Impact of Pulmonary Artery Pressure on Exercise Function in Severe COPD

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Background: Although pulmonary hypertension commonly complicates COPD, the functional consequences of increased pulmonary artery pressures in patients with this condition remain poorly defined.

Methods: We conducted a cross-sectional analysis of a cohort of 362 patients with severe COPD who were evaluated for lung transplantation. Patients with pulmonary hemodynamics measured by cardiac catheterization and available 6-min walk test results were included. The association of mean pulmonary artery pressure (mPAP) with pulmonary function, echocardiographic variables, and 6-min walk distance was assessed.

Results: The prevalence of pulmonary hypertension (mPAP, > 25 mm Hg; pulmonary artery occlusion pressure [PAOP], < 16 mm Hg) was 23% (95% confidence interval, 19 to 27%). In bivariate analysis, higher mPAP was associated with lower FVC and FEV₁, higher PCO₂ and lower PO₂ in arterial blood, and more right heart dysfunction. Multivariate analysis demonstrated that higher mPAP was associated with shorter distance walked in 6 min, even after adjustment for age, gender, race, height, weight, FEV₁, and PAOP (−11 m for every 5 mm Hg rise in mPAP; 95% confidence interval, −21 to −0.7; $p = 0.04$).

Conclusions: Higher pulmonary artery pressures are associated with reduced exercise function in patients with severe COPD, even after controlling for demographics, anthropometrics, severity of airflow obstruction, and PAOP. Whether treatments aimed at lowering pulmonary artery pressures may improve clinical outcomes in COPD, however, remains unknown.

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Abbreviations: mPAP = mean pulmonary artery pressure; OSA = obstructive sleep apnea; PAOP = pulmonary artery occlusion pressure; PVR = pulmonary vascular resistance

COPD affects > 12 million people in the United States and ranks fourth among the leading causes of death.¹ Estimates of the prevalence of pulmonary hypertension in selected groups of patients with COPD have been highly variable, from as low as 35%² to as high as 91%.³ Prior investigations have suggested that the presence of pulmonary hypertension predicts both an increased risk of hospitalization for acute exacerbation of COPD⁴ and a high rate of mortality.^{2,5} Although these associations have been assumed to be attributable to the impact of pulmonary vascular disease on gas exchange and right heart function, the sequelae of increased pulmonary artery pressures in COPD patients are poorly understood. The effect of abnormal pulmonary mechanics on left-sided cardiac filling pressure (eg, left ventricular end-diastolic pressure)

complicates the study of the role of the pulmonary vasculature independent of these other parameters. Noninvasive techniques for assessing pulmonary hemodynamics in COPD are limited by poor sensitivity and specificity.⁶ As such, investigators have used a variety of definitions and measurement techniques for pulmonary hypertension in COPD where there are no population-based studies to guide the establishment of “normal” pulmonary hemodynamics.

Functional assessment in COPD is better understood. Six-minute walk testing,⁷ a reliable and valid measure of functional status in patients with COPD, predicts mortality, particularly in cases of severe COPD.⁸ The effects of pulmonary vascular disease on 6-min walk distance in COPD, however, have not been reported, and a recent review⁹ noted the paucity of data defining the relationship between

pulmonary hypertension and exercise function in this population. We aimed to determine the association between mean pulmonary artery pressure (mPAP) and 6-min walk distance in patients with severe COPD.

MATERIALS AND METHODS

Study Design

We performed a cross-sectional analysis of a retrospective cohort of consecutive patients with COPD who were evaluated for lung transplantation at the Hospital of the University of Pennsylvania (Philadelphia, PA) between September 1991 and October 2003. We included all patients with COPD who had a smoking history of at least 10 pack-years and who had undergone right heart catheterization and 6-min walk testing. We excluded patients with asthma (defined by a reported history of asthma beginning in childhood, expert opinion of the evaluating pulmonologist, or both), pneumoconioses, and α_1 -antitrypsin deficiency. Patients with α_1 -antitrypsin deficiency tended to be younger, with a different distribution of disease and an increased risk of associated cirrhosis and portal hypertension, which itself can lead to pulmonary hypertension. We also excluded patients with concomitant interstitial lung disease, collagen vascular disease (defined by history and serologies), sarcoidosis, HIV infection, or prior use of anorexigens.

Pulmonary function testing was performed according to American Thoracic Society standards.¹⁰ Although the 1994 update to the American Thoracic Society standards for spirometry was published during the study period, adoption of these standards did not result in substantive changes to our standard methods. Lung volumes were determined by plethysmography. Predicted normal values for pulmonary function testing were determined using a single set of standardized equations^{11–13} for all patients throughout the study period. Arterial blood gas measurement was performed, with the patient breathing ambient air when possible. Experienced respiratory care practitioners conducted 6-min walk testing, using a 100-foot course marked in 10-foot lengths. Oxygen saturation was monitored throughout the study by continuous pulse oximetry. Supplemental oxygen was used as necessary to maintain oxygen saturation at $\geq 88\%$ during both rest and exercise, both for safety reasons and for achieving a more accurate measure of the patient's functional capacity on appropriate therapy. For patients whose oxygen saturation dropped

below 88% during the 6-min walk test, the study was terminated and then restarted with new or increased supplemental oxygen after a rest period (on oxygen) of at least 15 min.

All patients underwent transthoracic echocardiogram at rest. Doppler and two-dimensional images were obtained from parasternal long-axis and short-axis, apical four-chamber, and subcostal four-chamber views. A cardiologist reviewed the echocardiograms to assess the pericardium, valvular anatomy and function, left-sided and right-sided chamber size, and cardiac function. Right ventricular size and function were evaluated qualitatively. Color-flow Doppler was used to assess tricuspid regurgitant flow, and maximal jet velocity was measured by continuous-wave Doppler without the use of IV contrast. The transtricuspid pressure gradient was estimated based on the modified Bernoulli equation and was then added to an estimate of the right atrial pressure to obtain an estimate of pulmonary artery systolic pressure in the absence of right ventricular outflow obstruction.¹⁴ Right atrial pressure was estimated to be 5, 10, or 15 mm Hg based on the variation in the size of inferior vena cava with inspiration, as follows: complete collapse, 5 mm Hg; partial collapse, 10 mm Hg; and no collapse, 15 mm Hg.

Right heart catheterization was performed with patients at rest in the supine position. Supplemental oxygen was used as necessary to maintain oxygen saturation at $> 90\%$. Right heart and pulmonary artery pressures were measured by direct pressure transduction. The cardiac output was calculated by the Fick method.

Statistical Analysis

For all analyses, mPAP in quintiles or as a continuous variable served as the independent variable. Bivariate analyses were performed using linear regression or logistic regression, as appropriate. Multivariate linear regression was used to determine whether higher mPAP was associated with shorter distance walked in 6 min independent of potential confounders. Potential confounding variables were entered into the multivariable model with mPAP one at a time and retained if they altered the coefficient of an mPAP quintile by $> 20\%$. Age, gender, race, height, weight, and quintiles of pulmonary artery occlusion pressure (PAOP) were forced into the model.

Standard linear regression diagnostics were performed, including plotting of residuals vs fitted values, residuals vs predictors, and leverage vs squared residuals. All analyses were conducted with statistical software (STATA, version 8.2; StataCorp LP; College Station, TX). The study protocol and waiver of informed consent were approved by the Institutional Review Board of the University of Pennsylvania.

RESULTS

A total of 473 patients with COPD were evaluated for lung transplantation during the study period. Of these, 407 patients met the study eligibility criteria. Twenty-five additional patients (6%) were excluded from analysis due to missing cardiac catheterization data, and 20 patients (5%) were excluded due to missing 6-min walk data, leaving 362 patients included in the final analysis. Patients excluded from analysis due to missing data were slightly older (mean [$\pm$ SD] age, 59 ± 5 vs 56 ± 5 years, respectively) but were otherwise similar to the study sample with regard to other variables of interest (data not shown). The overall prevalence of pulmonary

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Table 1—Demographics, Relevant History, and Pulmonary Function by Quintile of mPAP

Variables	No.	Quintile 1 (n = 61)	Quintile 2 (n = 69)	Quintile 3 (n = 79)	Quintile 4 (n = 63)	Quintile 5 (n = 90)	p Value (Test for Trend)
Age, yr	362	57 ± 4.5	56 ± 4.4	55 ± 5.4	56 ± 4.5	56 ± 5.0	0.34
Female sex	362	34 (56)	36 (52)	46 (58)	31 (49)	45 (50)	0.43
Race	362						
White		56 (92)	68 (99)	73 (92)	54 (86)	82 (91)	0.09
Black		4 (7)	1 (1)	6 (8)	8 (13)	8 (9)	
Hispanic		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	
Asian		0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	
Height, cm	362	167 ± 9	166 ± 9	167 ± 9	169 ± 10	168 ± 10	0.12
Weight, lb	362	135 ± 28	140 ± 29	143 ± 34	157 ± 29	158 ± 39	< 0.001
Body mass index, kg/m ²	362	22.0 ± 3.8	23.1 ± 4.1	23.2 ± 4.5	25.5 ± 4.5	25.2 ± 5.3	< 0.001
History of OSA	362	0 (0)	0 (0)	2 (2.5)	2 (3.2)	4 (4.4)	0.04
History of pulmonary embolism	362	1 (1.6)	1 (1.5)	2 (2.5)	1 (1.6)	1 (1.1)	0.80
Tobacco exposure, pack-yr	362	53 ± 25	58 ± 29	51 ± 24	67 ± 34	54 ± 28	0.48
FVC, L	362	2.43 ± 0.82	2.26 ± 0.77	2.16 ± 0.69	2.27 ± 0.72	2.16 ± 0.71	0.07
FVC, % predicted	362	63 ± 14	58 ± 15	55 ± 13	59 ± 17	55 ± 15	0.005
FEV ₁ , L	362	0.66 ± 0.23	0.64 ± 0.27	0.60 ± 0.19	0.63 ± 0.20	0.60 ± 0.21	0.07
FEV ₁ , % predicted	362	22 ± 6	21 ± 7	20 ± 5	22 ± 6	19 ± 6	0.01
FEV ₁ /FVC ratio, %	362	28 ± 5	29 ± 6	28 ± 6	30 ± 10	28 ± 7	0.69
TLC, L	339	7.32 ± 1.58	7.52 ± 1.38	7.83 ± 1.86	7.45 ± 1.64	7.52 ± 1.78	0.67
TLC, % predicted	339	129 ± 17	133 ± 17	138 ± 27	131 ± 23	130 ± 21	0.80
Residual volume, L	338	4.79 ± 1.20	5.13 ± 1.15	5.55 ± 1.54	5.08 ± 1.30	5.29 ± 1.38	0.09
Residual volume, % predicted	338	244 ± 59	264 ± 53	285 ± 82	261 ± 60	268 ± 62	0.12
DLCO, mL/min/mm Hg	208	8.8 ± 3.7	9.9 ± 5.5	8.9 ± 3.6	8.4 ± 3.7	9.6 ± 4.9	0.99
DLCO, % predicted	208	30 ± 11	33 ± 15	30 ± 11	28 ± 11	30 ± 13	0.55

Data are expressed as the mean ± SD for continuous variables or No. (%) for categorical variables. Quintile 1 = mPAP 13 to 18 mm Hg; Quintile 2 = mPAP 19 to 21 mm Hg; Quintile 3 = mPAP 22 to 24 mm Hg; Quintile 4 = mPAP 25 to 27 mm Hg; Quintile 5 = mPAP 28 to 50 mm Hg; DLCO = diffusing capacity of the lung for carbon monoxide; TLC = total lung capacity.

hypertension, defined as mPAP > 25 mm Hg and PAOP < 16 mm Hg, was 23% (95% confidence interval, 19 to 27%).

Demographic and pulmonary function data are shown in Table 1. In univariate analyses, increasing mPAP was associated with higher body mass index, greater frequency of reported obstructive sleep apnea (OSA), and lower percent-predicted FEV₁ and FVC. Additionally, higher mPAP was associated with lower PO₂ in arterial blood, more frequent resting hypoxemia, and elevated alveolar-arterial oxygen gradient (Table 2). Higher mPAP also was associated with lower pH, higher PCO₂, and higher bicarbonate concentration, though the differences were small in magnitude. No association was found between mPAP and use of any particular medication (data not shown), including oral corticosteroids, inhaled corticosteroids, short-acting and long-acting β-agonists, short-acting and long-acting anticholinergics, theophylline, calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, and digoxin.

There was an increased frequency of right atrial dilatation, right ventricular dilatation, right ventricular hypertrophy, and right ventricular dysfunction

by echocardiogram in patients with higher mPAP (Table 3). Cardiac catheterization data demonstrated that higher mPAP was associated with higher right atrial pressure, higher PAOP, and higher pulmonary vascular resistance (PVR), but there was no significant association of mPAP with cardiac index (Table 4).

Bivariate linear regression modeling demonstrated a significant inverse monotonic association between mPAP and 6-min walk distance (Table 5, model 1). Multivariable linear regression showed similar results despite sequential adjustment for age, gender, race, height, and weight (Table 5, model 2), quintiles of PAOP (Table 5, model 3), and FEV₁ (Table 5, model 4, and Fig 1). The fully adjusted multivariable linear regression model with mPAP as a continuous variable demonstrated that for every 5 mm Hg rise in mPAP, the 6-min walk distance dropped by just > 11 m (95% confidence interval, −21 to −0.7; p = 0.04). Although a history of OSA was reported more frequently in patients with higher mPAP, this variable did not confound the relationship between mPAP and 6-min walk distance and, therefore, was not included in the final model. In a secondary analysis, we excluded all patients with OSA (n = 8),

Table 2—Relevant Laboratory Data and Oxygen Requirements by Quintile of mPAP

Variables	No.	Quintile 1 (n = 61)	Quintile 2 (n = 69)	Quintile 3 (n = 79)	Quintile 4 (n = 63)	Quintile 5 (n = 90)	p Value (Test for Trend)
Hematocrit, %	357	42 ± 4	42 ± 4	41 ± 3	42 ± 4	41 ± 4	0.48
PH	337	7.44 ± 0.03	7.42 ± 0.04	7.42 ± 0.04	7.42 ± 0.04	7.41 ± 0.03	< 0.001
PaCO ₂ , mm Hg	337	43 ± 7	46 ± 9	48 ± 10	47 ± 9	51 ± 10	< 0.001
Breathing room air PaO ₂ , mm Hg	296	73 ± 12	68 ± 12	66 ± 13	64 ± 10	62 ± 12	< 0.001
Bicarbonate concentration, mEq/L	328	29 ± 5	30 ± 4	31 ± 5	31 ± 5	32 ± 6	0.003
Alveolar-arterial oxygen gradient, mm Hg	337	24 ± 10	29 ± 15	29 ± 16	29 ± 13	30 ± 15	0.03
Hypoxemia (PaO ₂ < 60 mm Hg breathing room air)	296	7 (12.5)	16 (29)	17 (28)	16 (30)	32 (45)	< 0.001

Data are expressed as the mean ± SD for continuous variables or No. (%) for categorical variables. See Table 1 for definitions not used in the text.

which did not substantially alter the results of our multivariate analysis (10.6 m decrease in 6-min walk distance for every 5 mm Hg rise in mPAP; $p = 0.045$). Similarly, differences in medication use, including long-acting and short-acting β -agonists and anticholinergics, inhaled corticosteroids, theophylline, and anti-hypertensive agents, did not confound the relationship between mPAP and 6-min walk distance.

DISCUSSION

Among patients with severe COPD, higher mPAP is known to be associated with important physiologic consequences, including more severe hypoxemia^{3,15} and greater right heart dysfunction.¹⁶ To our knowledge, however, this study is the first to demonstrate

that higher mPAP is associated with more significant exercise impairment independent of demographics, anthropomorphics, PAOP, and even FEV₁. The impact of mPAP on exercise capacity, even after considering these traditional determinants of function in COPD, provides several insights into the potential contribution of pulmonary vascular disease to the morbidity of COPD.

COPD commonly is associated with mildly increased mPAP. However, only 23% of our patients met our definition of pulmonary hypertension (mPAP > 25 mm Hg and PAOP < 16 mm Hg). This lower prevalence compared to published estimates likely reflects our more restrictive definition. In fact, using one of the more liberal definitions from the literature³ (mPAP > 20 mm Hg), the prevalence of

Table 3—ECG Data by Quintile of mPAP

Variables	No.	Quintile 1 (n = 61)	Quintile 2 (n = 69)	Quintile 3 (n = 79)	Quintile 4 (n = 63)	Quintile 5 (n = 90)	p Value (Test for Trend)
Right atrial dilatation	301	12 (24)	19 (35)	22 (32)	17 (33)	36 (47)	0.02
Right ventricular dilatation	332	17 (29)	23 (38)	32 (44)	20 (35)	43 (51)	0.03
Right ventricular hypertrophy	311	12 (23)	17 (29)	17 (25)	13 (27)	37 (46)	0.008
Right ventricular dysfunction	283	4 (8)	3 (5)	5 (9)	5 (10)	13 (18)	0.04
Septal paradox	105	8 (53)	7 (35)	12 (43)	6 (43)	17 (61)	0.29
Pulmonary artery systolic pressure, mm Hg	157	41 ± 11	43 ± 10	45 ± 12	41 ± 10	49 ± 17	0.02
Left ventricular ejection fraction, %	224	62 ± 7	60 ± 10	64 ± 9	59 ± 11	61 ± 12	0.51
Left ventricular dysfunction	342	1 (2)	7 (11)	3 (4)	5 (8)	8 (9)	0.23

Data are expressed as the mean ± SD for continuous variables or No. (%) for categorical variables. See Table 1 for definitions not used in the text.

Table 4—Cardiac Catheterization Data by Quintile of mPAP

Variables	No.	Quintile 1 (n = 61)	Quintile 2 (n = 69)	Quintile 3 (n = 79)	Quintile 4 (n = 63)	Quintile 5 (n = 90)	p Value (Test for Trend)
Right atrial pressure, mm Hg	360	4 ± 2	6 ± 3	8 ± 3	9 ± 3	11 ± 4	< 0.001
PA systolic pressure, mm Hg	362	28 ± 5	32 ± 3	35 ± 4	39 ± 4	45 ± 7	< 0.001
PA diastolic pressure, mm Hg	362	12 ± 3	15 ± 2	17 ± 3	20 ± 3	24 ± 5	< 0.001
mPAP, mm Hg	362	17 ± 2	20 ± 1	23 ± 1	26 ± 1	31 ± 4	< 0.001
PA occlusion pressure, mm Hg	362	7 ± 3	9 ± 3	11 ± 4	13 ± 4	15 ± 4	< 0.001
Cardiac index, L/min/m ²	349	2.8 ± 0.5	2.7 ± 0.4	2.8 ± 0.7	2.5 ± 0.4	2.9 ± 0.5	0.46
PVR, dyne · s · cm ⁻⁵	349	170 ± 68	199 ± 85	215 ± 97	244 ± 86	266 ± 104	< 0.001

Data are expressed as the mean ± SD, unless otherwise indicated. PA = pulmonary artery. See Table 1 for definitions not used in the text.

pulmonary hypertension in our cohort would have been 68%, which is similar to previous studies³ in severe COPD. Although our definition is more restrictive, we propose that it is more informative because it excludes patients who have pulmonary venous hypertension (*ie*, elevated PAOP) rather than intrinsic pulmonary vascular disease.

Vasoconstriction and vascular remodeling due to chronic alveolar hypoxia, the loss of lung parenchyma due to tissue destruction, and pulmonary venous hypertension have long been considered the predominant mechanisms that lead to pulmonary hypertension in patients with COPD.¹⁷ Other postulated mechanisms include spillover of small airway inflammation into the vascular compartment¹⁸ and increased shear stress on the pulmonary vascular wall due to increased blood viscosity or luminal narrowing.¹⁹ Histopathologic studies²⁰ across the spectrum of COPD severity have shown significant alterations in pulmonary vascular structure. Both mild and severe COPD are associated with intimal thickening in the small muscular pulmonary arteries^{18,21} and medial hypertrophy.²⁰ Even smokers with normal lung function exhibit some degree of intimal thickening.²³ Furthermore, the pulmonary artery endothelium from patients with both mild and severe

COPD manifests impaired endothelial-dependent vasodilatation.^{23,24} Collectively, these data suggest a role for pulmonary vasculopathy in contributing to physiologic abnormalities in COPD throughout the range of disease severity.

Impairment of right heart function due to pulmonary hypertension has long been postulated to contribute to exercise limitation in COPD,¹⁶ and our study provides direct evidence supporting this theory by demonstrating that pulmonary artery pressures may have a significant impact on 6-min walk distance in this population. Interestingly, 6-min walk distance in our cohort decreased monotonically across the full spectrum of pulmonary pressures, even at levels below the typical cutoff for pulmonary hypertension in most studies. This finding suggests that the impact of elevated pulmonary artery pressures and PVR on function is not defined by a threshold but is incremental, leading to exercise impairment even at “sub-clinical” levels of elevated PVR. Whether treatment aimed at lowering pulmonary artery pressures in COPD would similarly yield significant improvements in exercise capacity across the spectrum of pulmonary artery pressures is unknown. A recent clinical trial²⁵ of bosentan in patients with severe COPD showed no beneficial effect on exercise ca-

Table 5—6-Min Walk Distance by Quintiles of mPAP

Model	Covariates Included in Model	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p Value
1	None	283 ± 8	276 ± 6	268 ± 5	261 ± 6	251 ± 8	0.007
2	Age, sex, race,* height, and weight	272 ± 11	263 ± 9	253 ± 9	244 ± 9	232 ± 10	0.001
3	Model 2 + quintiles of PAOP	274 ± 54	264 ± 52	254 ± 51	243 ± 50	229 ± 48	0.002
4	Model 3 + FEV ₁	300 ± 51	293 ± 49	287 ± 48	280 ± 47	271 ± 46	0.04

Data are expressed as least square mean ± SE, unless otherwise indicated. Covariates assumed to take the mean value for the entire sample, female sex, and white race. PAOP quintile classified as an indicator variable. See Table 1 for definitions not used in the text.

*One Hispanic and one Asian patient were included with white patients. Separate classification of these patients did not alter the results.

FIGURE 1. Six-minute walk distance declines with increasing mPAP even after adjustment for age, gender, race, height, weight, FEV₁, and PAOP. Data are presented as the least square means from linear regression with SE bars. The p value reflects the overall test for trend.

capacity, and actually showed a decrement in quality of life. Similarly, two recent studies^{26,27} of short-term and long-term sildenafil administration in patients with COPD showed effects on pulmonary artery pressure but no impact on right ventricular function or exercise.

The mechanism of exercise limitation due to higher, but mostly normal, resting pulmonary artery pressures in COPD is likely multifactorial. First, pulmonary vascular remodeling induces ventilation-perfusion mismatch, leading to worsening of hypoxemia. The association of increasing mPAP with more severe hypoxemia has been well established.^{3,15} Although systemic arterial hypoxemia may promote increases in mPAP by inducing hypoxic vasoconstriction, its contribution is likely minimal. Hypoxic vasoconstriction is governed more by local alterations in alveolar oxygen content than by mixed venous oxygen content.²⁸ As such, the systemic arterial hypoxemia associated with higher mPAP may well be the end result of ventilation-perfusion mismatch induced by pulmonary vasculopathy rather than a cause of pulmonary hypertension itself. Given that ventilation-perfusion mismatch may be on the causal pathway linking higher mPAP to exercise limitation, we purposefully did not include measures of oxygenation or diffusion in our final multivariate model to prevent model misspecification. All patients were treated with supplemental oxygen therapy as needed to maintain oxygen saturation with all activities, including 6-min walk testing.

The use of supplemental oxygen is known to increase 6-min walk distance in COPD,^{29,30} and as such, the selective administration of supplemental oxygen to our patients may have biased the estimates

of 6-min walk distance. However, given that patients with higher mPAP were somewhat more likely to receive oxygen supplementation (and required greater doses of oxygen supplementation), we would expect that the selective use of oxygen would result in an increased 6-min walk distance among those with high mPAP. Thus, selective oxygen use would bias our study toward the null, making patients with higher mPAP seem closer in functional capacity to those with lower pressures. Instead, we found that, despite greater use of supplemental oxygen, patients with higher mPAP had lower 6-min walk distance than those with lower mPAP, suggesting that the true effect of mPAP on 6-min walk distance may be even more pronounced than that observed in our study.

A second mechanism for exercise limitation with higher mPAP may be the failure of the pulmonary vascular bed to accommodate an increased cardiac output during exercise. In our study, higher mPAP was strongly associated with right atrial dilatation, right ventricular dilatation, right ventricular hypertrophy, and right ventricular dysfunction by echocardiogram and increased right atrial pressure by right heart catheterization. However, mPAP was not associated with cardiac index at rest. The significance of echocardiographic indexes of right heart function in COPD is controversial.^{17,31} In fact, our observation that cardiac index was similar throughout the range of mPAP supports the absence of hemodynamically significant right heart failure at these relatively low levels of resting pulmonary artery pressure and PVR.

In contrast to healthy patients, however, patients with COPD commonly fail to augment right heart function with exercise, even when resting right heart function is normal.^{30,32} The pulmonary vasculopathy provoked by COPD may prevent the normal accommodation of increased pulmonary blood flow required for exercise. The recent clinical trials^{26,27} that showed reductions in mPAP without concomitant increases in right ventricular output with exercise suggest a more complex cardiopulmonary interaction. Given this pathophysiology, we speculate that the right heart abnormalities we observed by echocardiography reflect end-organ damage induced by increased right ventricular afterload during stressors such as exercise or sleep. In fact, patients with higher mPAP had greater body mass index and were more likely to report a history of OSA in univariate analyses. Our multivariable analysis controlled for height and weight, but a history of OSA did not confound the relationship between mPAP and 6-min walk distance and, therefore, was not included in our final model. A secondary analysis excluding patients with sleep apnea did not substantially alter our results.

Another potential mechanism of association between higher mPAP and reduced exercise function

involves the systemic effects of pulmonary vascular disease and COPD. Patients with COPD exhibit systemic vascular dysfunction,³³ a condition known to limit exercise capacity in other disease states, such as congestive heart failure. Additionally, skeletal muscle dysfunction promotes exercise limitation in both COPD³⁴ and pulmonary hypertension³⁵ individually, suggesting that this mechanism may be enhanced when these conditions coexist.

Last, the association we observed between mPAP and 6-min walk distance potentially could be due to confounding. However, our multivariable model excluded confounding by age, gender, height, weight, PAOP, and FEV₁. Further, a careful examination for potential confounding by differences in use of respiratory and cardiovascular medications revealed no significant effect on our observed associations; thus, these variables were not included in our final model. Similarly, concomitant medical conditions, such as interstitial lung disease, OSA, collagen vascular disease, history of pulmonary embolism, and HIV infection, were either excluded from our cohort or explored and found not to have any effect.

Our study has several limitations. Our design was cross sectional, making firm conclusions about causality of associations impossible. In addition, we excluded a small number of patients because of missing data. Finally, our cohort represents a selected group of patients with severe COPD referred for lung transplantation. As a result, the findings of this study are not necessarily generalizable to all patients with COPD.

In conclusion, we have demonstrated that higher mPAP in patients with COPD is associated with impaired exercise tolerance as measured by 6-min walk distance, independent of demographics, anthropometrics, severity of airflow obstruction, and pulmonary venous hypertension. As previously demonstrated, higher mPAP also was associated with more severe hypoxemia and greater right heart dysfunction, each of which may play a role in the causal pathway linking higher mPAP with reduced exercise function. Our results emphasize that even mild elevations in resting mPAP and PVR within the normal range may have real functional consequences in this population, and to our knowledge, this study is the first to demonstrate the impact of pulmonary hemodynamics on 6-min walk distance in patients with COPD. Whether treatment of pulmonary hypertension in COPD can reverse this functional deficit remains unproven, but our findings suggest that treatment aimed at lowering pulmonary arterial pressure in COPD might yield improvement in exercise tolerance, even in the absence of severe pulmonary hypertension.

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Author contributions: Dr. Sims conceived the study, collected all data, performed all analyses, and wrote the manuscript. Dr. Margolis supervised the conduct of the study and edited the manuscript. Dr. Localio provided biostatistical support. Dr. Panettieri edited the manuscript. Drs. Kawut and Christie assisted in interpretation of the data and edited the manuscript.

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REFERENCES

- 1 National Heart, Lung, and Blood Institute. Data fact sheet: chronic obstructive pulmonary disease (COPD). Bethesda, MD: National Heart, Lung, and Blood Institute, 2003; 1–6
- 2 Weitzenblum E, Hirth C, Ducolone A, et al. Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease. *Thorax* 1981; 36:752–758
- 3 Scharf SM, Iqbal M, Keller C, et al. Hemodynamic characterization of patients with severe emphysema. *Am J Respir Crit Care Med* 2002; 166:314–322
- 4 Kessler R, Faller M, Fourgaut G, et al. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159:158–164
- 5 Oswald-Mammosser M, Weitzenblum E, Quoix E, et al. Prognostic factors in COPD patients receiving long-term oxygen therapy: importance of pulmonary artery pressure. *Chest* 1995; 107:1193–1198
- 6 Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med* 2003; 167:735–740
- 7 Solway S, Brooks D, Lacasse Y, et al. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. *Chest* 2001; 119:256–270
- 8 Pinto-Plata VM, Cote C, Cabral H, et al. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. *Eur Respir J* 2004; 23:28–33
- 9 Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. *Eur Respir J* 2008; 32:1371–1385
- 10 American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995; 152:1107–1136
- 11 Crapo RO, Morris AH. Standardized single breath normal values for carbon monoxide diffusing capacity. *Am Rev Respir Dis* 1981; 123:185–189
- 12 Crapo RO, Morris AH, Clayton PD, et al. Lung volumes in healthy nonsmoking adults. *Bull Eur Physiopathol Respir* 1982; 18:419–425
- 13 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *Am J Respir Crit Care Med* 1999; 159:179–187
- 14 Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation* 1984; 70:657–662

- 15 Kessler R, Faller M, Weitzenblum E, et al. "Natural history" of pulmonary hypertension in a series of 131 patients with chronic obstructive lung disease. *Am J Respir Crit Care Med* 2001; 164:219–224
- 16 Loke J, Mahler DA, Man SF, et al. Exercise impairment in chronic obstructive pulmonary disease. *Clin Chest Med* 1984; 5:121–143
- 17 MacNee W. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease: part one. *Am J Respir Crit Care Med* 1994; 150:833–852
- 18 Peinado VI, Barbera JA, Abate P, et al. Inflammatory reaction in pulmonary muscular arteries of patients with mild chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159:1605–1611
- 19 Weisse AB, Moschos CB, Frank MJ, et al. Hemodynamic effects of staged hematocrit reduction in patients with stable cor pulmonale and severely elevated hematocrit levels. *Am J Med* 1975; 58:92–98
- 20 Falk JA, Kadiev S, Criner GJ, et al. Cardiac disease in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2008; 5:543–548
- 21 Wright JL, Petty T, Thurlbeck WM. Analysis of the structure of the muscular pulmonary arteries in patients with pulmonary hypertension and COPD: National Institutes of Health nocturnal oxygen therapy trial. *Lung* 1992; 170:109–124
- 22 Hale KA, Niewoehner DE, Cosio MG. Morphologic changes in the muscular pulmonary arteries: relationship to cigarette smoking, airway disease, and emphysema. *Am Rev Respir Dis* 1980; 122:273–278
- 23 Peinado VI, Barbera JA, Ramirez J, et al. Endothelial dysfunction in pulmonary arteries of patients with mild COPD. *Am J Physiol* 1998; 274:L908–L913
- 24 Dinh-Xuan AT, Higenbottam TW, Clelland CA, et al. Impairment of endothelium-dependent pulmonary-artery relaxation in chronic obstructive lung disease. *N Engl J Med* 1991; 324:1539–1547
- 25 Stolz D, Rasch H, Linka A, et al. A randomized, controlled trial of bosentan in severe COPD. *Eur Respir J* 2008; 32:1371–1385
- 26 Holverda S, Rietema H, Bogaard HJ, et al. Acute effects of sildenafil on exercise pulmonary hemodynamics and capacity in patients with COPD. *Pulm Pharmacol Ther* 2008; 21:558–564
- 27 Rietema H, Holverda S, Bogaard HJ, et al. Sildenafil treatment in COPD does not affect stroke volume or exercise capacity. *Eur Respir J* 2008; 31:759–764
- 28 Naeije R, Brimiouille S. Physiology in medicine: importance of hypoxic pulmonary vasoconstriction in maintaining arterial oxygenation during acute respiratory failure. *Crit Care* 2001; 5:67–71
- 29 Leach RM, Davidson AC, Chinn S, et al. Portable liquid oxygen and exercise ability in severe respiratory disability. *Thorax* 1992; 47:781–789
- 30 Leggett RJ, Flenley DC. Portable oxygen and exercise tolerance in patients with chronic hypoxic cor pulmonale. *BMJ* 1977; 2:84–86
- 31 Weitzenblum E, Chaouat A. Right ventricular function in COPD: can it be assessed reliably by the measurement of right ventricular ejection fraction? *Chest* 1998; 113:567–569
- 32 Oliver RM, Fleming JS, Waller DG. Right ventricular function at rest and during exercise in chronic obstructive pulmonary disease: comparison of two radionuclide techniques. *Chest* 1993; 103:74–80
- 33 Barr RG, Mesia-Vela S, Austin JH, et al. Impaired flow-mediated dilation is associated with low pulmonary function and emphysema in ex-smokers: the Emphysema and Cancer Action Project (EMCAP) study. *Am J Respir Crit Care Med* 2007; 176:1200–1207
- 34 Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med* 1996; 153:976–980
- 35 Bauer R, Dehnert C, Schoene P, et al. Skeletal muscle dysfunction in patients with idiopathic pulmonary arterial hypertension. *Respir Med* 2007; 101:2366–2369