Hemodynamic Characterization of Patients with Severe Emphysema

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In 120 patients with severe emphysema evaluated for participation in the National Emphysema Treatment Trial, pulmonary hemodynamics and ventricular function were assessed. Pulmonary function tests were (%predicted): FEV_1 = 27%; residual volume = 224.6%; diffusion capacity = 26.7%. In 90.8% of patients, end-expiratory pulmonary artery mean pressure was > 20 mm Hg; in 61.4%, end-expiratory wedge pressure was > 12 mm Hg. Cardiac index was normal. Mean pulmonary artery pressure correlated inversely with arterial Po_2, and severity of emphysema, and directly with wedge pressure. Multiple stepwise regression revealed that arterial Po_2 was not an independent predictor of mean pulmonary artery pressure. No correlation was found between indices of emphysema severity and PA pressures. Diastolic ventricular pressures were increased without evidence of systolic dysfunction. We conclude that (*1*) elevations of pulmonary vascular pressures are common, (*2*) pulmonary hypertension may be related to factors other than hypoxia, (*3*) pulmonary hypertension does not impair resting systemic O_2 delivery, and (*4*) elevated cardiac diastolic pressures do not represent systolic dysfunction.

Keywords: emphysema; pulmonary hypertension; cardiovascular function

Pulmonary hypertension and cor pulmonale are important predictors of mortality in chronic obstructive pulmonary disease (COPD) (1–4) and contributes to disability in this disease (5, 6). Relatively few studies of cardiovascular function in COPD have focused specifically on patients with emphysema. These studies have often relied on clinical criteria to distinguish emphysema from chronic bronchitis. However, clinical findings correlate poorly with the extent of anatomic emphysema on computed tomographic (CT) scans or histologic specimens (7–10). Thus, such studies may not have clearly differentiated patients with emphysema from those with chronic bronchitis.

The National Emphysema Treatment Trial is an ongoing multicenter prospective, randomized, controlled trial comparing lung volume reduction surgery plus medical therapy to medical therapy alone in patients with severe emphysema. Subjects who are enrolled have been anatomically, physiologically, and clinically well-characterized with a battery of pulmonary and cardiac tests including high-resolution CT scanning. At 3 of the 17 participating centers, all patients have additionally undergone right heart catheterization and multigated blood pool radionuclide ventriculography. This provides a unique opportunity to study resting cardiovascular function in a relatively homogeneous group of patients with severe emphysema.

In this paper, we characterized resting cardiovascular function of these patients at the time of their baseline evaluation. In addition to determining the prevalence of cardiovascular dysfunction and pulmonary hypertension in an observational study, we have also tested the following hypotheses: (*1*) pulmonary hypertension is associated with arterial hypoxemia; (*2*) cardiac output decreases as pulmonary hypertension becomes more severe; (*3*) pulmonary hypertension impairs resting right ventricular function; and (*4*) elevated intracardiac pressures reflect mechanical heart–lung interactions due to elevations in lung volume rather than intrinsic myocardial disease or ventricular interdependence effects.

METHODS

The Institutional Review Boards at each institution approved protocols and all patients signed informed consent before participating in these studies.

Patient Population

One hundred twenty patients were studied on evaluation for entry into the National Emphysema Treatment Trial. Details of the trial have been published (11). Patients had activity-limiting dyspnea and emphysema as judged by CT scanning. Patients were excluded if they smoked within 4 months of evaluation, or had previously diagnosed pulmonary vascular disease, ischemic heart disease, congestive heart failure, intrathoracic disease, or previous lung surgery. In the present paper, we included patients who did not continue to randomization in the National Emphysema Treatment Trial if the reason for this was pulmonary nodule, pulmonary hypertension discovered at screening, emphysema deemed too severe by CT scan, missed data time windows, subject withdrawal after rehabilitation, or physician judgment. Ninety of our 120 patients were eventually randomized.

Pulmonary function testing consisted of spirometry, lung volumes (plethysmography), and single-breath CO diffusion capacity ($D_{L_{CO}}$) (uncorrected for hemoglobin). Arterial blood (room air–subjects seated) was drawn for measuring gas tensions. Pulmonary function variables were expressed as percent predicted (12–14), indicated by a % following the variable.

Right heart catheterization was performed at rest with patients supine. Oxygen was given if needed to achieve saturation > 92%. Right atrial (RA), right ventricular, pulmonary arterial (PA), pulmonary wedge (Pw), systemic arterial pressures, arterial and mixed venous O_2 saturations, and cardiac output by thermodilution were measured. All pressures were taken at end-expiration. In 73 patients, right ventricular ejection fraction was measured at catheterization using a rapid response thermistor-tipped catheter (15). Mean PA pressures were calculated from end-expiratory PA pressures (mean PA = $PA_{diastolic}$ + [pulse pressure/3]). Pulmonary vascular resistance (PVR) was calculated as PVR = [(PA mean – Pw)/CO] × 79.9 (dynes-sec-cm^{-5}).

(Received in original form July 5, 2001; accepted in final form May 1, 2002)

Supported by the National Institutes of Health (NIH contract numbers: N01-HR-76106, NO1-HR-76115, NO1-HR-76116, and NO1-HR-76108, and by NIH Grant RFP HR 97-02).

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This article has an online data supplement, which is accessible from this issue's table of contents online at www.atsjournals.org.

Am J Respir Crit Care Med Vol 166. pp 314–322, 2002
DOI: 10.1164/rccm.2107027
Internet address: www.atsjournals.org

Within a few days of the catheterization, 92 patients underwent gated pool radionuclide angiography at rest while supine for measurement of left ventricular ejection fraction. We assumed that cardiac output measured at rest at catheterization and at gated pool scan were equal and calculated stroke volume, left ventricular and right ventricular end-diastolic and end-systolic volumes. We divided appropriate cardiovascular parameters by body surface area to obtain indices.

CT Scanning

Using standardized protocols, helical and high-resolution CT scans were obtained while supine in full inspiration. The lung fields on each side were divided into upper, middle, and lower zones. The degree of emphysema for each zone was visually quantified at each institution on a scale from 0 (no emphysema) to 4 (severe emphysema) by radiologists who had received training in the trial's CT standards. Grading for each zone was based on a judgment of how much, as a percentage of the volume of the zone, was involved with emphysema. For example, "severe" was defined as > 75% of the zone involved with emphysema. The emphysema score was the sum of the emphysema scores for the six lung zones.

Statistical Methods

The primary statistical goal of this study was to estimate the prevalence of pulmonary hypertension in this population and determine which factors are associated with it. We determined the frequency distribution of PA systolic and mean pressures as well as Pw. In addition, in keeping with clinical practice and previous literature (7, 8, 10), pulmonary hypertension was defined as PA end-expiratory systolic pressure of > 30 or PA mean pressure > 20. To estimate the prevalence of pulmonary hypertension of different severities, we categorized PA systolic pressure as follows: none to mild = PAsystolic < 30, moderate = PAsystolic 30–45, and severe = PAsystolic > 45 mm Hg. We also categorized PA mean pressure as follows: none to mild = PAmean < 20, moderate = PAmean 20–35, and severe = PA mean > 35 mm Hg. Finally, we stratified Pw as follows: low = < 7, normal = 7–12, elevated = 12.1–20, and very elevated = > 20 mm Hg. For analysis of factors associated with pulmonary hypertension and other hemodynamic functions, we defined pulmonary hypertension in terms of PAmean pressure. Univariate regression analysis was performed as indicated. Multiple backward regression analysis was done as indicated for any given independent variable using variables that were significant predictors on the univariate analysis. Data were analyzed using SigmaStat 2.03 (SPSS Inc., Chicago, IL), and GB-stat (Dynamic Microsystems, Silver Spring, MD). For some analyses, the cohort had missing data values. The number of observations are indicated where results are presented.

RESULTS

Of the 120 patients, 73 were males and 47 females. Ages ranged (in years) from 51–79. Racial distribution was as follows: 112 whites, 7 African Americans, and 1 other. Body mass index (BMI), age, pulmonary function, gas exchange, and emphysema scores are shown in Table 1. The patients had severe airflow obstruction, hyperinflation, and substantial air trapping. There was a wide range of arterial Po_2, percent predicted $D_{L_{CO}}$ ($D_{L_{CO}}$%), and CT emphysema scores.

Table 2 shows the variables measured at catheterization. Mean, systolic, and diastolic PA pressures as well as Pw and RA pressure were on average above the normal range. However, cardiac output and cardiac index were low normal, as were the mean values of left and right ventricular ejection fractions. Thus, even with high diastolic filling pressure, systolic function as assessed by EF appeared to be well preserved. Figure 1 shows the frequency distributions of PA systolic and mean pressures, and Pw, which appeared unimodal.

Table 3 shows the prevalence of the ranges of PA pressures according the categories given above. 90.8% of the patients had moderate to severe elevations of PA systolic and mean pressures. For Pw, 61.4% had values above the normal range (> 12 mm Hg).

TABLE 1. DEMOGRAPHICS, RESPIRATORY FUNCTION, AND EMPHYSEMA SCORES

Variable	n	Mean	SD
BMI	120	25.3	4.2
Age, yr	120	65.7	5.9
Pa_{O_2}	120	65.9	10.0
Pa_{CO_2}	120	42.0	5.9
pH	120	7.42	0.02
Emphysema score	119	17.4	3.9
FEV_1, L	120	0.79	0.23
FEV_1%	120	27.0	7.0
TLC%	120	125.0	12.5
FRC%	119	251.9	56.3
RV%	120	224.6	46.4
$D_{L_{CO}}$%	120	26.7	10.0
Hgb	113	14.2	1.4

Definition of abbreviations: BMI = body mass index (kg/m^2); $D_{L_{CO}}$% = percent predicted CO diffusion capacity; FEV_1% = percent predicted FEV_1; FRC% = percent predicted FRC; Hgb = hemoglobin (g/dl); n = number of observations; pH = arterial pH (units); RV% = percent predicted residual volume.

Table 4 lists the results of univariate regression analyses. Only the significant correlations are shown. Table E1 in the online data supplement gives all of the univariate regression analyses performed; the raw data are given in Table E2.

TABLE 2. HEMODYNAMIC DATA—MEASURED

Variable	n	Mean	SD
MAP	116	100.2	13.4
RAPex	120	9.6	5.5
RVSex	120	37.5	6.8
RVDex	119	9.4	5.7
PASex	120	37.6	7.1
PADex	120	20.6	4.8
PAM	120	26.3	5.2
Pw_{EX}	120	14.1	4.7
SAT_AO_2	119	0.95	0.03
SAT_VO_2	118	0.69	0.05
CO	118	5.2	1.2
CI	118	2.9	0.7
PVR	118	193	95.2
HR, bpm	120	83.2	11.8
RVEF	73	0.34	0.08
LVEF	92	0.61	0.09
SV, ml	118	63.4	14.0
SVI	118	34.8	7.9
RVEDV	73	200.4	52.6
RVEDVI	73	109.0	27.2
LVEDV	92	105.4	23.6
LVEDVI	92	57.6	13.2
RVESV	73	13.7	48.0
RVESVI	73	73.1	25.3
LVESV	92	42.3	16.5
LVESVI	92	23.2	9.3

Definition of abbreviations: CI = cardiac index (L/min/m^2); CO = cardiac output (L/min); HR = heart rate; LVEDV = left ventricular end-diastolic volume (ml); LVEDVI = left ventricular end-diastolic volume index (ml/m^2); LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume (ml); LVESVI = left ventricular end-systolic volume index (ml/m^2); MAP = mean arterial pressure; n = number of observations; PADex = end-expiratory pulmonary arterial diastolic pressure; PAM = mean pulmonary arterial pressure; PASex = end-expiratory peak systolic pulmonary arterial pressure; PVR = pulmonary vascular resistance (dyne · sec/cm^5); Pw_{EX} = end-expiratory pulmonary wedge pressure; RAPex = end-expiratory right atrial pressure; RVDex = end-expiratory right ventricular end-diastolic pressure; RVEDV = right ventricular end-diastolic volume (ml); RVEDVI = right ventricular end-diastolic volume index (ml/m^2); RVESV = right ventricular end-systolic volume (ml); RVESVI = right ventricular end-systolic volume index (ml/m^2); RVEF = right ventricular ejection fraction; RVSex = end-expiratory peak systolic right ventricular pressure; SAT_AO_2 = arterial O_2 saturation; SAT_VO_2 = mixed venous O_2 saturation; SV = stroke volume; SVI = stroke volume index (SV/m^2).

All pressures are in mm Hg.

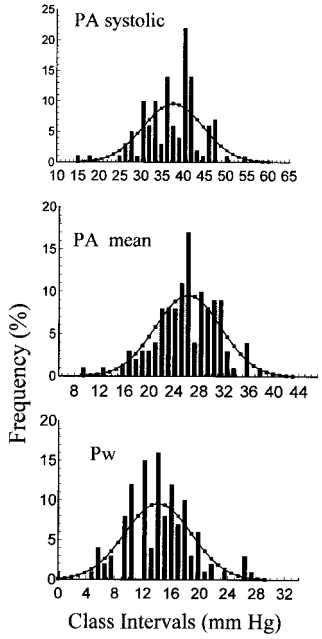

Figure 1. Frequency distributions of PA systolic, PA mean, and pulmonary wedge (Pw) pressures (mm Hg).

Determinates of PA Pressures

To test Hypothesis 1 (that pulmonary hypertension is associated with hypoxemia), PA mean pressure was regressed against all the variables in Table E1 in the online data supplement. In this analysis, arterial P_{O_2}, FEV_1%, and $D_{L_{CO}}$% were inversely correlated with and Pw was directly correlated with PA mean pressure. PA mean pressure was not, however, correlated with CT emphysema scores. Figure 2 shows the predictors of PA mean pressure that remained significant in the multiple regression analysis. When the factors listed in Table 4 as determinants of PA pressure were entered into a multiple regression model, arterial P_{O_2} was no longer a significant independent predictor of PA mean pressure. The final regression equation predicting PA mean pressure was: PA mean = 24.98 − 0.19 (FEV_1%) − 0.09 ($D_{L_{CO}}$%) + 0.63 (Pw), $R^2 = 0.46$, $p < 0.0001$; $n = 120$.

Correlates of Cardiac Index

To test Hypothesis 2 (that pulmonary hypertension impairs systemic blood flow), we performed univariate regression analyses between cardiac index and the factors listed in Table E1 in the online data supplement. Table 4 shows that cardiac index was positively correlated with right ventricular ejection fraction, left ventricular end-diastolic volume index, left ventricular end-systolic volume index, and right ventricular end-diastolic volume index, but was inversely correlated with arterial P_{O_2}. Of note, there was no significant correlation between cardiac index and PA systolic or mean pressures, Pw, or the pressure gradient across the pulmonary bed (PA mean–Pw). Multiple backward stepwise regression revealed that only left ventricular end-diastolic volume index and left ventricular end-systolic volume index were independent predictors of cardiac index. Cardiac index = 0.048 + 0.076(left ventricular end-diastolic volume index) − 0.068(left ventricular end-systolic volume index); $R^2 = 0.67$, $p < 0.0001$.

Thus, a considerable proportion of the variance (67%) of cardiac index was explained by indices of left ventricular function, and pulmonary hypertension was independent of both pulmonary hypertension and right ventricular function.

Correlates of Right Ventricular Function

We wished to determine whether right ventricular afterload, as indicated by PA mean pressure or PVR, was a predictor of right ventricular systolic function as measured by right ventricular ejection fraction (Hypothesis 3). As shown in Table 4, PA mean pressure was inversely correlated with right ventricular ejection fraction, and positively correlated with right ventricular end-diastolic and end-systolic volume indices (Table 4). Right ventricular ejection fraction was also inversely correlated with PVR. Neither right ventricular ejection fraction nor right ventricular volume indices correlated with measures of airflow obstruction. When the factors listed in Table 4 (determinants of right ventricular function) were entered into the multiple regression analysis, PVR and left ventricular ejection fraction were not independent predictors of right ventricular ejection fraction. The multivariate regression equation for right ventricular ejection fraction was: Right ventricular ejection fraction = 0.604 − 0.002 (arterial P_{O_2}) − 0.004 (PA mean); $R^2 = 0.13$, $p = 0.007$.

Thus, not unexpectedly, PA mean pressure, an index of right ventricular afterload, was a significant predictor of both right ventricular preload (right ventricular end-diastolic volume index) and end-systolic right ventricular volume (right ventricular end-systolic volume index).

Right to Left Heart Interactions (Ventricular Interdependence)

To explore whether dysfunction of one ventricle influenced the other (Hypothesis 4), we performed a series of correlations between indices of right and left ventricular function. We found significant direct correlations between ventricular filling pressures (RA pressure and Pw) and preload (right ventricular end-diastolic volume index and left ventricular end-diastolic volume index). There was a borderline correlation between measures of systolic function, right ventricular ejection fraction, and left ventricular ejection fraction [right ventricular ejection fraction = 0.21 + 0.21 (left ventricular ejection fraction); $R^2 = 0.06$, $p = 0.0503$].

Correlation between Lung Volume and Ventricular Filling Pressures

To determine if the degree of hyperinflation predicted the level of RA pressures or Pw, we performed univariate regression analyses

TABLE 3. PREVALENCE OF ABNORMAL PULMONARY ARTERY PRESSURES IN PATIENTS WITH SEVERE EMPHYSEMA

PA systolic pressure range	No.	%	PA mean pressure range	No.	%	Pw pressure range	No.	%
< 30	11	9.2	≤ 20	11	9.2	< 7	8	6.7
> 30 ≤ 45	93	77.5	> 20 ≤ 35	103	85.8	≥ 7 ≤ 12	38	31.7
> 45	16	13.3	> 35	6	5.0	> 12 ≤ 20	66	55.0
						> 20	8	6.4

Definition of abbreviations: PA = pulmonary artery; Pw = pulmonary occlusion pressure.
All pressures in mm Hg.

TABLE 4. UNIVARIATE REGRESSION ANALYSIS; SIGNIFICANT CORRELATIONS

Dependent Variable	Independent Variable	n	Coefficient	Adj R^2	p Value
Correlates of PA pressure					
PAm	Pa_{O_2}	120	−0.105	0.032	0.028
	FEV_1%	120	−0.255	0.109	0.000
	Pw	120	0.637	0.321	<0.000
	RA	120	0.323	0.109	<0.000
	D_{LCO}%	120	−0.143	0.066	0.003
Correlates of CI					
CI	RVEF	73	3.043	0.120	0.001
	LVEDVI	92	0.035	0.440	<0.000
	LVESVI	92	0.024	0.092	0.002
	RVEDVI	73	0.007	0.077	0.010
	Pa_{O_2}	118	−0.017	0.047	0.010
	Pa_{CO_2}	118	0.029	0.050	0.008
Correlates of RV function					
RVEF	PAm	73	−0.004	0.046	0.038
	LVEF	66	0.209	0.043	0.050
	Pa_{O_2}	73	−0.002	0.041	0.046
	PVR	73	−0.0002	0.069	0.014
RVEDVI	PAm	73	1.333	0.045	0.038
RVESVI	PAm	73	1.419	0.064	0.017
Measures of RV-LV Interdependence					
RA	Pw	120	0.588	0.249	0.001
RVEDVI	LVEDVI	66	0.935	0.143	0.001
Correlates of Pulmonary Vascular Resistance					
PVR	D_{LCO}%	117	−2.047	0.042	0.015
Correlates of CT emphysema score					
CT score	D_{LCO}%	119	−0.130	0.103	0.000

Definition of abbreviations: CI = cardiac index (L/min/m^2); CT score = emphysema score from CT scan; D_{LCO}% = carbon monoxide diffusing capacity (% predicted); FEV_1% = FEV_1 percent predicted; LVEDVI = left ventricular end-diastolic volume index (ml/m^2); LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index (ml/m^2); N = number of observations for each correlation; PAm = mean pulmonary artery pressures (mm Hg); PVR = pulmonary vascular resistance (dynes · sec · cm^{-5}); Pw = Pulmonary wedge pressure (mm Hg); RA = right atrial pressures (mm Hg); RVEDVI = right ventricular end-diastolic volume index (ml/m^2); RVEF = right ventricular ejection fraction.

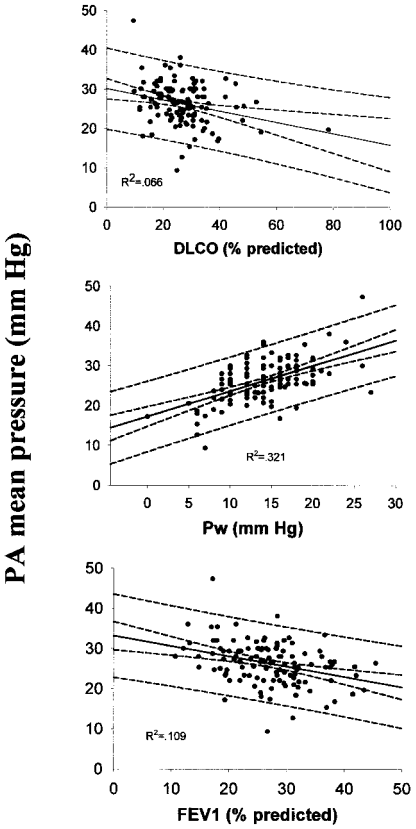

Figure 2. Correlations between D_{LCO}%, Pw, FEV_1%, and PA mean pressure. Shown are the data points, the regression line, 95% confidence intervals for the regression, and 95% confidence intervals for the data points.

between functional residual volume% and these measures of ventricular filling. Neither regression was statistically significant.

Correlation between Indices of Emphysema Severity

Both CT scores and D_{LCO}% are indices of the severity of tissue destruction in emphysema. Table 4 shows the correlation of these indices.

Additional correlations are graphed in the online data supplement, Figures E1–E6. These are: PA mean versus arterial P_{O_2}, cardiac output (Figure E1); cardiac index (Figure E2); arterial saturation, CT score (Figure E3); and O_2 saturation (Figure E4). Figure E5 shows the correlation between the pressure gradient across the pulmonary bed and cardiac index, and Figure E6 shows the correlation between CT score of emphysema severity and D_L%.

DISCUSSION

This study is the first to combine pulmonary function testing, right heart catheterization, high-resolution CT, and radionuclide angiography to describe cardiovascular function in a large, well-characterized group of patients with severe emphysema. We demonstrated a high prevalence of moderate to severe pulmonary hypertension, and of elevated Pw. Mean cardiac index was in the low normal range. By multiple regression, D_{LCO}%, Pw, and FEV_1%, but not arterial P_{O_2}, were significant predictors of PA mean. Cardiac index was positively correlated with indices of ventricular function, but not with PA mean pressure. On multiple regression, only left ventricular ejection fraction, arterial P_{O_2}, and PA mean pressure were independent correlates of right ventricular ejection fraction. Indices of left and right ventricular filling were directly correlated with each other. Finally, we found few correlates of PVR. In the ensuing discussion, we will consider these findings in the light of the currently available literature.

Gated pool radionuclide measurements of left ventricular ejection fraction were obtained at different times than measurements of right ventricular ejection fraction, cardiac output, and HR, but were obtained within a few days of catheterization under similar conditions. We believe that our assumption of similar cardiac outputs under similar conditions (resting supine, on oxygen if necessary) were reasonable and enabled us to reliably calculate ventricular volumes. For safety reasons, we provided O_2 as needed during gated pool studies and catheterization. Thus, we did not examine the effects of hypoxic pulmonary vasoconstriction on pulmonary pressures. Because all patients with resting hypoxia were receiving domiciliary oxygen, pulmonary vascular tone at the time of testing was likely similar to that which the patient had throughout the day. In addition, this was a relatively nonhypoxic population, the mean P_{O_2} being around 65 mm Hg. Further, 86 of 120 patients had a resting arterial $P_{O_2} \geq 60$ mm Hg. It is likely that few of these patients required O_2 at cardiac catheterization. Thus, we believe that hypoxic pulmonary vasoreactivity reversed by O_2 was not an important contribution to the hemodynamic values reported at catheterization.

We use both CT emphysema score and D_{LCO}% as independent measures of the degree of capillary destruction. We acknowledge potential difficulties with interobserver variability

with the interpretation of visual scores collected from several institutions by several radiologists. Nevertheless, emphysema scores were positively correlated with D_{LCO}% (Table 4). Thus, we believe that the reported emphysema scores are representative of the degree of parenchymal damage, and the associated loss of capillary surface area as reflected in the D_{LCO}%.

Classically, pulmonary hypertension in emphysema has been attributed to three factors: hypoxia leading to vasoconstriction and vascular remodeling, compression of alveolar vessels from hyperinflation, and/or physical obliteration of pulmonary vasculature. Other possible influences include transmission of end-expiratory intrathoracic pressure elevated due to dynamic or static hyperinflation or use of expiratory muscles. Animal studies of emphysema generally demonstrated mild to moderate pulmonary hypertension (16), but reached different conclusions as to its cause, and have raised some interesting alternate possibilities. Some studies (17, 18) have emphasized the role of vascular reactivity, whereas others (19, 20) have emphasized the impact of vascular obliteration by parenchymal destruction. The finding of inflammatory markers in the lungs and pulmonary vessels of patients with COPD (21, 22) and smokers also suggests that inflammation plays a role in vascular remodeling or obstruction. On the other hand, recent animal studies (23) showed that inhibition of vascular endothelial growth factor receptors leads to emphysema and epithelial and endothelial apoptosis. These data suggest that noninflammatory processes originating in pulmonary vasculature can also contribute to the pathogenesis of emphysema.

In the present study, there was a high prevalence of pulmonary hypertension defined from PA pressures, including severe pulmonary hypertension (Figure 1, Table 3). Burrows and coworkers (3) found that patients with emphysema had higher PVR and lower cardiac outputs than patients without emphysema. By contrast, Boushy and North (24) failed to confirm this finding. Difficulty distinguishing emphysema from chronic bronchitis clinically could account for the different findings.

Oswald-Mammosser and colleagues (25) found a prevalence of resting pulmonary hypertension of only 20.5% in a large series of patients with emphysema. In a recent study of patients with COPD (mean FEV_1 44.6% predicted), this same group (26) demonstrated that the evolution of pulmonary hypertension in patients with no previous evidence of resting pulmonary hypertension was slow. Even after a 7-year follow-up, few patients had resting pulmonary hypertension. However, in comparison with our patients (mean FEV_1 27% predicted) the patients studied by Oswald-Mammoser and colleagues had considerably less severe disease. Further, we found that as FEV_1 worsened, so did the degree of PH. Combining the data of Oswald-Mammoser and colleagues (25, 26) with that from our study leads to the conclusion that worsening pulmonary hypertension is associated with worsening airflow obstruction.

We were surprised that arterial P_{O_2} was not an independent correlate of PA mean on multivariate analysis, suggesting that hypoxic vasoconstriction or remodeling are not related to pathogenesis of pulmonary hypertension in severe emphysema. There are several explanations for this finding. First, severe hypoxia (resting arterial $P_{O_2} < 45$ mm Hg) or O_2 requirements > 6 L/min during 6-minute walk testing, were exclusions to National Emphysema Treatment Trial participation. This narrowed the range of arterial P_{O_2} in the subjects, which may have obscured a relation between PA mean and arterial P_{O_2}. Consistent with these explanations, Kessler and coworkers (26) found that in COPD patients with arterial $P_{O_2} >$ 60 mm Hg, hypoxic vasoconstriction plays a minor role in generating pulmonary hypertension. Our mean arterial P_{O_2} of 65 mm Hg would therefore put our patients in this range. Second, arterial P_{O_2} was measured on room air, but all hypoxic subjects were receiving domiciliary O_2 and were catheterized while on supplemental O_2. Thus, hypoxic vasoconstriction and remodeling may have been reversed by acute and long-term O_2 administration.

The D_{LCO}%, Pw, and severity of airflow obstruction (FEV_1%) remained as independent correlates of PA mean pressure, together explaining 46% of its variance. Oswald-Mammosser and colleagues (25) also found a correlation between PA pressures D_{LCO}%. To the extent that D_{LCO}% reflects destruction of pulmonary microvessels, it is axiomatic that sufficient loss of D_{LCO} would elevate PA mean pressure. The correlation between PA mean and Pw is not necessarily so straightforward. Auto-positive end-expiratory pressure in patients with emphysema (27) could lead to compression of capillaries and create "zone II" conditions, where alveolar pressure would be the back pressure to pulmonary flow (28). This situation would dissociate Pw from PA pressure. By contrast, we found a direct correlation between these variables. Thus, we believe that Pw is acting as the backpressure to PA flow, and auto-positive end-expiratory pressure is not an important mechanism increasing PA pressure in severe emphysema at rest. These findings are consistent with previous studies in lung mechanics in patients with severe emphysema that found little or no auto-positive end-expiratory pressure at rest (29).

The reason for the inverse correlation between airflow limitation (FEV_1%) and PA mean pressure is uncertain. Although it is possible that greater airflow limitation could lead to greater hyperinflation and compression of alveolar vessels, we found no correlation between functional residual volume% and PA pressures. Alternatively, with increasing severity of airflow obstruction, end-expiratory intrathoracic pressure increases, which would be transmitted to the pulmonary vasculature. Finally, because pulmonary vessels and airways share the bronchovascular sheath, dilated proximal pulmonary arteries may encroach on proximal airways, further decreasing FEV_1%.

Hyperinflation of the lungs could, by directly compressing the heart and intrathoracic vessels, elevate intracardiac pressures. Indeed, this is known to occur during exercise in patients with COPD (30, 31). Although this is a possibility in our severely hyperinflated patients, there was no correlation between lung volume and PA mean, or ventricular diastolic pressures (RA and Pw). Thus, if hyperinflation plays a role elevating intracardiac or PA mean pressures, the relationship is complex and requires that other factors, such as lung and chest wall compliance, be taken into account.

As expected, right ventricular ejection fraction decreased as our measured indices of afterload (PA pressures, PVR) increased, and indices of right ventricular volumes increased with increased PA pressures. These data suggest that decreased right ventricular ejection fraction and increased right ventricular volumes may not indicate changes in contractility, but simply a change in afterload. End-systolic pressure volume curves would have been necessary to differentiate changes in afterload from changes in contractility (32). The inverse correlation between arterial P_{O_2} and right ventricular function is interesting. Although we do not know why this is so, it is possible that heightened sympathoadrenal tone with lower arterial P_{O_2} leads to enhanced ventricular contractility. Consistent with this notion, there was also an inverse correlation between arterial P_{O_2} and cardiac index. These findings suggest global changes in cardiac function, rather than isolated effects on right ventricular in severe emphysema.

There has been considerable debate regarding whether COPD itself causes left ventricular dysfunction, with conflicting

conclusions in the literature (33–39). Previous studies have neither been limited to patients with emphysema nor stratified patients by the severity of airflow obstruction or blood gas abnormalities. Thus, hypoxia, hypercapnia, or differences in sympathoadrenal tone could have contributed to left ventricular dysfunction. In spite of the high prevalence of elevated Pw in our patients, we found little evidence of left ventricular systolic dysfunction, as evidenced by left ventricular dilation or decreased ejection fraction. Similar findings had been reported in the studies of Weg and associates (40) in a small group of patients awaiting lung reduction surgery.

Previous studies have demonstrated that diastolic enlargement of one ventricle results in decreased diastolic filling of the other (41, 42). This effect, called diastolic interdependence, is mediated through the septum and augmented by the pericardium. Indeed, it has been reported that in patients with COPD, enlargement of the right ventricle is associated with decreased left ventricular diastolic dimensions (43). In the current population, we had expected that interdependence effects would have led to a reciprocal relationship between right ventricular and left ventricular end-diastolic dimensions, with decreasing left ventricular end-diastolic volume index associated with increased right ventricular end-diastolic volume index. This was not observed, and instead (Table 4) we observed a direct correlation between right ventricular end-diastolic and left ventricular end-diastolic volume indices, as well as between RA pressure and Pw. Our findings suggest that indices of right- and left-sided function simply reflected the state of overall myocardial function.

We hypothesized that pulmonary hypertension would reduce cardiac index in these patients, and that therefore cardiac index would be inversely correlated with pulmonary artery pressure. However, cardiac index correlated neither with PA pressure, nor the pressure gradient across the pulmonary vascular bed. The relationship between PA pressure and cardiac index would be governed by two factors. On one hand, as PVR increases, PA pressure at any given cardiac index increases. This increased right ventricular afterload would tend to impede cardiac index, especially at higher PA pressure. On the other hand, for any given PVR, increased venous return would increase PA pressure (Ohm's law). The convergence of these two opposing effects could obscure one or the other factor depending on PVR and right ventricular function. Hence, we found little evidence that in emphysema patients, pulmonary hypertension impeded peripheral O_2 delivery at rest. It is likely, however, that with exercise pulmonary artery pressures would be greater in these patients because of loss of pulmonary vascular reserve (30, 44), a factor that could limit cardiac index during exercise.

In conclusion, in a well-characterized population of patients with advanced emphysema, the prevalence of elevations in PA pressures and Pw was high. However, pulmonary hypertension was not associated with severe right or left ventricular dysfunction, or limitation of cardiac index at rest. Indices of right and left ventricular function were directly correlated, suggesting that interdependence effects were small and that indices of ventricular function reflect overall myocardial function. Although cardiovascular function may become impaired with exercise, resting function is well preserved despite advanced emphysema.

Acknowledgment: The authors wish to thank Dr. Steven Piantodosi for his review and comments on the manuscript.

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APPENDIX

NETT CREDIT ROSTER

Source of Funding

The National Emphysema Treatment Trial (NETT) is supported by the National Heart, Lung, and Blood Institute (NHLBI); the Health Care Financing Administration (HCFA); and the Agency for Healthcare, Research and Quality (AHRQ).

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