

Severe Pulmonary Hypertension and Chronic Obstructive Pulmonary Disease

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Rationale: Severe pulmonary hypertension occurs occasionally in patients with chronic obstructive pulmonary disease (COPD), but no detailed description of these patients is available. **Objectives:** To identify and characterize patients with COPD and severe pulmonary hypertension. **Methods:** Retrospective study of 27 patients with COPD with severe pulmonary hypertension (pulmonary artery mean pressure [Ppa], ≥ 40 mm Hg) among 998 patients who underwent right heart catheterization between 1990 and 2002 as part of a workup for chronic respiratory failure during a period of disease stability. **Results:** Of the 27 patients, 16 had another disease capable of causing pulmonary hypertension. The remaining 11 (11 of 998, 1.1%) patients had COPD as the only cause of pulmonary hypertension, with a median Ppa of 48 mm Hg (interquartile range, 46–50). They had an unusual pattern of cardiopulmonary abnormalities with mild to moderate airway obstruction, severe hypoxemia, hypocapnia, and a very low diffusing capacity for carbon monoxide ($p < 0.01$ compared with a control group of patients with COPD). Exertional dyspnea was more severe ($p < 0.01$) and survival was shorter ($p = 0.0026$) than in the control subjects. **Conclusions:** Severe pulmonary hypertension is uncommon in patients with COPD. When it occurs, another cause must be sought. COPD with severe pulmonary hypertension and no other possible cause shares features with pulmonary vascular diseases, such as idiopathic pulmonary hypertension.

Keywords: chronic obstructive pulmonary disease; pulmonary artery pressure; pulmonary hypertension; respiratory function tests

It has long been established that chronic obstructive pulmonary disease (COPD) can lead to pulmonary hypertension (PH) and cor pulmonale (1, 2). The classification scheme for PH developed during the 1998 World Health Organization meeting (3) distinguishes PH associated with respiratory system disorders and/or hypoxemia from pulmonary vascular diseases, such as idiopathic PH and chronic thromboembolic PH. PH associated with respiratory system disorders is defined as a pulmonary artery mean pressure (Ppa) at rest of 20 mm Hg or greater (4, 5) and is almost entirely ascribable to an increase in pulmonary vascular resistance. The most common cause is COPD. Although many factors can lead to an increase in pulmonary vascular resistance, alveolar hypoxia predominates by far (6).

In COPD, contrary to pulmonary vascular diseases, the Ppa increase during periods of stable disease is usually mild to moderate (Ppa, 20–35 mm Hg), and both cardiac output and right heart filling pressure are typically within the normal range (7–11). However, severe PH occurs occasionally in patients with COPD.

Stevens and coworkers (12) reported that 5 of 600 patients with COPD evaluated at a large tertiary-care PH clinic had severe PH defined as a Ppa of 40 mm Hg or greater. Similarly, pulmonary hemodynamic data from the 120 participants in the National Emphysema Treatment Trial (13) showed that only 5% of patients with severe emphysema had Ppa values greater than 35 mm Hg. No detailed description of patients with COPD with severe PH is available. Given that arterial PO_2 (Pa_{O_2}) and FEV_1 seem to be the most reliable lung function tests for evaluating PH severity (2), severe airflow limitation and profound hypoxemia would be expected in patients who have COPD with severe PH.

To obtain detailed information on patients with COPD and severe PH, we retrospectively reviewed the medical charts of 27 cases identified in a cohort of 998 patients with COPD referred to our center for evaluation of chronic respiratory failure. We routinely looked for comorbid conditions that might lead to severe PH, and we compared the patients with such conditions to a random sample of 30 patients taken from the same cohort, which was used as a control group. Some of the results have been reported in abstract form (14).

METHODS

Subjects

All patients referred to our department from August 1990 to December 2002 for chronic respiratory failure underwent measurements of pulmonary volumes and arterial blood gases, and 1,756 of them also underwent right heart catheterization. During the same period, 1,264 patients with COPD and chronic respiratory failure were admitted, including 998 who underwent right heart catheterization (Figure 1). All these patients were current or past smokers and had nonreversible airflow limitation with an FEV_1 /slow VC ratio of 0.60 or less. Patients were investigated during a period of disease stability, at least 6 weeks after termination of the most recent exacerbation. Right heart catheterization was performed after obtaining informed consent and before initiating long-term oxygen therapy or therapy for PH. Table E1 on the online supplement reports the characteristics of the source population ($n = 998$). Our institutional review board approved the study.

Among the 998 patients with COPD, 27 had a Ppa of 40 mm Hg or greater. This unusually high value prompted a routine search for concomitant conditions known to cause PH, including acute or chronic pulmonary embolism, sleep-disordered breathing, restrictive pulmonary disease, left heart disease, congenital heart defects, family history of PH, portal hypertension, collagen vascular diseases, HIV infection, and use of appetite suppressants. Sleep apnea syndrome was defined as more than 20 apneas and/or hypopneas per hour of sleep. Left heart disease was defined as a medical history of coronary artery disease or systemic hypertension and a pulmonary capillary wedge pressure of 15 mm Hg or greater with a left ventricular ejection fraction less than 40%, as measured by echocardiography. As a control group, we took a random sample of 30 patients with COPD from our database of 875 men investigated for COPD during the same period (Figure 1). Among these 30 patients, 16 had PH defined as a Ppa of 20 mm Hg or greater at rest.

After the initial evaluation, all patients were evaluated at least once every 6 months. Long-term oxygen therapy was prescribed initially or during follow-up when Pa_{O_2} during a period of disease stability was 55 mm Hg or less or was between 55 and 60 mm Hg in patients with

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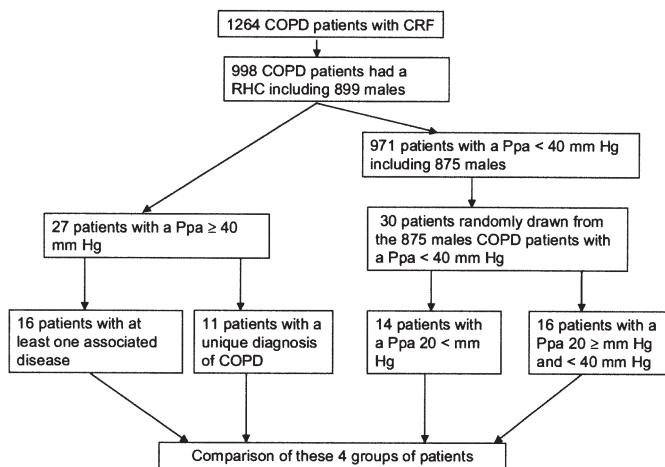


Figure 1. Study profile. COPD = chronic obstructive pulmonary disease; CRF = chronic respiratory failure; Ppa = pulmonary artery mean pressure; RHC = right heart catheterization.

PH, peripheral edema, polycythemia (hematocrit, > 55%), or sleep-related oxygen desaturation.

Methods

Dyspnea severity was assessed using a scale from 0 to 5 as follows: 0 indicated no breathlessness; 1, breathlessness on strenuous exertion (e.g., climbing two or three floors); 2, breathlessness on moderate exertion (e.g., climbing one floor or walking fast); 3, breathlessness on mild exertion (e.g., walking at normal speed); 4, breathlessness on minimal exertion (e.g., walking slowly); and 5, breathlessness on trivial exertion (e.g., taking a shower or bath). Pulmonary function testing consisted of spirometry, plethysmography measurement of static lung volumes, and single-breath carbon monoxide diffusion capacity (DL_{CO}). Pulmonary function variables other than DL_{CO} were expressed as percent predicted. Reference values were those of the European Respiratory Society (15). Arterial blood (room air) was drawn for measuring Pa_{O_2} , Pa_{CO_2} , and pH during right heart catheterization in the supine position.

We used a previously described technique for right heart catheterization (11) with small-diameter floated Grandjean catheters (16). This minimally invasive procedure was offered to all patients referred to our department for chronic respiratory failure. When severe PH was suspected from noninvasive tests or when pulmonary pressures could not be measured using a Grandjean catheter, we used a Swan-Ganz catheter. Cardiac output was calculated according to Fick's equation applied to oxygen under steady-state conditions. Oxygen uptake was measured breath by breath with an open circuit. An acute reversibility test involving nitric oxide inhalation for 10 minutes was performed in seven patients with severe PH and no other causes of PH; throughout the test, arterial oxygen saturation was maintained above 90%. In eight patients with severe PH and no other causes of PH, arterial and central venous blood was collected after 20 minutes of inhalation of pure oxygen, and the right-to-left shunt was calculated as the ratio of the oxygen content difference between end-capillary and arterial blood over the difference between end-capillary and mixed venous blood.

All 27 patients with severe PH underwent ventilation-perfusion scintigraphy, transthoracic or transesophageal echocardiography, and full-night pulse oximetry. Patients with no identifiable causes of PH other than COPD underwent abdominal ultrasonography, serologic tests for hepatitis and HIV, and a serum antinuclear antibody assay. When sleep apnea syndrome was suspected because of nocturnal oximetry results or sleep-related symptoms, a full-night polysomnography was obtained.

In all 27 patients, emphysema was assessed quantitatively using high-resolution computed tomography during breath holding at functional residual capacity, with 1-mm collimation. We used a visual scale from 0 to 48 (17) to score the extent of emphysema. Spiral computed tomography angiography was performed in 17 of the 27 patients with severe PH.

Statistical Analysis

SPSS software 10.0.7 (SPSS, Inc., Chicago, IL) was used for all statistical analyses. Because comparisons involved small samples ($n = 30$), and a number of variables had nonnormal distributions, we used nonparametric tests. Confidence intervals were computed according to the binomial law. Results are expressed as medians with interquartile ranges. Correlation coefficients were calculated using Spearman's rank test. When between-group comparisons using the Kruskal-Wallis test showed significant differences, we compared the groups using a Mann-Whitney U test. Survival after the initial workup was evaluated using Kaplan-Meier plots in patients with COPD as the only identifiable cause of PH. Survival rates were compared using the log-rank test. Significance was set at 0.05.

RESULTS

Of the 27 patients with severe PH ($Ppa, \geq 40$ mm Hg; Figure 1), 16 (13 men) had another possible cause to the Ppa elevation. In four patients, possible causes were appetite suppressant exposure, collagen vascular disease, or portal hypertension. In addition, four patients had left ventricular disease, two had chronic thromboembolic PH, and six had severe restrictive pulmonary disease. Among these last six patients, four were obese and had obstructive sleep apnea syndrome. Individual anthropometric data, lung function test results, arterial blood gases, and right heart catheterization findings in these 16 patients are reported in Table E2. Thus, among patients with severe PH ($Ppa, \geq 40$ mm Hg), only 11 (11 of 998, 1.1% [95% confidence interval, 0.55–1.96%]) had COPD as the only identifiable cause of PH. These 11 patients were men who ranged in age from 54 to 77 years. Individual values, median, and interquartile ranges of pulmonary function tests, arterial blood gases, pulmonary hemodynamics, and emphysema score values are shown in Tables 1 and 2. Most of these patients were heavy smokers, had moderate to severe airway obstruction, and suffered severe exertional dyspnea. All 11 patients were hypoxemic and most of them were hypocapnic. DL_{CO} was measured in nine patients and was extremely low (4.6 ml/minute/mm Hg; interquartile range, 4.2–6.7). High-resolution computed tomography consistently showed emphysema. Severe cardiac dysfunction was present in four patients with a right atrial pressure greater than 8 mm Hg and a cardiac index lower than 2 L/minute/ m^2 . Right-to-left shunting was measured in eight patients and showed an abnormally high value, with a median of 19% (interquartile range, 14–20). No significant changes in Ppa or pulmonary vascular resistance versus baseline were observed during acute reversibility testing with nitric oxide inhalation. Contrast echocardiography was performed in 10 patients but showed no intracardiac right-to-left shunt. Ventilation-perfusion scans disclosed matched defects, none of which suggested acute or chronic pulmonary thromboembolism. Furthermore, no evidence of pulmonary thromboembolism was found by spiral computed tomographic angiography, which was done in 7 of the 11 patients. No correlations were found between Ppa and any of the other variables (Tables 3 and 4, Figure 2). Median survival in these 11 patients was 26 months (Figure 3).

The main characteristics of the 30 control subjects are reported in Tables 5 and 6, and Table E3. All 30 patients were or had been heavy smokers. Airway obstruction was moderate to severe. Controls with PH had significantly lower FEV_1 and Pa_{O_2} values and significantly higher Pa_{CO_2} values than did control subjects without PH. All 30 control subjects had a right atrial pressure in the normal range and about one-fourth had a slight decrease in cardiac output. Ppa was significantly correlated with VC, FEV_1 , Pa_{O_2} , and Pa_{CO_2} (Tables 3 and 4). The strongest correlation was between Ppa and Pa_{O_2} ($r = -0.655$, $p < 0.001$; Figure 2). Furthermore, the emphysema score was significantly correlated with DL_{CO} ($r = -0.727$, $p < 0.001$).

TABLE 1. INDIVIDUAL VALUES (ANTHROPOMETRIC AND PULMONARY FUNCTION DATA) OF THE 11 PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH SEVERE PULMONARY HYPERTENSION AND NO OTHER POSSIBLE CAUSE OF PULMONARY HYPERTENSION

Patient	Age (yr)	BMI (kg/m ²)	Tobacco (pack-yr)	Dyspnea (grade/5)	VC (%pred)	FEV ₁ (%pred)	FEV ₁ /VC (%)	TLC (%pred)	DL _{CO} (ml/min/mm Hg)	ES
1	67	24	40	5	86	49	43	95	4.6	18
2	55	18	40	3	89	44	38	113	7.5	30
3	77	24	70	4	93	69	53	97	6.0	22
4	67	21	40	4	95	50	39	124	3.3	22
5	66	27	30	4	76	51	49	85	4.0	2
6	65	30	60	3	69	49	52			2
7	54	32	50	4	97	39	30	116	11.5	16
8	69	28	60	3	78	56	53	80	4.7	8
9	62	16	40	4	63	44	53	80		14
10	68	26	44	4	107	57	39	105	4.4	18
11	67	32	85	4	74	49	49		4.4	12
Median	67	26	44	4	86	50	49	97	4.6	16
IQR	63:68	21:30	40:60	3.5:4.0	74:95	44:56	39:53	83:115	4.2:6.7	8:22

Definition of abbreviations: BMI = body mass index; DL_{CO} = diffusion capacity for carbon monoxide; ES = emphysema score; IQR = interquartile range; TLC = total lung capacity.

The between-group comparison is shown in Tables 5 and 6. All patient groups were matched on age, sex, body mass index, and smoking history. Exertional dyspnea was significantly more severe in patients with severe PH and no cause other than COPD than in the two control subgroups as defined previously. Compared with the three other groups (Tables 5 and 6), patients with severe PH and no cause other than COPD had significantly lower DL_{CO} and Pa_{CO₂} values; their hypoxemia was more severe compared with the control subgroup with Ppa of 20 mm Hg or greater, although their airway obstruction was less pronounced. Right atrial pressure was significantly higher and cardiac index significantly lower in the group of patients with severe PH and no other cause, compared with the control subgroup with Ppa of 20 mm Hg or greater. Figure 3 shows the probability of survival. Survival was significantly shorter in the patients with severe PH and no other cause than in the control groups (p = 0.0026).

DISCUSSION

The main findings from our study are as follows. First, in patients with COPD investigated during a period of disease stability,

severe PH is uncommon (< 5% of patients). Second, lung function tests, including DL_{CO} and arterial blood gases, differed between patients with COPD with severe PH and no other cause and patients with COPD with mild to moderate PH. Third, many patients with COPD with severe PH have an additional cause of pulmonary pressure elevation, such as left ventricular disease, pulmonary embolism, or sleep apnea syndrome; these conditions should be looked for routinely, as they may be treatable. Finally, severe PH seems responsible for severe exertional dyspnea and reduced survival.

Patients investigated in our laboratory over the last 15 years have been referred mainly for two reasons: (1) complete investigation of chronic respiratory failure, particularly in patients with COPD, and (2) evaluation of suspected pulmonary vascular disease; we excluded these patients from the present study. One of the aims of the present study was to evaluate the proportion of patients with COPD who have severe PH with COPD as the only cause and a possible need for specific treatment aimed at reducing the functional limitations induced by PH. Consequently, we used a relatively high Ppa cutoff (≥ 40 mm Hg) to define severe PH. With this definition, 27 of 998 patients with

TABLE 2. INDIVIDUAL VALUES (ARTERIAL BLOOD GASES AND PULMONARY HEMODYNAMICS) OF THE 11 PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH SEVERE PULMONARY HYPERTENSION AND NO OTHER POSSIBLE CAUSE OF PULMONARY HYPERTENSION

Patient	Pa _{O₂} (mm Hg)	Pa _{CO₂} (mm Hg)	A-a O ₂ (mm Hg)	Pa _{O₂} under Pure O ₂ (mm Hg)	Q _{5/T} (%)	RAP (mm Hg)	Ppa (mm Hg)	CI (L/min/m ²)	ΔPpa (mm Hg)
1	52	35	50	350	20	7	48	2.25	-8.0
2	59	26	56			5	49	2.15	-4.5
3	41	29	67	296	19	5	50	2.84	
4	35	30	77	446	9	9	46	1.97	0
5	42	26	72	183	15	15	48	1.23	
6	48	37	53	202	33	3	45	2.43	-7.0
7	53	37	42			4	42	2.48	
8	46	38	49	446	8	16	48	1.83	
9	62	28	50			9	51	1.64	-5.0
10	41	34	66	382	14	8	50	2.34	1
11	39	32	68	226	19	5	54	3.09	-5.0
Median	46	32	56	323	19	7	48	2.25	-5
IQR	41:53	28:37	50:68	208:430	14:20	5:9	46:50	1.83:2.48	-7:0

Definition of abbreviations: A-a O₂ = alveolar arterial P_{O₂} difference; CI = cardiac index; IQR = interquartile range; Ppa = pulmonary artery mean pressure; ΔPpa = change in Ppa under inhaled nitric oxide and O₂; Q_{5/T} = right-to-left shunt; RAP = right atrial pressure.

TABLE 3. UNIVARIATE REGRESSION ANALYSIS IN THE GROUP OF 11 PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH SEVERE PULMONARY HYPERTENSION AND NO OTHER POSSIBLE CAUSE OF PULMONARY HYPERTENSION

Dependent Variable	Independent Variable	n	Coefficient	p
Ppa	VC	11	-0.252	= 0.455
	FEV ₁	11	0.261	= 0.438
	FEV ₁ /VC	11	0.426	= 0.192
	DL _{CO}	9	-0.025	> 0.5
	ES	11	0.106	> 0.5
	Pa _{O₂}	11	-0.146	> 0.5
	Pa _{CO₂}	11	-0.362	= 0.273
Q _{ST}	7	-0.413	= 0.357	

Definition of abbreviations: DL_{CO} = diffusion capacity for carbon monoxide; ES = emphysema score; Ppa = pulmonary artery mean pressure; Q_{ST} = right-to-left shunt.

COPD had severe PH and only 11 (11 of 998, 1.1% [95% confidence interval, 0.55–1.96%]) had COPD as the only detectable cause of severe PH. Because our patients were recruited in a tertiary-care pulmonology department, this number probably overestimates the true prevalence of severe PH in patients with moderate to severe COPD. It confirms that this prevalence is low, probably less than 5%.

One important finding from our study is that when severe PH is diagnosed in patients with COPD, another cause of this abnormality is often present. Most notably, obstructive sleep apnea syndrome and obesity-hypoventilation syndrome may increase the severity of alveolar hypoxia, thereby elevating pulmonary vascular resistance and causing a marked rise in Ppa (2, 18). Therefore, patients with COPD and a Ppa of more than 35 to 40 mm Hg or systolic pulmonary artery pressure of more than 50 to 55 mm Hg should undergo a thorough workup to look for other causes of PH.

In idiopathic PH, symptom severity is closely linked to the decrease in cardiac output and increase in right atrial pressure (19). On the contrary, in most patients with COPD, exertional symptoms are mainly ascribable to airway obstruction, and right ventricular performance is usually satisfactory (20). Among our 11 patients with severe PH and no other identifiable cause, most had a decrease in cardiac output and about half had a large increase in right atrial pressure. Although these variables constitute crude estimates of the contractile performance of the right ventricle, our findings suggest that the 11 patients who had

TABLE 4. UNIVARIATE REGRESSION ANALYSIS IN THE 30 PATIENTS OF THE CONTROL GROUP

Dependent Variable	Independent Variable	n	Coefficient	p
Ppa	VC	30	-0.344	= 0.063
	FEV ₁	30	-0.469	= 0.009
	FEV ₁ /VC	30	-0.236	= 0.210
	DL _{CO}	22	-0.228	= 0.306
	ES	29	0.175	= 0.365
	Pa _{O₂}	30	-0.655	< 0.001
	Pa _{CO₂}	30	0.487	= 0.006
ES	DL _{CO}	22	-0.727	< 0.001
	TLC	24	0.336	= 0.108

Definition of abbreviations: DL_{CO} = diffusing capacity for carbon monoxide; ES = emphysema score; Ppa = pulmonary artery mean pressure; Q_{ST} = right-to-left shunt; TLC = total lung capacity.

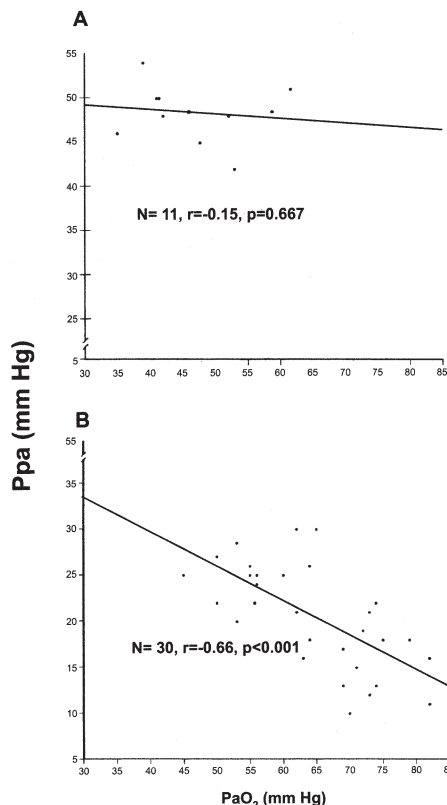


Figure 2. Relation between Ppa and Pa_{O₂} in patients with severe pulmonary hypertension and no other detectable cause of pulmonary hypertension (A) versus the control group (B).

COPD with severe PH had right heart dysfunction similar to that observed in idiopathic PH (21), which was possibly responsible for decreased exercise tolerance.

In patients with COPD in a period of stability, the main cause of hypoxemia is the presence of lung units with a low ventilation-perfusion ratio. When severe airway obstruction is

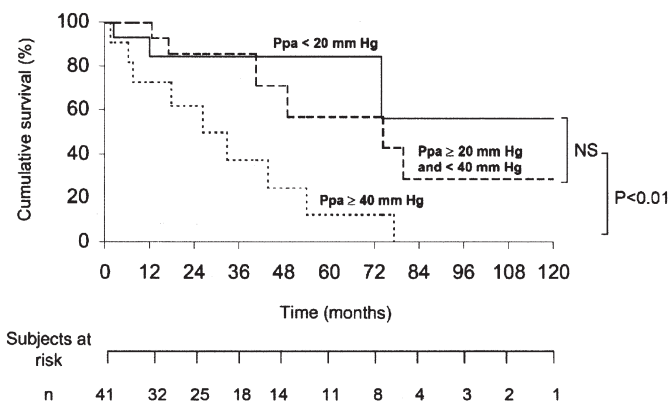


Figure 3. Survival of patients with COPD and no other detectable cause of pulmonary hypertension. The probability of survival of each group according to the Ppa was estimated using the Kaplan-Meier method and compared using the log-rank test. Eleven patients with a Ppa of 40 mm Hg or greater, 16 patients with Ppa of less than 40 mm Hg and 20 mm Hg or greater, and 14 patients with Ppa less than 20 mm Hg were at risk at baseline. NS = not significant.

TABLE 5. DEMOGRAPHICS, RESPIRATORY FUNCTION, AND EMPHYSEMA SCORE

Variable Median (IQR)	Severe PH without Associated Disease (n = 11)	Severe PH with Associated Disease (n = 16)	Control Subgroup, Ppa < 20 mm Hg (n = 14)	Control Subgroup, Ppa ≥ 20 mm Hg (n = 16)	p Value, Kruskal-Wallis Test
Age, yr	67 (62–68)	61 (56–68)	62 (53–75)	66 (63–73)	= 0.255
BMI, kg/m ²	26 (21–30)	26 (22–33)	22 (19–28)	25 (21–28)	= 0.400
Tobacco, pack-yr	44 (40–60)	40 (40–50)	45 (30–55)	50 (40–60)	> 0.5
Dyspnea, grade/5	4.0 (3.5–4.0)*†	4.0 (3.0–4.0)	3.0 (2.0–3.0)	3.0 (2.5–3.0)	< 0.001
VC, % predicted	86 (74–95)†	66 (57–91)	73 (65–80)	65 (56–70)	= 0.021
FEV ₁ , % predicted	50 (44–56)†	41 (35–63)	35 (29–50)§	27 (23–34)	< 0.001
FEV ₁ /VC, %	49 (39–53)†	49 (43–55)	39 (31–52)	34 (26–38)	= 0.001
TLC, % predicted	97 (83–115)	83 (74–92)	95 (88–114)	105 (94–121)	> 0.5
DL _{CO} , ml/min/mm Hg	4.6 (4.2–6.7)**‡	10.4 (8.2–16.6)	13.0 (11.0–17.0)	10.3 (8.9–12.8)	= 0.005
ES	16 (8–22)‡	5 (4–9)	13 (6–20)	19 (14–24)	< 0.001

Definition of abbreviations: BMI = body mass index; DL_{CO} = diffusion capacity for carbon monoxide; ES = emphysema score; IQR = interquartile range; PH = pulmonary hypertension; Ppa = pulmonary artery mean pressure; TLC = total lung capacity.

* p < 0.01, severe PH without associated disease versus control group; Ppa < 20 mm Hg.

† p < 0.01, severe PH without associated disease versus control group; Ppa ≥ 20 mm Hg.

‡ p < 0.01, severe PH without associated disease versus severe PH with associated disease.

§ p < 0.05, control group, Ppa < 20 mm Hg, versus control group, Ppa ≥ 20 mm Hg.

present, alveolar hypoventilation contributes to decrease Pa_{O₂} values. Obstruction was only moderate in our 11 patients with severe PH (median FEV₁, 50% of predicted), suggesting that the mechanisms causing hypoxemia were perhaps different from those in most patients with COPD. Hypoxemia severity probably depends in part on the presence of a right-to-left shunt. We were unable to localize a shunt, but we excluded a large cardiac septal defect.

In COPD, the pulmonary vascular resistance increase has been ascribed mainly to hypoxia leading to vasoconstriction and vascular remodeling (22, 23). Other factors may include hypercapnic acidosis, hyperviscosity, mechanical factors, and loss of pulmonary vessels because of parenchymal destruction. However, these other factors could not explain the development of severe PH in our patients with COPD without other detectable causes of PH. The severe PH in these patients was probably caused by vascular remodeling, possibly with greater degrees of cell proliferation and matrix protein deposition than are usually observed in COPD.

Hypotheses that might explain the severe PH in our 11 patients with COPD include high susceptibility to alveolar hypoxia (24) and/or to tobacco (25, 26) and fortuitous occurrence of both COPD and idiopathic PH. The present study supplies little

information on the history of the disease. All patients with severe PH and no other identifiable cause had a smoking history, airway obstruction, and emphysema by high-resolution computed tomography, which may have led to pulmonary vessel alterations. Furthermore, although idiopathic PH can occur at any age, the age in our 11 patients was closer to the mean age in patients with COPD (27) than in patients with idiopathic PH (28). An attractive hypothesis is high susceptibility to PH in these 11 patients with COPD. A similar combination of an environmental factor and a genetic determinant affecting the pulmonary circulation has been observed both in patients with COPD (29) and in patients exposed to fenfluramine derivatives (30).

Irrespective of the mechanism leading to severe PH, our 11 patients with COPD as the only detectable cause of severe PH should be considered as having pulmonary vascular disease, given the severity of their exertional dyspnea and the reduction in their life expectancy. At present, oxygen is the only recommended treatment for PH associated with respiratory system disorders and/or hypoxemia. Our findings indicate that new pharmacologic agents for idiopathic PH should be evaluated in patients with COPD with severe PH and no other cause.

In conclusion, in a large cohort of patients with COPD investigated in a pulmonary hemodynamics laboratory, severe PH was

TABLE 6. ARTERIAL BLOOD GASES AND HEMODYNAMIC DATA

Variable Median (IQR)	Severe PH without Associated Disease (n = 11)	Severe PH with Associated Disease (n = 16)	Control Group, Ppa < 20 mm Hg (n = 14)	Control Group, Ppa ≥ 20 mm Hg (n = 16)	p Value, Kruskal-Wallis Test
Pa _{O₂} , mm Hg	46 (41–53)*†	54 (42–67)	72 (68–76)§	56 (54–64)	< 0.001
Pa _{CO₂} , mm Hg	32 (28–37)**‡	47 (34–51)	40 (37–42)§	47 (44–49)	< 0.001
A-aO ₂ , mm Hg	56 (50–68)*†	37 (20–49)	28 (25–34)	30 (27–37)	< 0.001
RAP, mm Hg	7.0 (5.0–9.0)*†	5.0 (3.0–9.7)	1.0 (–0.5–2.5)	3.0 (1.3–4.0)	< 0.001
Ppa, mm Hg	48 (46–50)*†	43 (42–49)	16 (13–18)§	25 (22–27)	< 0.001
Ppcw, mm Hg	6.0 (4.0–7.0)	9.0 (4.0–18.0)	7.5 (7.0–7.5)	7.0 (6.5–7.5)	> 0.5
CI, L/min/m ²	2.3 (1.8–2.5)*†	2.8 (1.9–3.8)	3.3 (2.9–4.0)	2.8 (2.4–3.1)	= 0.002
TPR, IU/m ²	21.3 (17.6–26.6)*†	14.9 (11.0–28.4)	4.0 (3.7–5.5)§	9.0 (7.4–9.9)	< 0.001

Definition of abbreviation: A-a O₂ = alveolar-arterial Po₂ difference; CI = cardiac output; IQR = interquartile range; IU = international unit; PH = pulmonary hypertension; Ppa = pulmonary artery mean pressure; Ppcw = pulmonary capillary wedge pressure; RAP = right atrial pressure; TPR = total pulmonary resistance.

* p < 0.01, severe PH without associated disease versus control group; Ppa < 20 mm Hg.

† p < 0.01, severe PH without associated disease versus control group; Ppa ≥ 20 mm Hg.

‡ p < 0.01, severe PH without associated disease versus severe PH with associated disease.

§ p < 0.05, control group, Ppa < 20 mm Hg, versus control group, Ppa ≥ 20 mm Hg.

extremely uncommon. When severe PH (Ppa, ≥ 40 mm Hg) is found in a patient with COPD, another cause, which may be treatable, should be sought. Patients with COPD as the only detectable cause of severe PH exhibit a distinctive clinical pattern with hypocapnia, very low DL_{CO}, and hemodynamic alterations reminiscent of those seen in idiopathic PH. These patients have severe exertional dyspnea and a short life expectancy. Therefore, they should be classified as having pulmonary vascular disease and considered potential candidates for evaluating new pharmacologic agents used to treat idiopathic PH.

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