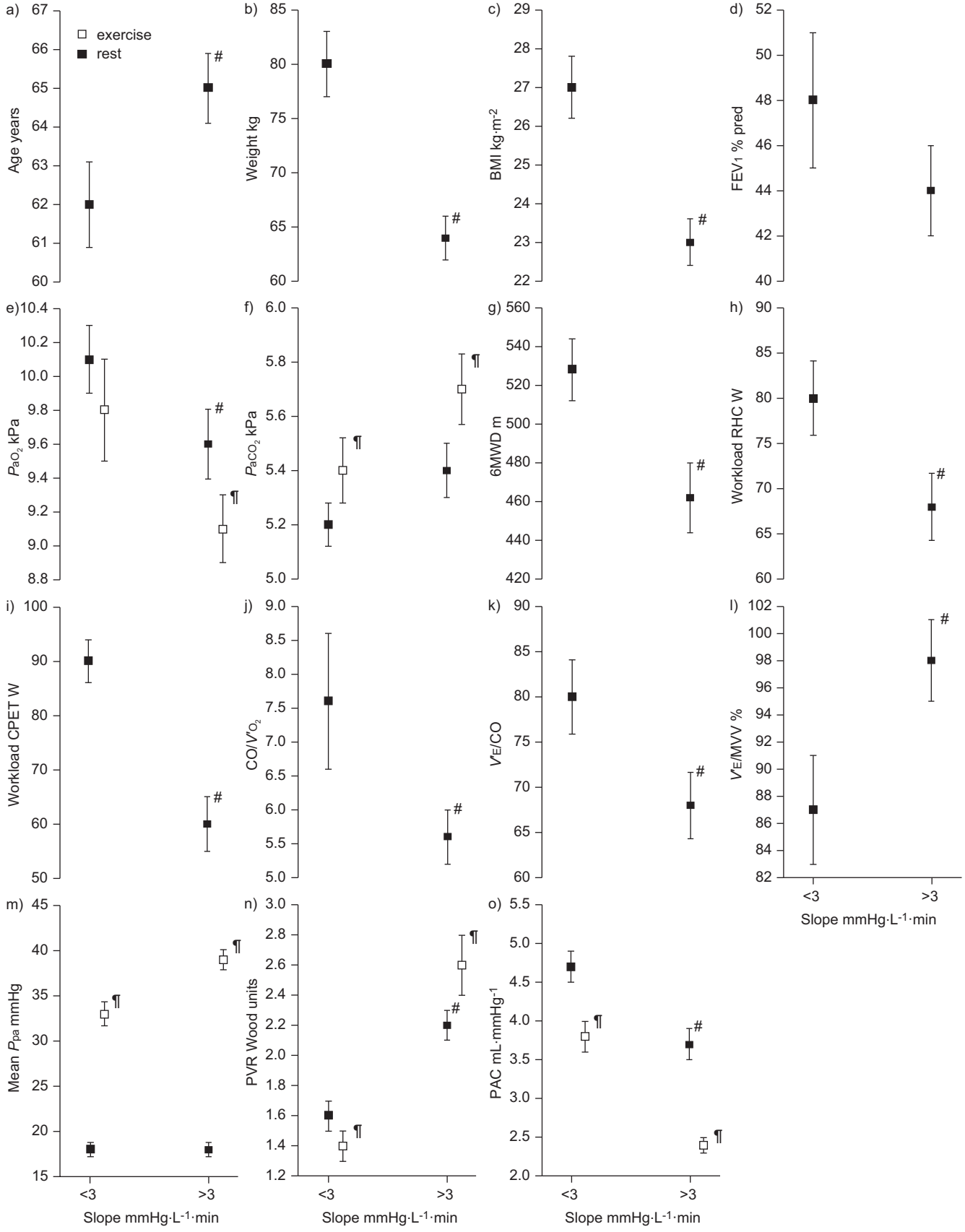

FIGURE 6. Figure caption can be found on the following page.

FIGURE 6. Illustration of key differences and similarities of nonpulmonary hypertension (non-PH) patients with change (Δ) in mean pulmonary artery pressure (P_{pa})/Δ in cardiac output (CO) slope <3 mmHg·L^{-1} (n=30) and >3 mmHg·L^{-1} (n=42). Those <3 mmHg·L^{-1} are considered to represent ''true circulatory normal'' and those >3 mmHg·L^{-1} to represent the exercise-induced PH population. BMI: body mass index; FEV1: forced expiratory volume in 1 s; % pred: % predicted; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; 6MWD: 6-min walk distance; RHC: right heart catheterisation; CPET: cardiopulmonary exercise test; V'_{O_2}: oxygen uptake; V'_E: minute ventilation; MVV: maximal voluntary ventilation; PVR: pulmonary vacular resistance; PAC: pulmonary artery compliance. Data are presented as mean±SEM. #: p<0.05, significantly different from <3 mmHg·L^{-1}min, ¶: p<0.05, significantly different from rest to exercise. No significance difference between the groups with regard to presence of emphysema.

previous studies on healthy controls, our data indicate a pathological mean P_{pa} response to exercise also exists in a large proportion of the COPD patients without PH (fig. 5). A cut-off point for mean P_{pa}/CO of >3 mmHg·L^{-1}·min, as proposed by LEWIS [14], should reinforce this notion. Moreover, in contrast to mean P_{pa} at rest, mean P_{pa} during exercise has been shown to be strongly related to pulmonary arterial wall thickness in COPD; the authors suggested that this reflects reduced distensability and recruitability of pulmonary vessels in COPD, and that the degree of remodelling could not be estimated by mean P_{pa} at rest [24]. Our study also confirmed a poor relationship between mean P_{pa} at rest and Δmean P_{pa}/ΔCO.

Contribution of TPG and P_{pcw} to the exercise-induced increment in mean P_{pa}

Previous haemodynamic studies in healthy subjects have demonstrated a greater contribution of ΔP_{pcw} compared with ΔTPG to exercise-induced increase in mean P_{pa} with a ratio of ~2 [25–27]. In our study, an inverse ratio for both non-PH and PH groups was observed, consistent with a larger contribution of ΔTPG to the increase in mean P_{pa} compared with ΔP_{pcw}, reflecting pre-capillary pathology in the non-PH and PH groups. In both groups, this increase of ΔTPG was related to pathological PVR response. In healthy subjects, PVR and also TPR are normally slightly reduced during exercise [11], probably due to passive recruitment and distension of a compliant pulmonary circulation and/or an active flow-mediated vasodilatation. Our patients without PH showed the same PVR and TPR response pattern as the PH group, indicative of early and significant pre-capillary vascular changes also existing in this group. Furthermore, during exercise, the non-PH group had a considerably larger drop in compliance relative to the change in PVR compared with the PH group, which is consistent with the findings of SAOUTI *et al*. [28], who suggested that a small increase in PVR accompanied by a relatively larger drop in PAC to be a hallmark of early changes in the pulmonary vascular bed.

Exercise decline in P_{aO_2} and haemodynamics

In the present study, only a minor exercise-induced decline in P_{aO_2} was observed, which is in contrast to data presented by BOERRIGTER *et al*. [29], but is comparable with the observations by CHRISTENSEN *et al*. [30]. Augmented pressure responses during exercise partly occurred in our non-PH population in the presence of minor decline in P_{a,O_2} during exercise, and could indicate a mechanism other than hypoxaemia.

Clinical implications

GOLD classification is valuable in terms of differentiation of airway disease severity [2] but, in our study, showed a poor relationship with mean P_{pa} at rest (fig. 1). Its use as a predictor for PH is thus restricted. Furthermore, the results demonstrated that patients classified as GOLD III had mean P_{pa} distribution from low normal (mean P_{pa} 10 mmHg) to severe PH (mean P_{pa} 38 mmHg). A similar pattern was shown for GOLD stages II and IV, and half of the patients in GOLD stage IV did not have PH according to current guidelines (fig. 1).

The present study has also demonstrated that higher resting mean P_{pa} is associated with impaired functional capacity (6MWD) independent of demographics, P_{pcw} and GOLD classification. To our knowledge, this study is the first to report reduced functional capacity related to higher resting mean P_{pa} in an outpatient population. Similar findings have been reported in severe COPD patients listed for lung transplantation [31]. Interestingly, 6MWD, in our cohort decreased gradually by increasing PVR at peak exercise, even when controlling for confounding variables. A strong correlation between exercise afterload variables, PVR and PAC, and maximum workload was observed, and could further endorse the clinical relevance of exercise-induced PH. Patients with exercise-induced PH are particularly prone to developing persistent PH in the long term, as exercise mean P_{pa} >30 mmHg is a marker of disease progression [32]. Thus, the present non-PH group, and especially those with Δmean P_{pa}/ΔCO >3 mmHg·L^{-1}·min, should be followed up longitudinally to see if they develop PH.

Study limitations

The local ethical committee in Norway does not approve invasive RHCs on healthy controls and, therefore, the present study did not provide haemodynamic data for a healthy age- and sex-matched control group. However, comparable data on haemodynamic exercise responses in historical controls have been published, albeit with a limited numbers of articles in the population aged >50 years.

14% of the patients showed exercise P_{pcw} >20 mmHg, and hence a post-capillary contribution to elevated mean P_{pa} during exercise cannot be entirely excluded. An upper limit for P_{pcw} was not adopted due to the paucity of data supporting the previously used cut-off point of 20 mmHg in a population aged >50 years. CO was measured by the thermodilution technique only once at maximal exercise at highest f_C. Rapid decline in both P_{pa} and f_C were observed when exercise was discontinued, and several CO measurements would thus have underestimated peak CO.

CPET was performed separately 24 h prior to RHC, which reflects the standard in our laboratory. A concomitant performance of these two procedures would have been preferable. It is, however, reasonable to assume that clinical and haemodynamic

conditions did not differ in this short period of time, and the exercise levels were similar during CPET and RHC.

Upright positioning during exercise most closely mimics normal physical activity. However, the RHC exercise test in this study was performed in the supine position due to more stable and reliable pressure curves in this position. Despite the postural impact on haemodynamic variables, the relative changes between rest and exercise haemodynamics are most likely to be comparable.

It has been postulated that dynamic lung hyperinflation in COPD may contribute to the development of exercise-induced PH. At the time of inclusion, measurements of inspiratory capacity were not routinely performed in our exercise laboratory and, therefore, it is difficult to conclude with certainty that the exaggerated response of Δmean $P_{pa}/\Delta CO$ and PVR in COPD compared with historical controls is due solely to a vasculopathy.

Our patients represent a well-selected group of patients from an outpatient population. The main purpose was to study exclusively pre-capillary prevalence of PH and pre-capillary haemodynamic responses to exercise. Therefore, our findings are not necessarily applicable to all COPD patients.

Conclusions

The present study showed a prevalence of PH of 5%, 27% and 53% in a cohort of COPD outpatients in GOLD stage II, III and IV, respectively. Exercise revealed abnormal haemodynamic responses in the PH group. However, similar and comparable haemodynamic response patterns were also observed in a large section of the non-PH group. Resting haemodynamics, however, were inadequate to identify early pulmonary vascular disease. The future definition of PH on exercise should rely on the slope of mean P_{pa}, related to CO or workload, rather than the absolute values of mean P_{pa}, to account for the large interindividual variability in physical performance in COPD patients.

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STATEMENT OF INTEREST

None declared.

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