

# Pulmonary hemodynamic profile in chronic obstructive pulmonary disease

Karina Portillo<sup>1</sup>  
 Yolanda Torralba<sup>1,2</sup>  
 Isabel Blanco<sup>1,2</sup>  
 Felip Burgos<sup>1,2</sup>  
 Roberto Rodriguez-Roisin<sup>1,2</sup>  
 Jose Rios<sup>3</sup>  
 Josep Roca<sup>1,2</sup>  
 Joan A Barberà<sup>1,2</sup>

<sup>1</sup>Department of Pulmonary Medicine, Hospital Clínic-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain; <sup>2</sup>Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain; <sup>3</sup>Biostatistics and Data Management Core Facility, Hospital Clínic-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Biostatistics Unit, School of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain

**Introduction:** Few data are available in regards to the prevalence of pulmonary hypertension (PH) in the broad spectrum of COPD. This study was aimed at assessing the prevalence of PH in a cohort of COPD patients across the severity of airflow limitation, and reporting the hemodynamic characteristics at rest and during exercise.

**Methods:** We performed a retrospective analysis on COPD patients who underwent right-heart catheterization in our center with measurements obtained at rest (n=139) and during exercise (n=85). PH was defined as mean pulmonary artery pressure (mPAP)  $\geq 25$  mmHg and pulmonary capillary wedge pressure  $< 15$  mmHg. Exercise-induced PH (EIPH) was defined by a ratio of  $\Delta$ mPAP/ $\Delta$ cardiac output  $> 3$ .

**Results:** PH was present in 25 patients (18%). According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification, PH prevalence in GOLD 2 was 7% (3 patients); 25% (14 patients) in GOLD 3; and 22% (8 patients) in GOLD 4. Severe PH (mPAP  $\geq 35$  mmHg) was identified in four patients (2.8%). Arterial partial oxygen pressure was the outcome most strongly associated with PH ( $r = -0.29$ ,  $P < 0.001$ ). EIPH was observed in 60 patients (71%) and had a similar prevalence in both GOLD 2 and 3, and was present in all GOLD 4 patients. Patients with PH had lower cardiac index during exercise than patients without PH ( $5.0 \pm 1.2$  versus  $6.7 \pm 1.4$  L/min/m<sup>2</sup>, respectively;  $P = 0.001$ ).

**Conclusion:** PH has a similar prevalence in COPD patients with severe and very-severe airflow limitation, being associated with the presence of arterial hypoxemia. In contrast, EIPH is highly prevalent, even in moderate COPD, and might contribute to limiting exercise tolerance.

**Keywords:** pulmonary hypertension, right heart catheterization, cardiac index, GOLD

## Introduction

Pulmonary hypertension (PH) is a relevant complication in the natural history of patients with chronic obstructive pulmonary disease (COPD), since its presence is associated with shorter survival, increased risk of exacerbations, and greater use of health care resources.<sup>1</sup> The actual prevalence of PH in COPD remains unsettled and varies widely according to the targeted population, the definition applied, and the diagnostic approach used to identify PH.<sup>2</sup> Right-heart catheterization is the gold standard to diagnose PH.<sup>3</sup> In COPD, most hemodynamic studies have been performed in patients with advanced disease in whom PH is expected to occur more frequently, with a prevalence of PH ranging from 23%–91%.<sup>4–12</sup> Information on the prevalence of PH in patients with milder disease is scarce. Based on the former Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric classification,<sup>13</sup> Hilde et al<sup>14</sup> reported a prevalence of 5%, 27%, and 53% in patients with GOLD stages 2, 3, and 4, respectively.

Patients with COPD may develop PH during exercise, a condition associated with an increased risk for subsequently developing PH at rest.<sup>12</sup> Current understanding of

Correspondence: Joan A Barberà  
 Department of Pulmonary Medicine,  
 Hospital Clínic, Villarroel 170, 08036  
 Barcelona, Spain  
 Tel +34 932 275 747  
 Fax +34 932 255 455  
 Email jbarbera@clinic.ub.es

the hemodynamic response of the pulmonary circulation to exercise in patients with COPD and its impact over exercise intolerance is limited. Studies have shown a cardiovascular limitation to exercise in patients with severe PH which seems to be distinct from the ventilatory exhaustion usually observed in COPD.<sup>15,16</sup>

In order to expand our understanding of the hemodynamic profile of PH across the spirometric degrees of COPD, we analyzed data from 139 COPD patients assessed by right-heart catheterization at rest. A subset of these patients (n=85) had hemodynamic measurements during exercise. The main objective of the present study was to assess the prevalence of PH in this cohort of patients according to the GOLD spirometric grades. Secondary aims were to describe the hemodynamic characteristics at rest and during exercise, and to analyze the potential relationships between pulmonary hemodynamics and lung function tests.

## Methods

This was a retrospective study, which included data from seven previously reported studies.<sup>17–23</sup> All studies were approved by our institutional ethics committee and the procedures were performed after obtaining written informed consent. All involved patients were clinically stable (ie, at least 3 months from the last COPD exacerbation), without cardiac failure or other coexisting chronic respiratory disease, and received regular treatment for COPD, including long-term oxygen if it was deemed necessary. No patient was treated with PH targeted therapy, namely prostanoids, endothelin-receptor antagonists, or phosphodiesterase-5 inhibitors. All were current (n=53) or former (n=86) smokers ( $\geq 10$  pack-year). Patients were classified according to the GOLD spirometric grade system.<sup>24</sup>

PH was defined by a mean pulmonary artery pressure (mPAP)  $\geq 25$  mmHg and a pulmonary capillary wedge pressure (PCWP)  $< 15$  mmHg.<sup>2</sup> Severe PH was considered when mPAP was  $\geq 35$  mmHg or  $\geq 25$  mmHg along with a cardiac index (CI)  $< 2.0$  L/min/m<sup>2</sup>, according to the most updated clinical classification of PH in chronic lung diseases.<sup>3</sup> An abnormal increase of mPAP during exercise was considered when the change in mPAP ( $[\Delta\text{mPAP}]$  in mmHg) was  $> 3$ -times greater than the change in cardiac output ( $[\text{CO}]$  in L/min) ( $\Delta\text{CO}$ ).<sup>14,25</sup> As age may influence exercise mPAP, we also analyzed the mPAP values during exercise according to those reported by Kovacs et al<sup>26</sup> who established the upper limit of normal as 30 mmHg for subjects  $< 50$  years and as 46 mmHg for subjects  $\geq 50$  years.

## Measurements

### Lung function

Forced spirometry, static lung volumes, and single-breath carbon monoxide diffusing capacity (DLco) were measured according to the American Thoracic Society/European Respiratory Society recommendations,<sup>27</sup> using our own predicted equations.<sup>28–29</sup> Arterial blood gas samples were drawn for measuring partial pressure of arterial oxygen (PaO<sub>2</sub>), partial pressure of arterial carbon dioxide (PaCO<sub>2</sub>), and pH at rest and during exercise.

### Right-heart catheterization

A triple-lumen Swan–Ganz catheter (Edwards Laboratories, Santa Ana, CA, USA) was placed into the pulmonary artery under pressure wave monitoring (M1166A; Hewlett-Packard, Boeblingen, Germany). Transducers were zeroed at the level of right atrium. Right atrial pressure (RAP), pulmonary artery pressure (PAP), and PCWP were measured at the end of expiration. CO was measured by thermodilution and expressed as the mean of three measurements. CI, pulmonary vascular resistance (PVR), and total pulmonary resistance were calculated using standard formulae.<sup>30</sup>

### Exercise measurements

Prior to catheterization, the highest workload that patients could tolerate was determined by an incremental exercise test on a cycle ergometer in 85 subjects. The workload was increased using a ramp of 5 Watts every minute until the maximal load limited by symptoms was achieved. Hemodynamic and gas exchange measurements were performed in the semirecumbent position at a workload equivalent to 60% of the maximal workload tolerated in the previous incremental test.

## Statistical analysis

Data are expressed as mean  $\pm$  standard deviation unless otherwise stated. One-way analysis of variance with Bonferroni correction was used to compare more than two groups. Relationships between variables were assessed using Pearson's or Spearman's correlation coefficients depending on data distribution. Changes in hemodynamic data from rest to exercise were compared using paired *t*-tests. The Mann–Whitney *U*-test was used to assess CI during exercise in patients with and without PH. Estimations of risk for PH were made using odds ratios and their 95% confidence intervals from univariate logistic regression models for PaO<sub>2</sub>, DLco, PaCO<sub>2</sub>, inspiratory capacity, or forced expiratory volume in 1 second (FEV<sub>1</sub>). In order to assess a multivariate model, we

used a forward stepwise procedure with a criterion of 0.05 to select variables for the final model. All data were analyzed with SPSS version 18 and  $P$ -values  $<0.05$  were considered as statistically significant.

## Results

The means ( $\pm$  standard deviation) of demographic and lung function measurements for all participants are given in Table 1 as a function of the current GOLD spirometric classification.<sup>24</sup> One hundred and thirty-nine patients (134 men, 5 women) were included. Mean age was  $63\pm 8$  years. The mean of post-bronchodilator FEV<sub>1</sub> was  $41\%\pm 16\%$  of predicted; PaO<sub>2</sub> was  $69\pm 12$  mmHg; PaCO<sub>2</sub> was  $40\pm 6$ ; and alveolar–arterial oxygen partial pressure difference (AaPO<sub>2</sub>) was  $32\pm 10$  mmHg. Thirty-seven patients were under long-term oxygen therapy.

### Hemodynamic characteristics at rest

Table 2 shows the hemodynamic measurements at rest. The mean mPAP of the whole cohort was  $20\pm 8$  mmHg. PH was present in 25 patients (18% of cases of the whole cohort). Most of them had severe or very-severe airflow limitation, although PH prevalence was similar in GOLD 3 and 4.

Mean PVR was normal in GOLD 2 and 3, although with a wide dispersion, and elevated in GOLD 4. RAP, PCWP, and

CI were on average within normal range in all GOLD grades. The CI correlated with FEV<sub>1</sub> ( $r=0.38$ ,  $P<0.001$ ). Severe PH was noticed in four patients (2.8% of the whole cohort). All of them were male. Their lung function and hemodynamic characteristics are listed in Table 3.

### Hemodynamic characteristics during exercise and changes in blood gases

Both mPAP and PCWP increased significantly during exercise in all GOLD grades (Figure 1; Table 4). An abnormal increase of mPAP during exercise, defined by a  $\Delta$ mPAP/ $\Delta$ CO ratio  $>3$ , was observed in 60 patients (71%): 28 patients (70%) were in GOLD 2, 26 (67%) in GOLD 3, and the remaining six patients in GOLD 4. During exercise, patients with PH, compared with those without PH, had lower CI ( $5.0\pm 1.2$  and  $6.7\pm 1.4$  L/min/m<sup>2</sup>, respectively;  $P=0.001$ ) (Figure 2). Patients with associated PH had, as compared with patients without PH, lower PaO<sub>2</sub> and higher PaCO<sub>2</sub> both at rest and during exercise (Table 5).

### Variables associated with PH

In the univariate analysis, the following outcomes were associated with the presence of PH at rest: PaO<sub>2</sub>; DLco (% predicted); PaCO<sub>2</sub>; inspiratory capacity (% predicted); and FEV<sub>1</sub> (% predicted). In the stepwise multiple regression

**Table 1** Anthropometric and functional characteristics of 139 patients grouped according to GOLD spirometric grades

	All	GOLD grade			ANOVA P-value
		2	3	4	
N	139	46	56	37	
Sex, M/F	134/5	46/0	53/3	35/2	
Age (yr)	63 $\pm$ 8	63 $\pm$ 8	63 $\pm$ 7	60 $\pm$ 7	NS
BMI (m/kg <sup>2</sup> )	25 $\pm$ 4	24 $\pm$ 4	26 $\pm$ 3	24 $\pm$ 4	NS
FVC (% pred)	72 $\pm$ 18	82 $\pm$ 14	71 $\pm$ 17*	60 $\pm$ 17*#	$<0.001$
FEV <sub>1</sub> (L)	1.3 $\pm$ 0.6	1.9 $\pm$ 0.5	1.2 $\pm$ 0.2*	0.7 $\pm$ 0.2*#	$<0.001$
FEV <sub>1</sub> (% pred)	41 $\pm$ 16	59 $\pm$ 7	39 $\pm$ 6*	20 $\pm$ 4*#	$<0.001$
FEV <sub>1</sub> /FVC (%)	40 $\pm$ 15	52 $\pm$ 8	41 $\pm$ 14*	25 $\pm$ 8*#	$<0.001$
TLC (% pred)	116 $\pm$ 21	113 $\pm$ 17	112 $\pm$ 22	124 $\pm$ 22#	0.004
RV (% pred)	200 $\pm$ 75	156 $\pm$ 44	191 $\pm$ 69*	266 $\pm$ 68*#	$<0.001$
IC (% pred)	62 $\pm$ 18	76 $\pm$ 16	63 $\pm$ 16*	47 $\pm$ 12*#	$<0.001$
RV/TLC (%)	61 $\pm$ 11	52 $\pm$ 8	59 $\pm$ 9*	71 $\pm$ 8*#	$<0.001$
IC/TLC ratio	0.26 $\pm$ 0.07	0.32 $\pm$ 0.06	0.27 $\pm$ 0.07*	0.18 $\pm$ 0.05*#	$<0.001$
DLco (% pred)	57 $\pm$ 25	72 $\pm$ 23	59 $\pm$ 21*	36 $\pm$ 15*#	$<0.001$
PaO <sub>2</sub> (mmHg)	69 $\pm$ 12	77 $\pm$ 10	68 $\pm$ 11*	62 $\pm$ 11*#	$<0.001$
PaCO <sub>2</sub> (mmHg)	40 $\pm$ 6	37 $\pm$ 4	41 $\pm$ 6*	45 $\pm$ 7*#	$<0.001$
AaPO <sub>2</sub> (mmHg)	32 $\pm$ 10	30 $\pm$ 11	32 $\pm$ 9	34 $\pm$ 10	NS

**Notes:** Data are presented as means  $\pm$  standard deviation. Significant differences within each variable are indicated as: \*different from GOLD grade 2; #different from GOLD grade 3.

**Abbreviations:** AaPO<sub>2</sub>, alveolar–arterial oxygen partial pressure difference; ANOVA, analysis of variance; BMI, body mass index; DLco, diffusing capacity for carbon dioxide; FEV<sub>1</sub>, post-bronchodilator forced expiratory volume in 1 second; FEV<sub>1</sub>/FVC, post-bronchodilator forced expiratory volume in 1 second/post-bronchodilator forced vital capacity; FVC, post-bronchodilator forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; IC, inspiratory capacity; IC/TLC, inspiratory capacity/total lung capacity ratio; M/F, male/female; NS, not significant; PaCO<sub>2</sub>, partial pressure of arterial carbon dioxide; PaO<sub>2</sub>, partial pressure of arterial oxygen; pred, predicted; RV, residual volume; RV/TLC, residual volume/total lung capacity ratio; TLC, total lung capacity.

**Table 2** Pulmonary hemodynamics at rest of 139 patients grouped according to the GOLD spirometric grades

	All	GOLD grade			ANOVA P-value
		2	3	4	
N	139	46	56	37	
mPAP (mmHg)	20±8	18±6	21±9	21±6	NS
PCWP (mmHg)	6±4	7±4	6±4	5±3	NS
RAP (mmHg)	2.9±3.2	3.4±3.5	2.1±3.2	2.7±2.7	NS
CO (L/min/m <sup>2</sup> )	5.6±1.4	6.3±1.5	5.5±1.3*	4.7±0.8*#	<0.001
CI (L/min/m <sup>2</sup> )	3.2±0.8	3.6±0.8	3.1±0.7*	2.8±0.6*#	<0.001
TPR (dyn·s·cm <sup>-5</sup> )	306±158	244±105	322±197*	355±191*#	0.004
PVR (dyn·s·cm <sup>-5</sup> )	218±143	160±88	233±185*	264±97*#	0.003
TPG	14±7	12±5	15±8	16±5*#	0.02
Patients with PH, n (%)	25 (18)	3 (7)	14 (25)	8 (22)	

**Notes:** Data are presented as mean ± standard deviation. Significant differences within each variable are indicated as: \*different from GOLD grade 2; #different from GOLD grade 3.

**Abbreviations:** ANOVA, analysis of variance; CI, cardiac index; CO, cardiac output; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; mPAP, mean pulmonary artery pressure; NS, not significant; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; TPG, transpulmonary pressure gradient; TPR, total pulmonary resistance.

model, PaO<sub>2</sub> was the only covariate associated with the presence of PH (Table 6).

## Discussion

The current study, which includes pulmonary hemodynamic measurements at rest and during exercise in a stable population of COPD across the whole spirometric spectrum of severity, identified several findings. First, the overall prevalence of PH in our cohort was relatively low (18%). Second, patients in GOLD 3 and 4 had similar a prevalence of PH. Third, a significant increase of both mPAP and PCWP during exercise was noticed in all patients with a high proportion of an “exercise hypertensive response” in the entire cohort. And fourth, CI during exercise was affected by the presence of PH.

Data about the prevalence of PH in COPD, particularly in patients with moderate-to-severe COPD, is limited. The prevalence found in our study was lower than in a recent study by Hilde et al<sup>14</sup> who reported a prevalence of PH of 27% in stable patients in GOLD 2–4. Interestingly, the prevalence of PH observed in the present study in patients with GOLD 2 and 3 was similar to that reported by Hilde et al.<sup>14</sup>

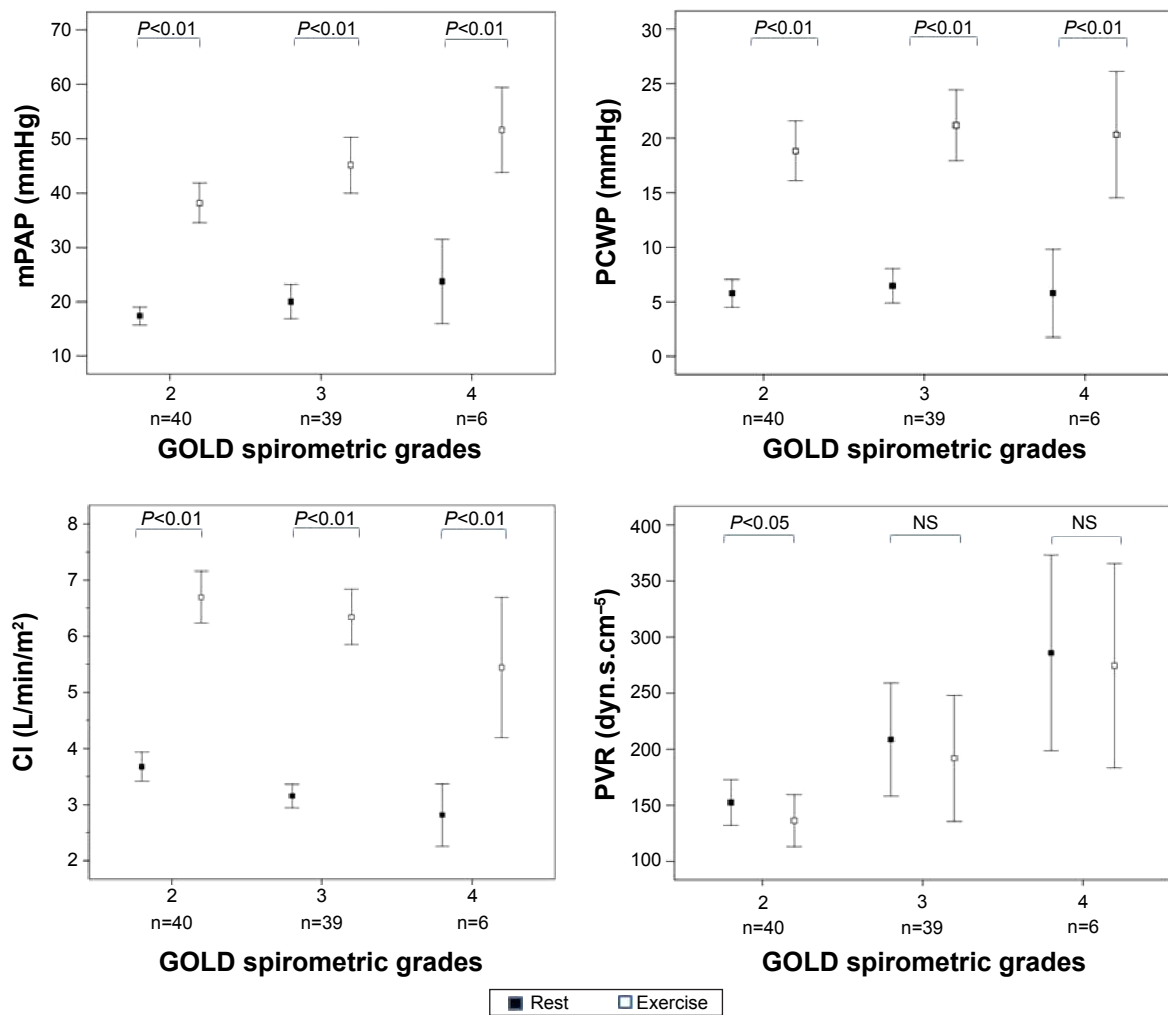
In contrast, the prevalence of PH in patients with GOLD 4 was lower in our study (22%) than in Hilde’s study (53%). This discrepancy may be due to the fact that the current GOLD spirometric classification, which we used, does not consider arterial blood gas measurements for the definition of GOLD 4.<sup>24</sup> Accordingly, in patients with severe-to-very-severe COPD, the degree of airflow limitation is not related to the presence of PH. What makes a difference regarding PH in those patients is the presence of concomitant abnormal pulmonary gas exchange. In fact, if we classify patients in our series according to the previous GOLD classification, the prevalence of PH in GOLD 4 stage is 33%, in line with that reported by Hilde et al.<sup>14</sup> That said, we cannot overlook that the current A-B-C-D GOLD classification, based on a multidimensional assessment of airflow limitation, symptoms, and risk of exacerbations,<sup>24</sup> might more accurately identify differences in PH prevalence between categories. Nevertheless, the retrospective nature of our study precludes such a combined assessment.

As previously reported, the degree of PH in this cohort was of mild-to-moderate magnitude with a well preserved CO, and mPAP correlated with airflow obstruction

**Table 3** Subject characteristics in four COPD patients with severe pulmonary hypertension

Age (years)	FEV <sub>1</sub> (% pred)	DLco (% pred)	PaO <sub>2</sub> (mmHg)	PaCO <sub>2</sub> (mmHg)	mPAP (mmHg)	PCWP (mmHg)	PVR (dyn·s·cm <sup>-5</sup> )	CI (L/min/m <sup>2</sup> )
58	35	34	44	46	35	4	594	2.75
65	51	24	50	35	43	6	566	2.69
58	46	22	50	38	38	2	1,080	1.79
61	39	21	46	44	61	11	941	2.38

**Abbreviations:** COPD, chronic obstructive pulmonary disease; CI, cardiac index; DLco, diffusing capacity for carbon dioxide; FEV<sub>1</sub>, post-bronchodilator forced expiratory volume in 1 second; mPAP, mean pulmonary artery pressure; NS, not significant; PaO<sub>2</sub>, partial pressure of arterial oxygen; PaCO<sub>2</sub>, partial pressure of arterial carbon dioxide; PCWP, pulmonary capillary wedge pressure; pred, predicted; PVR, pulmonary vascular resistance.



**Figure 1** Changes from rest to peak exercise in the hemodynamic variables in 85 patients who underwent exercise testing, grouped according GOLD stage.

**Note:** P-value differences from rest to exercise (paired t-tests).

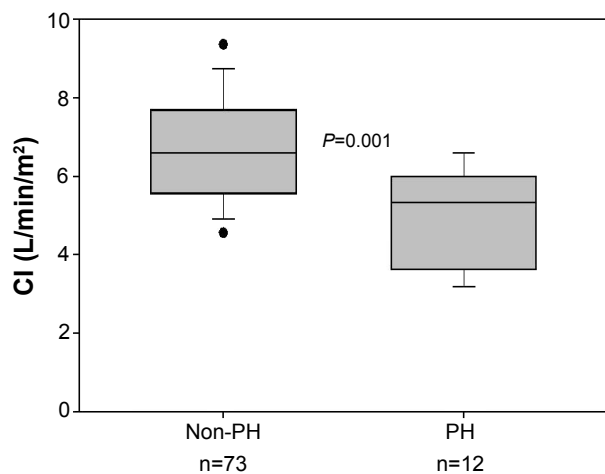
**Abbreviations:** CI, cardiac index; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; NS, not significant.

**Table 4** Pulmonary hemodynamics during submaximal exercise in patients grouped to the GOLD spirometric grades (n=85)

	All	GOLD grade			ANOVA P-value
		2	3	4	
Hemodynamics during exercise, N	85	40	39	6	
mPAP (mmHg)	42±14	38±11	45±15	52±7	0.019
PCWP (mmHg)	20±9	19±9	21±10	20±6	NS
CO (L/min/m <sup>2</sup> )	11.8±2.8	12.2±2.8	11.7±2.8	9.5±2.2	NS
CI (L/min/m <sup>2</sup> )	6.5±1.5	6.7±1.5	6.3±1.5	5.4±1.1	NS
TPR (dyn.s.cm <sup>-5</sup> )	315±174	265±105	345±215	454±146*	0.014
PVR (dyn.s.cm <sup>-5</sup> )	171±134	136±72	191±173	274±86	0.02
TPG (mmHg)	22±11	19±8	24±13	31±7*	0.02
ΔmPAP/ΔCO (mmHg/L/min)	4.8±3.7	4.1±2.2	5.4±4.8	6.4±2.7	
Abnormal mPAP <sup>a</sup> , n (%)	29 (34)	8 (20)	17 (46)	4 (67)	
ΔmPAP/ΔCO >3, n (%)	60 (71)	28 (70)	26 (67)	6 (100)	

**Notes:** Data are presented as mean ± standard deviation. <sup>a</sup>mPAP: <50 years, >30 mmHg; ≥50 years, >46 mmHg. According to Kovacs et al.<sup>26</sup> Significant differences within each variable are indicated as: \*different from GOLD grade 2.

**Abbreviations:** GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; Δ, change; ANOVA, analysis of variance; CI, cardiac index; CO, cardiac output; mPAP, mean pulmonary artery pressure; NS, not significant; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; TPG, transpulmonary pressure gradient; TPR, total pulmonary resistance.



**Figure 2** Cardiac index during exercise in patients with and without pulmonary hypertension (n=85).

**Note:** P-value indicates comparison between PH and non-PH (Mann–Whitney U-test).

**Abbreviations:** CI, cardiac index; PH, pulmonary hypertension.

severity.<sup>1,31</sup> In the whole cohort, both resting PCWP and RAP were within normal limits. The prevalence of patients with severe PH (2.8%) in our study is comparable with other reported series.<sup>6,7,9</sup> Likewise, patients with severe PH showed less severe airflow limitation, more severe arterial hypoxemia, and lower DLco than patients with moderate PH. It is important to identify these patients with predominant vascular involvement since they represent a clinically distinct phenotype within the COPD population that carries poor prognosis.<sup>6,9,32</sup>

The exercise-induced increase in mPAP was interpreted according to the increase in CO as proposed by recent reports.<sup>14,25</sup> The latter proposal is based on the concept that during exercise, the pulmonary microcirculation is progressively recruited under physiological conditions, resulting in the maintenance of relatively low arterial pressure despite increasing flow.<sup>33</sup> The abnormal increase in mPAP during exercise in COPD patients has been documented in different studies.<sup>12,14,16,34</sup> In spite of the fact that there is no current

**Table 5** Arterial blood gas profile at rest and during exercise in 85 patients with or without pulmonary hypertension

	No PH (n=73)	PH (n=12)	P-value
PaO <sub>2</sub> (mmHg)	76±8	65±14	0.020
PaO <sub>2</sub> exercise (mmHg)	74±12	54±11	0.001
PaCO <sub>2</sub> (mmHg)	38±4	44±6	0.006
PaCO <sub>2</sub> exercise (mmHg)	41±8	47±6	0.004

**Note:** Data are presented as mean ± standard deviation.

**Abbreviations:** PaCO<sub>2</sub>, partial pressure of arterial carbon dioxide; PaO<sub>2</sub>, partial pressure of arterial oxygen; PH, pulmonary hypertension.

definition of exercise-induced PH, we observed that 71% of the patients developed a “hypertensive response”, defined on the basis of pressure/flow relationships. Such an abnormal vascular response was noticed even in moderate grades of COPD severity, whereas it was present in all GOLD 4 patients. The clinical significance of the increased PAP during exercise remains to be established. Conceivably, it could limit exercise capacity. In fact, an increased mPAP has been associated with poor results in the 6 minutes walking test.<sup>5,10</sup> Furthermore, a PAP threshold >30 mmHg during exercise is a strong predictor for the development of PH in the long-term.<sup>12</sup> We also found that PVR does not decrease during exercise in GOLD grades 3 and 4, in contrast with what occurs in healthy subjects.<sup>35</sup> This fall in PVR during exercise is explained by the distensibility of resistive pulmonary vessels. Reduced pulmonary artery compliance observed in COPD might explain this response.<sup>14</sup> Furthermore, CI during exercise was lower in patients with associated PH. Although ventilatory impairment is the main factor limiting exercise tolerance in COPD, it cannot be disregarded that hemodynamic alterations may also contribute to exercise intolerance. Indeed, Boerrigter et al<sup>15</sup> reported a distinctive exercise pattern in COPD patients with severe PH (mPAP >40 mmHg). Although in our study the limited number of patients with severe PH precluded an analysis in this subset of patients, the finding of lower CI values during exercise in patients with PH concurs with the findings by Boerrigter et al.<sup>15</sup>

Pulmonary gas exchange impairment was associated with the presence of PH. However, the fact that patients without arterial hypoxemia also had PH in our cohort underlines the concept that the genesis of PH is complex and multifactorial.<sup>36</sup> The weak correlation in COPD between PH and lung function measurements has been largely known and fits with our results.<sup>7,11,34</sup> This makes it difficult in daily clinical practice to use predictive models to identify patients with pretest probability of presenting PH. Skjørtén et al<sup>37</sup> suggested that PaO<sub>2</sub> values at rest and peak exercise below 71 mmHg and 64 mmHg, respectively, indicate the need for further evaluation of coexisting PH. In our study, we failed to find an adequate model with functional variables that could help to predict the presence of PH.

Our investigation has some limitations. First, there is the possibility that selection bias might have influenced the significance of our findings due to its retrospective, single-center, and observational design. However, because the purpose of the study was to describe PH and hemodynamic characteristics in COPD patients with different grades of

**Table 6** Univariate and multivariate logistic regression analysis of variables associated with pulmonary hypertension

Independent variable	Univariate analysis		Multivariate analysis*	
	OR (CI 95%)	P-value	OR (95% confidence interval)	P-value
PaO <sub>2</sub> (mmHg)	0.92 (0.89–0.96)	<0.001	0.92 (0.88–0.97)	0.001
DLco (mmHg)	0.86 (0.78–0.94)	0.002		
PaCO <sub>2</sub> (mmHg)	1.07 (1.01–1.15)	0.025		
IC (% predicted)	0.97 (0.94–0.99)	0.028		
FEV <sub>1</sub> (% predicted)	0.96 (0.93–0.99)	0.026		

**Note:** \*From forward stepwise procedure.

**Abbreviations:** DLco, diffusing capacity for carbon dioxide; FEV<sub>1</sub>, post-bronchodilator forced expiratory volume in 1 second; IC, inspiratory capacity; OR, odds ratio; PaCO<sub>2</sub>, partial pressure of arterial carbon dioxide; PaO<sub>2</sub>, partial pressure of arterial oxygen.

airflow limitation, we believe that the population addresses the needs of the research question. Secondly, since there were no patients with mild airflow limitation (GOLD grade 1) in the study, our findings may not be extensively applicable to this population. Thirdly, the number of women included was small, such that our observations may not be generalized to all individuals with COPD. This sex bias is due to the lower prevalence of COPD in women than in men in our country and the underdiagnoses of COPD in women.<sup>38,39</sup> Finally, we do not exclude that previous oxygen therapy or vasodilator treatment in these patients could influence the hemodynamic measurements.

## Conclusion

In summary, the present study that analyzed a representative cohort of COPD patients with varying degrees of airflow limitation severity by means of right-heart catheterization shows that PH at rest is uncommon in patients with moderate airflow limitation but has a similar prevalence to patients with severe and very-severe airflow obstruction from other studies, highlighting that airflow limitation is a poor predictor of PH occurrence. In advanced COPD, the coexistence of pulmonary gas exchange impairment is of great influence on the development of PH. In contrast, an abnormal vascular response to exercise was observed in the majority of patients, even in those with mild airflow limitation, highlighting the notion that pulmonary vascular derangement is an early event in the natural history of COPD. Progression of these abnormalities may lead to the development of PH that restrains the increase of CO during exercise, which might contribute to limiting exercise tolerance.

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## Disclosure

The authors report no conflicts of interest in this work.

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