

# Exercise capacity in COPD patients with exercise-induced pulmonary hypertension

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**Background:** Pulmonary hypertension (PH) in patients with COPD is associated with reduced exercise capacity. A subgroup of COPD patients has normal mean pulmonary artery pressure (mPAP) at rest, but develops high mPAP relative to cardiac output (CO) during exercise, a condition we refer to as exercise-induced pulmonary hypertension (EIPH). We hypothesized that COPD patients with EIPH could be identified by cardiopulmonary exercise test (CPET) and that these patients have lower exercise capacity and more abnormal CPET parameters compared to COPD patients with normal hemodynamic exercise response.

**Methods:** Ninety-three stable outpatients with COPD underwent right heart catheterization with the measurement of mPAP, CO, and capillary wedge pressure at rest and during supine exercise. Resting mPAP <25 mmHg with  $\Delta$ mPAP/ $\Delta$ CO slope above or below 3 mmHg/L/min were defined as COPD-EIPH and COPD-normal, respectively. Pulmonary function tests and CPET with arterial blood gases were performed. Linear mixed models were fitted to estimate differences between the groups with adjustment for gender, age, and airflow obstruction.

**Results:** EIPH was observed in 45% of the study population. Maximal workload was lower in COPD-EIPH compared to COPD-normal, whereas other CPET measurements at peak exercise in % predicted values were similar between the two groups. After adjustment for gender, age, and airflow obstruction, patients with COPD-EIPH showed significantly greater increase in oxygen uptake, ventilation, respiratory frequency, heart rate, and lactate with increasing work load, as well as more reduction in pH compared to those with normal hemodynamic responses.

**Conclusion:** COPD-EIPH could not be discriminated from COPD-normal by CPET. However, COPD-EIPH experienced a higher cost of exercise in terms of higher oxygen uptake, ventilation, respiratory frequency, heart rate, and lactate for a given increase in workload compared to COPD-normal.

**Keywords:** COPD, pulmonary hypertension, right heart catheterization, cardiopulmonary exercise test

## Introduction

COPD may cause pulmonary hypertension (PH), a complication associated with reduced exercise capacity<sup>1,2</sup> and worse prognosis.<sup>3,4</sup> A subgroup of COPD patients with normal mean pulmonary artery pressure (mPAP) at rest experiences a substantial increase in mPAP during exercise, a condition that can be described as exercise-induced pulmonary hypertension (EIPH). The impact of EIPH on exercise capacity in COPD patients has not been explored previously. The stress imposed on the right ventricle by EIPH may result in altered physiological responses that can be assessed by cardiopulmonary exercise test (CPET).

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The definition of PH was changed by an expert consensus in 2008, whereby a rise in mPAP above 30 mmHg during exercise was omitted from the definition.<sup>5</sup> This has led to a discussion about how to classify hemodynamic pathology during exercise.<sup>6–10</sup> As healthy individuals may have mPAP >30 mmHg during exercise,<sup>11</sup> the former definition, which included only mPAP, often failed to discriminate pathologic from normal responses. This has resulted in a more complex evaluation of the pulmonary circulation during exercise, where composite variables are calculated. Among healthy individuals, the change in mPAP is related to the work performed, as an increase in mPAP is driven by increased cardiac output (CO). Thus, the slope of  $\Delta\text{mPAP}/\Delta\text{CO}$  has been proposed to define EIPH, as a steep slope indicates pathology.<sup>12</sup> A rise in mPAP during exercise beyond what is expected from CO reflects pathology due to reduced vessel distensibility (precapillary pathology) or increased left atrial pressure (postcapillary pathology).<sup>13</sup> COPD induces precapillary vasculopathy; however, a postcapillary component due to left ventricle diastolic dysfunction with increased left atrial pressure is common in patients with COPD.<sup>14–16</sup> In order to avoid postcapillary contribution to mPAP and  $\Delta\text{mPAP}/\Delta\text{CO}$  slope, patients with left heart disease were excluded from the study. Our group has previously reported  $\Delta\text{mPAP}/\Delta\text{CO}$  relationships in COPD outpatients with varying degrees of airflow obstruction, suggesting that  $\Delta\text{mPAP}/\Delta\text{CO}$  slope >3 mmHg/L/min defines an abnormal hemodynamic exercise response representing EIPH.<sup>17</sup>

The present study aimed to investigate exercise performance and physiological responses during CPET in COPD patients with and without EIPH defined as resting mPAP <25 mmHg and a  $\Delta\text{mPAP}/\Delta\text{CO}$  slope >3 mmHg/L/min. We hypothesized that COPD patients with EIPH could be identified by CPET and that these patients have lower exercise capacity and more abnormal CPET parameters compared to COPD patients with normal hemodynamic exercise response.

## Methods

### Study subjects

The present cross-sectional study consecutively included 93 outpatients with COPD at Oslo University Hospital, Aker from 2006 to 2010. Patients were Caucasians, aged 40–75 years with stable disease and >10 pack-years of tobacco consumption. Patients underwent thorough pre-inclusion screening. The COPD diagnosis was confirmed by post-bronchodilator spirometry. Clinical examination and electrocardiogram at rest and during exercise were performed

to exclude patients with conditions affecting left ventricle function. Obstructive sleep apnea syndrome, pulmonary embolism, systemic hypertension  $\geq 160/90$  mmHg, and use of beta-blockers were reasons for exclusion. A detailed description of the inclusion process and study procedures has been published previously.<sup>17,18</sup>

The study was approved by the Regional Ethics Committee South East Norway (274-07127a 1.2007.1085) and performed according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

### Study protocol

All study tests were performed within 2 consecutive days. Patients were instructed to take their regular medication. All tests were performed without supplemental oxygen.

Spirometry, body plethysmography, and diffusion capacity for carbon monoxide (DLCO) measurements (Master-Screen PFT; Jaeger, Würzburg, Germany) were performed according to guidelines.<sup>19</sup> Prior to exercise, patients ventilated with maximum effort for 10 seconds to estimate the maximal voluntary ventilation.

### CPET

CPET was performed on cycle ergometer with breath by breath measurement (Oxycon Delta; Jaeger) with all patients breathing ambient air. The same incremental protocol was applied for all patients, starting with 4 minutes of unloaded pedaling at 60 rpm, 4 minutes of 25 W, followed by increases of 10 W every 2 minutes until exhaustion. Variables for each exercise level were recorded every 30 seconds, and median value for each level was noted. Oxygen pulse was calculated by dividing  $\dot{V}\text{O}_2$  by HR. Ventilatory equivalent for CO<sub>2</sub> ( $\dot{V}\text{E}/\dot{V}\text{CO}_2$ ) was calculated and  $\dot{V}\text{E}/\dot{V}\text{CO}_2$  nadir was defined as the lowest value on the curve during exercise. Norwegian reference values for CPET were applied.<sup>20</sup> A radial artery cannula was inserted for blood samples at rest and repeatedly during exercise. Systemic blood pressure was measured invasively through the radial artery line.

### Echocardiography

Echocardiography was performed <120 minutes prior to right heart catheterization (RHC) as previously described.<sup>21</sup> Left ventricular (LV) ejection fraction and volumes were calculated by the biplane Simpson method using apical four- and two-chamber views.<sup>22</sup> Indexed left atrial volume was calculated using the four- and two-chamber views at end-systole.<sup>22</sup> Right ventricular (RV) functional parameters were obtained as previously reported.<sup>21</sup> The mitral inflow measurements

included peak early filling (E) and late diastolic filling (A) velocity and the E/A ratio by pulsed Doppler.<sup>23</sup> Early diastolic (E') peak velocity assessed by pulsed tissue Doppler imaging was measured in the four-chamber view at the bases of the septal and lateral mitral leaflet and averaged, and E/E' was calculated as a surrogate for LV filling pressure.<sup>23</sup>

### RHC at rest

RHC at rest (Mac-Lab; GE Healthcare, Milwaukee, WI, USA) was performed via the antecubital or femoral vein with the patient in the supine position. Zero reference level was at mid-axillary line at right atrial level. CO was estimated by thermodilution technique, averaging three or five measurements.<sup>24</sup> Measurements of mPAP, right atrial pressure, pulmonary arterial wedge pressure (PAWP), and right ventricle pressure were performed at end expiration. Pulmonary vascular resistance (PVR) was calculated as (mPAP-PAWP)/CO.

### RHC during exercise

RHC during exercise was performed with dynamic supine leg exercise (Ergomed 840L; Siemens, Erlangen, Germany), starting with 4 minutes unloaded pedaling at 60 rpm, then 20 W for 4 minutes, followed by 10 W increases every 2 minutes until exhaustion. PAWP and mPAP were measured at every load level, whereas CO was measured only at peak exercise.

### Exercise hemodynamics

Exercise-induced increase in mPAP was interpreted relative to increase in CO ( $\Delta\text{mPAP}/\Delta\text{CO}$  slope), and  $>3$  mmHg/L/min was used as cut off for pathology.  $\Delta\text{mPAP}/\Delta\text{CO}$  slope was calculated from measurements at rest and peak exercise.

Patients with resting mPAP  $\geq 25$  mmHg and PAWP  $< 15$  mmHg were defined as COPD-PH. Patients with resting mPAP  $< 25$  mmHg, resting PAWP  $< 15$  mmHg, and  $\Delta\text{mPAP}/\Delta\text{CO}$  slope above or below 3 mmHg/L/min were defined as COPD-EIPH or COPD-normal, respectively.

### Statistical methods

Continuous variables were reported as mean and standard deviation. Differences among three groups were assessed with one-way analysis of variance (ANOVA) or Kruskal-Wallis test and differences between two groups with independent-samples Student's *t*-test or Mann-Whitney *U*-test as appropriate. To analyze between-group differences in CPET parameters, linear mixed models (LMMs) were fitted for repeated measures. An unstructured covariance matrix

was used to model dependencies among measurements for each patient at multiple time points during exercise. Each time point represented a specific load. Measurements at all time points (loads) were considered, including rest. Models for each outcome included terms for time point (load level), grouping of patients (COPD-normal, COPD-EIPH, and COPD-PH), and interaction between load level and group. Furthermore, LMMs were adjusted for gender, age, and FEV<sub>1</sub> (L) to test for potential confounders. Estimates of intercept and slope for each CPET parameter were calculated, where the intercept represented the calculated level of a variable at baseline and the slope represented the change in a variable with increasing load. COPD-EIPH was the defined reference group. *p*-values  $< 0.05$  were considered statistically significant, and all tests were two-sided. Analyses were performed using IBM SPSS Statistics, version 24 (IBM Corporation, Armonk, NY, USA).

### Results

PH was identified in 22 patients. Among the remaining patients with mPAP  $< 25$  mmHg at rest, 42 demonstrated abnormal exercise response with  $\Delta\text{mPAP}/\Delta\text{CO}$  slope  $> 3$  mmHg/L/min. Only 29 patients had normal hemodynamic responses at rest and during exercise.

There were no differences between COPD-EIPH and COPD-normal regarding spirometric parameters, but both the groups had significantly less airflow obstruction than COPD-PH (Table 1). Compared to COPD-normal, COPD-EIPH had higher residual volume and lower DLCO.

The EIPH group included 62% women, which was significantly different from COPD-normal with 31% women (Table 1). The EIPH group was older compared to the other groups (Table 1).

All patients had PAWP  $< 15$  mmHg at rest. During exercise, there were no differences in mean peak PAWP for the three groups (Table 2), and mean peak PAWP was considered to be within normal limits. However, PAWP peak in the range 21–26 mmHg was observed in five, seven, and two patients in the COPD-normal, COPD-EIPH, and COPD-PH groups, respectively. As PAWP peak currently has no clearly defined upper limit of normal, these patients were not excluded from final analyses. Moreover, analyses omitting patients with exercise PAWP  $> 20$  mmHg were similar to analyses of the entire study population. Echocardiographic data (Table 1) did not indicate overt diastolic dysfunction, LV E/A was similar between the groups. Although LV E/E' was higher in COPD-PH compared to COPD-EIPH, mean values in all groups were within normal limits. Echocardiographic

**Table 1** Patient characteristics and echocardiographic data for 93 patients with COPD divided into three groups by mPAP at rest and  $\Delta$ mPAP/ $\Delta$ CO slope

Variable	mPAP <sub>rest</sub> <25 mmHg		mPAP <sub>rest</sub> $\geq$ 25 mmHg	p-value
	$\Delta$ mPAP/ $\Delta$ CO slope $\leq$ 3 mmHg/L/min	$\Delta$ mPAP/ $\Delta$ CO slope >3 mmHg/L/min		
	n=29	n=42	n=22	
Gender, female %	31	62*	59	0.03
Age, years <sup>a</sup>	62 (5)	66 (6)*	61 (8) <sup>#</sup>	0.03
Height, cm <sup>a</sup>	173 (8)	167 (9)*	169 (11)	0.02
BMI kg/m <sup>2</sup>	27 (4)	23 (4)*	25 (6)	0.004
Hemoglobin, g/dL	14.7 (1.4)	14.3 (1.0)	14.3 (1.1)	0.38
FEV <sub>1</sub> % pred.	51 (15)	45 (17)	29 (9)* <sup>#</sup>	<0.001
FVC % pred.	79 (20)	75 (21)	59 (16)* <sup>#</sup>	0.001
FEV <sub>1</sub> /FVC %	53 (9)	48 (11)	41 (11)*	0.001
TLC % pred.	114 (14)	129 (21)	136 (26)*	0.001
RV % pred. <sup>a</sup>	171 (41)	209 (65)*	253 (57)* <sup>#</sup>	<0.001
RV/TLC % <sup>a</sup>	54 (11)	62 (10)*	69 (9)* <sup>#</sup>	<0.001
DLCO % pred.	63 (16)	52 (20)*	30 (14)* <sup>#</sup>	<0.001
LV EF, %	58 (3)	57 (5)	58 (4)	0.63
LV E/A ratio (no unit)	1.08 (0.26)	1.05 (0.29)	1.06 (0.27)	0.89
LV E/E' ratio (no unit)	9.0 (2.2)	8.6 (2.2)	10.1 (2.0) <sup>#</sup>	0.03
LA volume, mL/m <sup>2</sup>	24 (5)	23 (5)	21 (6)	0.09
TAPSE, mm	22.9 (2.7)	21.3 (2.9)	18.8 (3.8)* <sup>#</sup>	<0.001
RV FAC, %	0.38 (0.08)	0.39 (0.07)	0.33 (0.08) <sup>#</sup>	0.02

**Notes:** ANOVA was performed for variables with normal distribution, otherwise non-parametric Kruskal–Wallis test was performed. Values are presented as mean (standard deviation) or %. For TLC and RV, n=90. For DLCO, n=83. \*p<0.05, significantly different from mPAP<sub>rest</sub> <25 mmHg and  $\Delta$ mPAP/ $\Delta$ CO slope  $\leq$ 3 mmHg/L/min. <sup>#</sup>p<0.05, significantly different from mPAP<sub>rest</sub> <25 mmHg and  $\Delta$ mPAP/ $\Delta$ CO slope >3 mmHg/L/min.

**Abbreviations:** mPAP, mean pulmonary artery pressure; CO, cardiac output; BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in 1 second; pred., predicted; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; DLCO, diffusion capacity of the lung for carbon monoxide; LV, left ventricular; EF, ejection fraction; E, transmitral early diastolic velocity; A, late diastolic velocity; E', septal mitral annular early diastolic tissue velocity; LA, left atrial; TAPSE, tricuspid annulus plane systolic excursion; RV, right ventricular; FAC, fractional area change.

**Table 2** Hemodynamic data by right heart catheterization at rest and peak exercise in 93 patients with COPD divided into three groups by mPAP at rest and  $\Delta$ mPAP/ $\Delta$ CO slope

Variable	mPAP <sub>rest</sub> <25 mmHg		mPAP <sub>rest</sub> $\geq$ 25 mmHg	p-value
	$\Delta$ mPAP/ $\Delta$ CO slope $\leq$ 3 mmHg/L/min	$\Delta$ mPAP/ $\Delta$ CO slope >3 mmHg/L/min		
	n=29	n=42	n=22	
mPAP rest, mmHg	17.9 (3.9)	18.1 (3.2)	28.7 (4.6)* <sup>#</sup>	<0.001
mPAP peak, mmHg	33.6 (7.0)	39.1 (7.1)*	48.6 (6.7)* <sup>#</sup>	<0.001
PAWP rest, mmHg	9.0 (3.2)	7.8 (3.4)	10.7 (2.8) <sup>#</sup>	0.01
PAWP peak, mmHg	16.7 (4.2)	16.7 (4.1)	15.8 (3.7)	0.69
CO rest, L/min	5.3 (0.8)	4.9 (1.0)	5.5 (1.2)	0.07
CO peak, L/min	12.3 (1.4)	9.0 (2.1)*	9.0 (2.6)*	<0.001
CI rest, L/min/m <sup>2</sup>	2.8 (0.4)	2.9 (0.4)	3.1 (0.5)*	0.04
CI peak, L/min/m <sup>2</sup>	6.4 (0.8)	5.2 (1.1)*	5.0 (1.0)*	<0.001
PVR rest, WU	1.67 (0.57)	2.19 (0.97)	3.43 (1.51)* <sup>#</sup>	<0.001
PVR peak, WU	1.38 (0.37)	2.65 (1.04)*	3.97 (1.56)* <sup>#</sup>	<0.001
TPR rest, WU	3.4 (0.8)	3.8 (1.0)	5.5 (1.6)* <sup>#</sup>	<0.001
TPR peak, WU	2.7 (0.5)	4.6 (1.3)*	5.8 (1.8)* <sup>#</sup>	<0.001
mRAP rest, mmHg	5.5 (3.3)	4.7 (3.2)	6.9 (3.0) <sup>#</sup>	0.03
mRAP peak, mmHg	9.3 (4.2)	9.6 (2.4)	10.7 (3.3)	0.27
$\Delta$ mPAP/ $\Delta$ CO slope, mmHg/L/min	2.3 (0.6)	6.2 (3.5)*	7.3 (5.0)*	<0.001

**Notes:** ANOVA between the three groups. Values are presented as mean (standard deviation). \*p<0.05, significantly different from mPAP<sub>rest</sub> <25 mmHg and  $\Delta$ mPAP/ $\Delta$ CO slope  $\leq$ 3 mmHg/L/min. <sup>#</sup>p<0.05, significantly different from mPAP<sub>rest</sub> <25 mmHg and  $\Delta$ mPAP/ $\Delta$ CO slope >3 mmHg/L/min.

**Abbreviations:** mPAP, mean pulmonary artery pressure; CO, cardiac output; PAWP, pulmonary arterial wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; TPR, total pulmonary resistance; mRAP, mean right atrial pressure.

evaluation of left ventricle ejection fraction (LV EF) and right ventricle fractional area change (RV FAC) was similar between COPD-EIPH and COPD-normal, indicating preserved systolic function (Table 1).

### CPET

At peak exercise, there were no significant differences between COPD-EIPH and COPD-normal in % predicted values for  $\dot{V}O_2$ , ventilation, oxygen pulse, or lactate, but one or both groups differed from COPD-PH (Table 3). Heart rate (HR) and systemic blood pressure at peak exercise were similar in all three groups. Equal, but slightly reduced ventilatory efficiency was observed for COPD-EIPH and COPD-normal, as  $\dot{V}E/\dot{V}CO_2$  slope was 34 and 35, respectively.  $\dot{V}E/\dot{V}CO_2$  nadir was higher in COPD-PH compared to COPD-normal, but similar in COPD-EIPH and COPD-normal.

Mean exercise time was 15 minutes, with a wide range of 2–30 minutes.

Figure 1 shows the development of central CPET variables during the entire course of exercise for each individual, as well as the average for the three groups. Similar to the visual impression in Figure 1, ANOVA confirmed that there were no differences between COPD-EIPH and COPD-normal for  $PaO_2$  and  $PaCO_2$ , but both the groups were different from COPD-PH (Table 3). For the other CPET variables, the pattern was less consistent, and we must emphasize that with increasing load, few patients were represented in the calculation of the mean. Moreover, the variables in Figure 1A are dependent on gender and age distribution, which were different between the groups. Another aspect is the difference in exercise performance between the groups; they all achieved different mean work load ( $p < 0.001$ ) (Table 3).

**Table 3** Cardiopulmonary exercise test characteristics at rest and during exercise in 93 patients with COPD divided into three groups by mPAP at rest and  $\Delta mPAP/\Delta CO$  slope

Variable	mPAP <sub>rest</sub> <25 mmHg		mPAP <sub>rest</sub> ≥25 mmHg	p-value
	$\Delta mPAP/\Delta CO$ slope ≤3 mmHg/L/min	$\Delta mPAP/\Delta CO$ slope >3 mmHg/L/min		
	n=29	n=42	n=22	
Peak load, watt	89 (23)	60 (31)*	40 (21)*#	<0.001
$\dot{V}O_2$ peak, mL/kg/min	18.3 (4.8)	17.1 (3.9)	13.9 (3.0)*#	0.001
$\dot{V}O_2$ peak/kg % pred.	57 (16)	59 (14)	46 (13)*#	0.003
MVV rest, L/min <sup>a</sup>	67 (25)	47 (21)*	34 (12)*#	<0.001
Ventilation peak, L/min <sup>a</sup>	53 (15)	42 (15)*	35 (12)*	<0.001
Ventilation peak % pred.	58 (17)	55 (20)	43 (15)*	0.01
Ventilatory reserve, %	16 (25)	5 (19)	-7 (19)*	0.001
$\dot{V}E/\dot{V}CO_2$ nadir	36 (7)	37 (6)	41 (8)*	0.05
$\dot{V}E/\dot{V}CO_2$ slope	35 (9)	34 (8)	32 (9)	0.53
Heart rate rest, beats/min	87 (18)	90 (16)	96 (18)	0.16
Heart rate peak, beats/min	134 (18)	134 (17)	130 (19)	0.68
O <sub>2</sub> -pulse peak mL/beat	10.9 (2.7)	8.3 (2.5)*	7.5 (2.1)*	<0.001
O <sub>2</sub> -pulse peak % pred.	72 (14)	64 (20)	55 (12)*	0.003
Systemic MAP rest, mmHg	95 (12)	95 (16)	93 (10)	0.77
Systemic MAP peak, mmHg	133 (21)	136 (28)	129 (23)	0.55
RER peak	0.96 (0.13)	0.95 (0.13)	0.90 (0.12)	0.20
PaO <sub>2</sub> rest, mmHg	77 (11)	72 (8)	61 (11)*#	<0.001
PaO <sub>2</sub> peak, mmHg	74 (12)	68 (12)	50 (8)*#	<0.001
PaCO <sub>2</sub> rest, mmHg	39 (3)	41 (5)	44 (5)*	0.008
PaCO <sub>2</sub> peak, mmHg	41 (5)	43 (7)	48 (8)*#	<0.001
SaO <sub>2</sub> rest, % <sup>a</sup>	96 (2)	95 (2)*	92 (5)*#	<0.001
SaO <sub>2</sub> peak, % <sup>a</sup>	94 (3)	93 (4)	84 (8)*#	<0.001
pH peak	7.36 (0.03)	7.36 (0.03)	7.35 (0.04)	0.86
Lactate peak, mmol/L <sup>a</sup>	5.6 (2.2)	5.6 (2.9)	4.1 (2.4)*#	0.03
Lactate peak % pred. <sup>a</sup>	75 (31)	81 (42)	57 (39)*#	0.02

**Notes:** ANOVA was performed for variables with normal distribution, otherwise non-parametric Kruskal–Wallis test was performed. Values are presented as mean (standard deviation). \* $p < 0.05$ , significantly different from mPAP<sub>rest</sub> <25 mmHg and  $\Delta mPAP/\Delta CO$  slope ≤3 mmHg/L/min. # $p < 0.05$ , significantly different from mPAP<sub>rest</sub> <25 mmHg and  $\Delta mPAP/\Delta CO$  slope >3 mmHg/L/min.

**Abbreviations:** mPAP, mean pulmonary artery pressure; CO, cardiac output;  $\dot{V}O_2$ , oxygen uptake; pred., predicted;  $\dot{V}E$ , ventilation;  $\dot{V}CO_2$ , carbon dioxide production; O<sub>2</sub>-pulse, oxygen pulse; MAP, mean arterial pressure; RER, respiratory exchange ratio; PaO<sub>2</sub>, arterial oxygen tension; PaCO<sub>2</sub>, arterial carbon dioxide tension; SaO<sub>2</sub>, oxygen saturation; MVV, maximal voluntary ventilation.

This difference would influence CPET results. For example, all groups had similar peak HR, but due to different peak work load, the HR response could still be different between the groups.

To be able to compare the three groups despite the differences, we have fitted a LMM which included the values of a variable at rest and all exercise levels for each patient, and adjusted for gender, age, and FEV<sub>1</sub>. Estimates of intercept and slope, as well as the difference between COPD-EIPH and the two other groups, are shown in Table 4. The intercept did not differ between COPD-EIPH and COPD-normal for any of the variables. The slope, however, was significantly different between COPD-EIPH and COPD-normal for

several CPET parameters. With increasing load, considering all measurements during exercise after adjustment for gender, age, and FEV<sub>1</sub>, COPD-EIPH showed a steeper slope with higher increase in  $\dot{V}O_2$  ( $p < 0.001$ ), ventilation ( $p = 0.05$ ), respiratory frequency ( $p = 0.004$ ), HR ( $p < 0.001$ ), and lactate ( $p = 0.002$ ) compared to COPD-normal (Table 4). For the same variables, there were no differences between COPD-EIPH and COPD-PH. COPD-EIPH demonstrated a modest, but significant reduction in pH compared to COPD-normal ( $p = 0.005$ ). For PaO<sub>2</sub>, we observed that the intercept was lower ( $p < 0.001$ ) and the decline steeper ( $p < 0.001$ ) in COPD-PH compared to COPD-EIPH, whereas there were no differences between COPD-EIPH and COPD-normal.

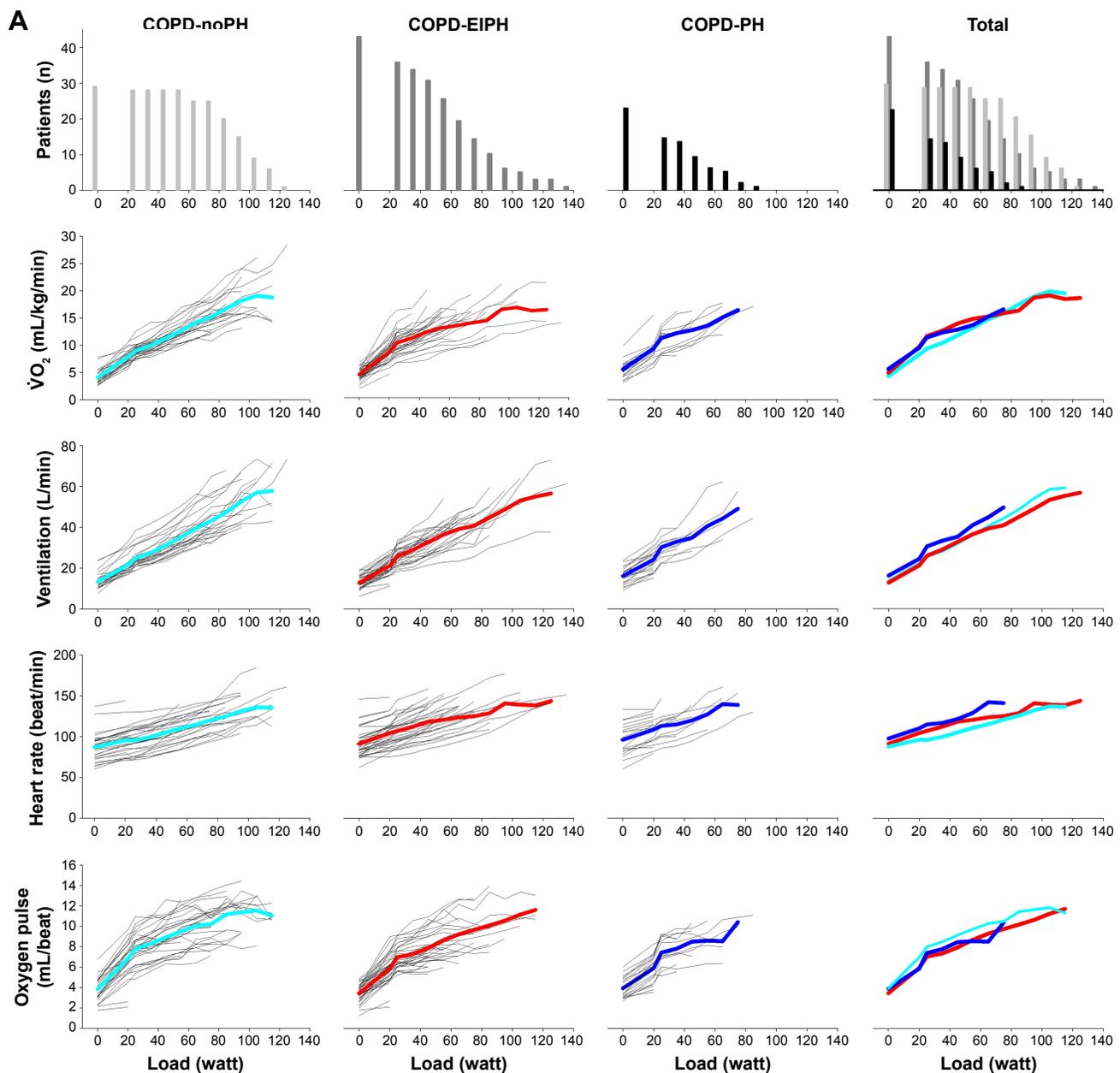
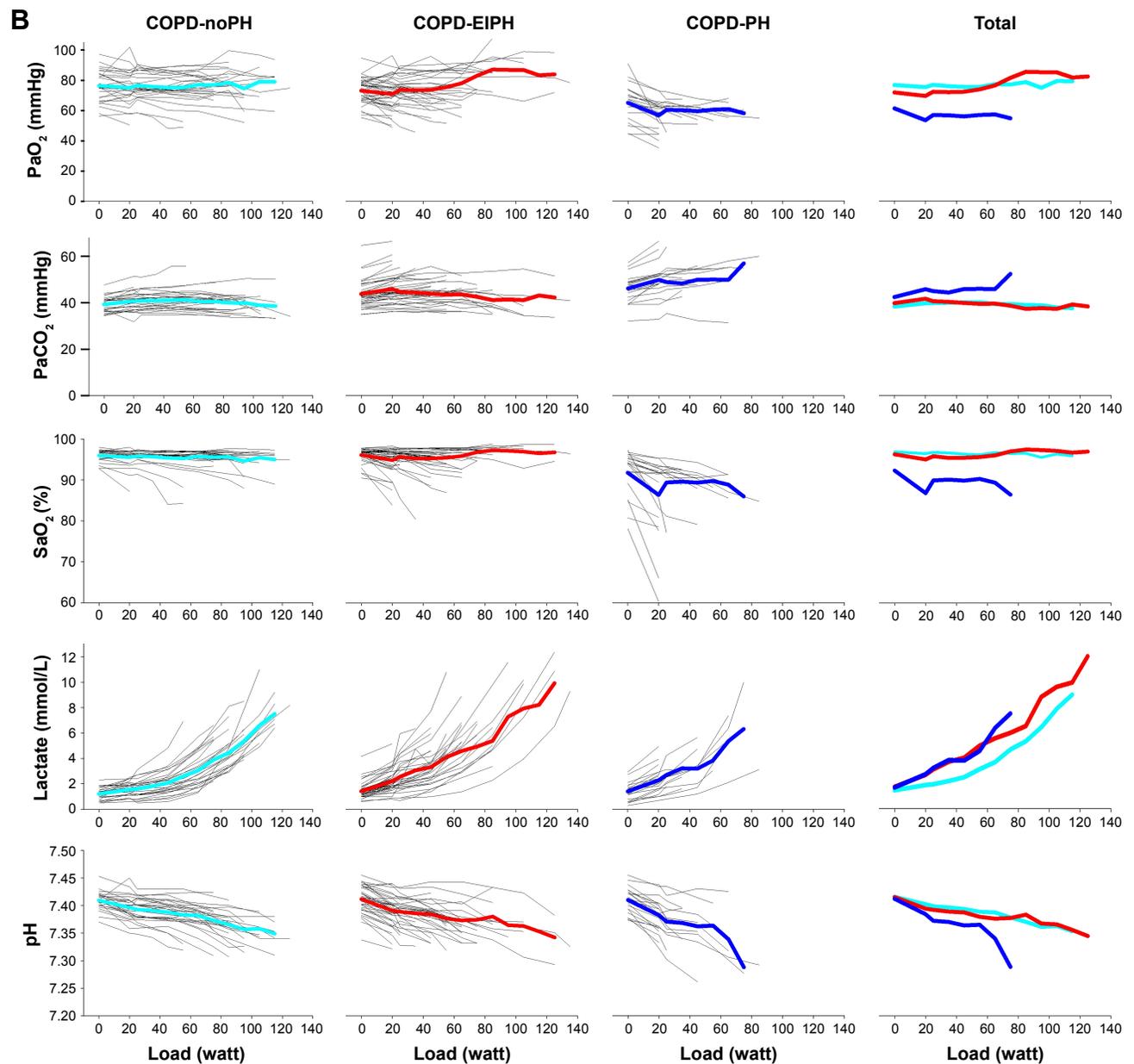


Figure I (Continued)



**Figure 1** (A) First horizontal panel shows the number of COPD patients able to exercise at a specific load; from left to right the graphs present patients with normal hemodynamic response, patients with exercise-induced pulmonary hypertension, patients with pulmonary hypertension and all patients. The next panels show the development of variables during exercise for each patients, as well as the mean values represented by light blue lines for COPD-normal, red lines for COPD-EIPH, and dark blue lines for COPD-PH. With increasing load, fewer patients are represented in the presentation of the mean. (B) Development of arterial blood gases, lactate, and pH during exercise. **Abbreviations:** EIPH, exercise-induced pulmonary hypertension; PaO<sub>2</sub>, arterial oxygen tension; PaCO<sub>2</sub>, arterial carbon dioxide tension; PH, pulmonary hypertension; SaO<sub>2</sub>, oxygen saturation; VO<sub>2</sub>, oxygen uptake.

For PaCO<sub>2</sub>, we observed a more pronounced increase during exercise in COPD-PH compared to COPD-EIPH, but no differences between COPD-EIPH and COPD-normal.

## Discussion

### CPET

In this study of stable outpatients with COPD in whom LV disease was excluded in advance, we have identified patients characterized by normal mPAP at rest accompanied by a disproportionate increase in mPAP relative to CO

during exercise, representing EIPH. This group could not be identified by CPET results at peak exercise. As differences in gender and age affected some of the CPET variables, it was relevant to compare the measurements as % predicted values, which were similar between the COPD-EIPH and COPD-normal groups. However, when we applied a statistical model that included measurements at every load level and adjusted for gender, age, and FEV<sub>1</sub>, the patients with COPD-EIPH experienced a higher cost of exercise in terms of higher oxygen uptake, ventilation, respiratory frequency,

**Table 4** Estimated differences between COPD patients with normal exercise responses, exercise-induced pulmonary hypertension, and pulmonary hypertension at rest in a linear mixed model that includes measurements at rest and each level of exercise, adjusted for gender, age, and FEV<sub>1</sub>

Variable		Estimate (95% CI)	Difference (95% CI)	p-value
<b><math>\dot{V}O_2</math>, mL/kg/min</b>	<b>Level/intercept</b>			
	COPD-EIPH (n=29)	2.5 (-0.5, 5.5)		0.10
	COPD-normal (n=42)		-0.3 (-0.8, 0.3)	0.34
	COPD-PH (n=22)		-0.1 (-0.8, 0.7)	0.82
	<b>Slope</b>			
	COPD-EIPH	1.9 (1.7, 2.1)		<0.001
COPD-normal		-0.5 (-0.8, -0.3)	<0.001	
COPD-PH		0.2 (-0.2, 0.6)	0.20	
<b>Ventilation, L/min</b>	<b>Level/intercept</b>			
	COPD-EIPH	1.5 (-7.7, 10.7)		0.75
	COPD-normal		1.2 (-0.7, 3.1)	0.20
	COPD-PH		3.3 (1.7, 5.6)	<b>0.04</b>
	<b>Slope</b>			
	COPD-EIPH	4.6 (4.2, 5.0)		<0.001
COPD-normal		-0.5 (-1.1, 0.0)	0.05	
COPD-PH		0.4 (-0.4, 1.1)	0.31	
<b>Respiratory frequency, breaths/min</b>	<b>Level/intercept</b>			
	COPD-EIPH	14 (2, 26)		0.02
	COPD-normal		1 (-1, 4)	0.27
	COPD-PH		3 (0.3, 6)	<0.001
	<b>Slope</b>			
	COPD-EIPH	2.3 (1.9, 2.6)		<0.001
COPD-normal		-0.6 (-1.1, -0.2)	<b>0.004</b>	
COPD-PH		0.0 (-0.6, 0.6)	0.91	
<b>Heart rate, beats/min</b>	<b>Level/intercept</b>			
	COPD-EIPH	111 (73, 149)		<0.001
	COPD-normal		5 (-5, 14)	0.32
	COPD-PH		-1 (-12, 9)	0.83
	<b>Slope</b>			
	COPD-EIPH	7.7 (6.8, 8.7)		<0.001
COPD-normal		-2.6 (-4.1, -1.1)	<0.001	
COPD-PH		1.1 (-0.7, 2.9)	0.23	
<b>O<sub>2</sub>-pulse, mL/beat</b>	<b>Level/intercept</b>			
	COPD-EIPH	2.5 (-0.01, 5.1)		0.05
	COPD-normal		0.3 (-0.2, 0.9)	0.24
	COPD-PH		0.2 (-0.4, 0.9)	0.48
	<b>Slope</b>			
	COPD-EIPH	0.65 (0.57, 0.73)		<0.001
COPD-normal		-0.01 (-0.12, 0.11)	0.90	
COPD-PH		-0.15 (-0.003, 0.33)	0.11	
<b>PaO<sub>2</sub>, mmHg</b>	<b>Level/intercept</b>			
	COPD-EIPH	61 (42, 80)		<0.001
	COPD-normal		-0.4 (-5, 4)	0.87
	COPD-PH		-6 (-11, -2)	<b>0.01</b>
	<b>Slope</b>			
	COPD-EIPH	-0.6 (-1.1, -0.1)		0.03
COPD-normal		0.3 (-0.5, 1.1)	0.41	
COPD-PH		-2.0 (-3.1, -1.0)	<0.001	
<b>PaCO<sub>2</sub>, mmHg</b>	<b>Level/intercept</b>			
	COPD-EIPH	48 (38, 62)		<0.001
	COPD-normal		-0.8 (-3.0, 1.5)	0.50
	COPD-PH		0.8 (-2.3, 3.0)	0.65

(Continued)

**Table 4** (Continued)

Variable		Estimate (95% CI)	Difference (95% CI)	p-value
<b>Lactate, mmol/L</b>	<b>Slope</b>			
	COPD-EIPH	0.5 (0.2, 0.7)		0.002
	COPD-normal		-0.2 (-0.7, 0.1)	0.15
	COPD-PH		0.9 (0.5, 1.4)	<b>&lt;0.001</b>
	<b>Level/intercept</b>			
	COPD-EIPH	-0.2 (-2.2, 1.8)		0.85
<b>pH</b>	COPD-normal		0.1 (-0.3, 0.5)	0.73
	COPD-PH		0.1 (-0.6, 0.5)	0.83
	<b>Slope</b>			
	COPD-EIPH	0.8 (0.6, 0.9)		<0.001
	COPD-normal		-0.3 (-0.4, 0.1)	<b>0.002</b>
	COPD-PH		0.1 (-0.1, 0.3)	0.52
<b>pH</b>	<b>Level/intercept</b>			
	COPD-EIPH	7.34 (7.31, 7.41)		<0.001
	COPD-normal		0.003 (-0.008, 0.138)	0.60
	COPD-PH		0.006 (-0.006, 0.019)	0.31
	<b>Slope</b>			
	COPD-EIPH	-0.01 (-0.01, -0.01)		<0.001
COPD-normal		0.004 (0.001, 0.006)	<b>0.005</b>	
COPD-PH		-0.006 (-0.01, -0.00)	<b>0.002</b>	

**Notes:** COPD-EIPH: mPAP<sub>rest</sub> <25 mmHg and  $\Delta$ mPAP/ $\Delta$ CO slope >3 mmHg/L/min. COPD-normal: mPAP<sub>rest</sub> <25 mmHg and  $\Delta$ mPAP/ $\Delta$ CO slope  $\leq$ 3 mmHg/L/min. COPD-PH: mPAP<sub>rest</sub>  $\geq$ 25 mmHg. Reference group: COPD-EIPH. Significant differences between groups are shown in bold.

**Abbreviations:** mPAP, mean pulmonary artery pressure; CO, cardiac output;  $\dot{V}O_2$ , oxygen uptake;  $\dot{V}O_2$ -pulse, oxygen pulse; PaO<sub>2</sub>, arterial oxygen tension; PaCO<sub>2</sub>, arterial carbon dioxide tension; SaO<sub>2</sub>, oxygen saturation; EIPH, exercise-induced pulmonary hypertension; PH, pulmonary hypertension.

HR, and lactate for a given increase in workload compared to those classified as COPD-normal. The increased ventilation likely reflects ventilation perfusion mismatch caused by lung parenchymal pathology and/or cardio-circulatory abnormality. Reduced ventilatory efficiency with slightly elevated  $\dot{V}E/\dot{V}CO_2$  slope and  $\dot{V}E/\dot{V}CO_2$  nadir further supports this explanation. The higher respiratory frequency indicates restricted tidal volumes and could be secondary to dynamic hyperinflation with reduced inspiratory capacity. This assumption is supported by higher residual volume and lower DLCO, indicating more emphysema in patients with COPD-EIPH compared to those classified as COPD-normal. The cost of extra ventilation could explain the higher  $\dot{V}O_2$  at a given external load. The higher HR reflects cardiovascular stress or deconditioning; as there was no significant difference in PaO<sub>2</sub>, tachycardia induced by hypoxemia seems less likely. The higher lactate and lower pH is associated with anaerobic exercise and inability to increase CO; this could be caused by the high mPAP during exercise or by deconditioning.

PaO<sub>2</sub> and PaCO<sub>2</sub> were similar in the COPD-EIPH and COPD-normal groups. As low PaO<sub>2</sub> is associated with increased mPAP at rest,<sup>3,25,26</sup> we were surprised to find that the brisk increase in mPAP relative to CO during exercise in COPD-EIPH compared to COPD-normal was not associated

with lower PaO<sub>2</sub>. However, similar PaO<sub>2</sub> in EIPH and hemodynamically normal patients was also observed by Degani-Costa et al in a study of patients with interstitial lung disease.<sup>27</sup> As all the significant differences we observed between COPD-EIPH and COPD-normal in LMM analyses are related to the slope rather than the intercept, we conclude that the change in a CPET variable for a given increase in workload is the best way to describe differences.

As all patients performed the same exercise protocol, we observed a wide range in the duration of exercise. The fit patients exercised for a longer period than recommended for CPET; however, test results would most probably have been the same with a shorter duration. The chosen exercise protocols allowed us to apply the LMMs and to compare similar exercise levels for CPET and RHC.

### Age and gender differences

When patients with mPAP <25 mmHg were divided into two groups by the  $\Delta$ mPAP/ $\Delta$ CO slope, differences in age ( $p=0.02$ ,  $t$ -test) and gender ( $p=0.01$ ) distribution were observed. All patients were  $\geq$ 50 years old. Fourteen patients (33%) with COPD-EIPH were aged  $\geq$ 70 years, in contrast to three patients (10%) classified as COPD-normal, and 70% of patients aged  $\geq$ 70 years were defined as COPD-EIPH. A steeper  $\Delta$ mPAP/ $\Delta$ CO slope with advancing age is in line

with the findings in healthy individuals.<sup>28–30</sup> Accordingly, age must be considered as a potential confounder in the observed characteristics of patients with EIPH. The difference in gender distribution, with significantly more women in the COPD-EIPH group compared to COPD-normal, was more unexpected. In a study based on exercise stress echocardiography, Argiento et al found similar mPAP–flow relationship for both the genders.<sup>28</sup> During exercise, healthy male patients achieved higher workload and CO, accompanied by higher mPAP, compared to healthy female patients, but the  $\Delta\text{mPAP}/\Delta\text{CO}$  slope was similar. Calculation of distensibility coefficient  $\alpha$  demonstrated that women below the age of 50 years have more distensible vessels, an effect that tapers off after menopause.<sup>28</sup> All our patients were older than 50 years, and very few studies have compared gender differences in  $\Delta\text{mPAP}/\Delta\text{CO}$  slope for healthy patients above this age. Our results suggest that the gender difference observed reflects that the women included in our study actually had more dysfunctional pulmonary circulation.

### PAWP and diastolic dysfunction

In our study population, a steep  $\Delta\text{mPAP}/\Delta\text{CO}$  slope was associated mainly with precapillary pathology of the pulmonary circulation. However, a steep slope may potentially result from LV pathology with increased PAWP. All patients had normal PAWP at rest. Mean PAWP peak was within normal limits and identical (16.7 mmHg) for COPD-normal and COPD-EIPH. However, in COPD-normal and COPD-EIPH, five (17%) and seven (17%) patients, respectively, experienced a PAWP peak of 21–26 mmHg. In the COPD-EIPH group, four of the seven patients with high PAWP peak had PVR >1.5 WU, indicating predominantly precapillary pathology, but for the other patients with high PAWP peak, diastolic dysfunction could not be completely ruled out.

### Clinical relevance

Due to differences in gender, age, and pulmonary function between the three groups, a direct comparison of CPET characteristics in COPD-normal and COPD-EIPH was difficult, and we were not able to discern CPET differences between the two groups in unadjusted analyses. After applying LMMs adjusted for these differences, several CPET variables differed between the groups, but as significant differences only appeared after multivariable adjustment, they may have more theoretical than clinical value; thus CPET does not appear to represent a suitable method to identify COPD-EIPH. Nevertheless, evaluation of the physiologic responses across an entire course of exercise provides insights to the

physiology of COPD. The clinical relevance of diagnosing PH in COPD remains under debate<sup>31</sup> and that of EIPH is even more uncertain.<sup>31–33</sup> However, a brisk increase in mPAP with exercise in COPD patients may be prognostic for subsequently developing PH<sup>34</sup> associated with increased morbidity and mortality.<sup>34</sup> Increase in  $\Delta\text{mPAP}/\Delta\text{CO}$  slope over time may indicate reduced  $\dot{V}\text{O}_2$  and exercise capacity, as recently shown in patients with scleroderma.<sup>35</sup> We therefore recommend that hemodynamic dysfunction is considered more often in the evaluation of patients with COPD.

### Limitations

Our results may not be applicable to the general COPD population as patients with common comorbidities affecting left heart function were excluded.

The  $\Delta\text{mPAP}/\Delta\text{CO}$  slope is defined by two measurement points, as CO was measured at rest and peak exercise. Multiple measurements of both mPAP and CO during exercise would have increased the accuracy of the slope.

Measurements of inspiratory capacity in order to assess dynamic hyperinflation were unfortunately not performed. It is likely that some of the study patients experienced dynamic hyperinflation to an extent that affected hemodynamic measurements. Exercise hemodynamics is difficult to interpret in COPD patients due to the augmented pressure swings during the respiratory cycle.<sup>36,37</sup> The intrathoracic pressure is most positive at end-expiration, where we have performed our hemodynamic measurements, and this may add to the intravascular pressure.<sup>13,36,37</sup> We have not been able to correct our invasive measurements for intrathoracic pressure, thus mPAP and PAWP may be overestimated in some patients. However, for the patients defined as EIPH by the relative change in mPAP to CO, the absolute value has less impact, as all measurements were performed at end-expiration.

Reference values for CPET are based on treadmill exercise, thus % predicted  $\dot{V}\text{O}_2$  may be slightly underestimated; however, this would not be expected to significantly affect the evaluation of differences between the groups.

### Conclusion

In this CPET study of COPD outpatients where LV disease was excluded in advance, we have identified a group of patients presenting with EIPH characterized by normal mPAP at rest accompanied by an disproportionate increase in mPAP relative to CO during exercise with  $\Delta\text{mPAP}/\Delta\text{CO}$  slope >3 mmHg/L/min. EIPH is common in COPD and was observed in 45% of the study population. COPD-EIPH

could not be discriminated from COPD-normal by a direct comparison of CPET data. However, when we considered the entire course of exercise and adjusted for differences in age, gender, and airflow obstruction, we observed that patients with COPD-EIPH experienced a higher cost of exercise in terms of greater increase in oxygen uptake, ventilation, respiratory frequency, HR, and lactate for a given increase in workload compared to patients with normal hemodynamic responses. This indicates that there are physiological differences between the two groups. Hemodynamic responses during exercise are important, and further studies, for both healthy controls and COPD patients, are requested.

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## Disclosure

The authors report no conflicts of interest in this work.

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