Impaired Left Ventricular Filling in COPD and Emphysema: Is It the Heart or the Lungs?

The Multi-Ethnic Study of Atherosclerosis COPD Study

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Background: COPD and heart failure with preserved ejection fraction overlap clinically, and impaired left ventricular (LV) filling is commonly reported in COPD. The mechanism underlying these observations is uncertain, but may include upstream pulmonary dysfunction causing low LV preload or intrinsic LV dysfunction causing high LV preload. The objective of this study is to determine if COPD and emphysema are associated with reduced pulmonary vein dimensions suggestive of low LV preload.

Methods: The population-based Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study recruited smokers aged 50 to 79 years who were free of clinical cardiovascular disease. COPD was defined by spirometry. Percent emphysema was defined as regions < -910 Hounsfield units on full-lung CT scan. Ostial pulmonary vein cross-sectional area was measured by contrast-enhanced cardiac magnetic resonance and expressed as the sum of all pulmonary vein areas. Linear regression was used to adjust for age, sex, race/ethnicity, body size, and smoking.

Results: Among 165 participants, the mean ($\pm$ SD) total pulmonary vein area was 558 ± 159 mm² in patients with COPD and 623 ± 145 mm² in control subjects. Total pulmonary vein area was smaller in patients with COPD (-57 mm²; 95% CI, -106 to -7 mm²; $P = .03$) and inversely associated with percent emphysema ($P < .001$) in fully adjusted models. Significant decrements in total pulmonary vein area were observed among participants with COPD alone, COPD with emphysema on CT scan, and emphysema without spirometrically defined COPD.

Conclusions: Pulmonary vein dimensions were reduced in COPD and emphysema. These findings support a mechanism of upstream pulmonary causes of underfilling of the LV in COPD and in patients with emphysema on CT scan.

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Abbreviations: E/A ratio = ratio of peak filling rates during early phase diastole and atrial contraction; E/A ratioMR = ratio of peak filling rates during early phase diastole and atrial contraction estimated by magnetic resonance; EDV = end-diastolic volume; LV = left ventricle; MESA = Multi-Ethnic Study of Atherosclerosis; MR = magnetic resonance; PVR = pulmonary vascular resistance; RV = right ventricle

Chronic lower respiratory disease is the third-leading cause of death in the United States.¹ The most morbid components of chronic lower respiratory disease are COPD, defined by spirometry as airflow obstruction that is not fully reversible, and pulmonary emphysema, defined by morphology as permanent enlargement of airspaces accompanied by destruction of their walls.^{2,3} Emphysema on CT imaging is present in approximately one-half of patients with COPD,^{4,7} and an esti-

mated 2% of the general population aged > 50 years has emphysema without spirometry-defined COPD.⁸

The number of Americans with a diagnosis of heart failure was 5.7 million in 2008, and approximately one-half of prevalent heart failure cases are characterized by preserved ejection fraction.^{9,10} By comparison, 12 million Americans have a diagnosis of COPD and an additional 12 million may have undiagnosed COPD and emphysema.¹¹

Heart failure with preserved ejection fraction and COPD overlap clinically: 41% of patients hospitalized for exacerbations of heart failure with preserved ejection fraction had COPD when tested systematically, and approximately 20% of patients hospitalized for COPD exacerbations have heart failure.^{12,13} Studies using echocardiography demonstrate a high prevalence of left ventricular (LV) diastolic dysfunction in COPD.¹⁴⁻¹⁶ Standard echocardiographic signs of diastolic dysfunction (eg, reversed ratio of peak filling rates during early-phase diastole and atrial contraction [E/A ratio]) are often interpreted as suggestive of high LV preload pressure; however, states of reduced LV filling pressure can also mimic these changes.¹⁷⁻¹⁹ Older articles in the literature, mostly using invasive methods, suggested reduced cardiac output in COPD with generally preserved LV ejection fraction.^{13,20,21} Whether chronic lower respiratory disease is associated with intrinsic LV dysfunction or impaired LV filling due to upstream causes remains poorly understood.¹⁷

Assessment of LV preload pressure typically requires cardiac catheterization; however, pulmonary vein dimensions have been shown to correlate with left atrial dimensions,^{22,23} which, in turn, correlate with measures of LV filling pressure.^{24,25} Therefore, we measured pulmonary vein dimensions using contrast-enhanced MRI in a study of patients with predominantly mild to moderate COPD and of control subjects. Reduced pulmonary vein cross-sectional area would favor a process resulting in reduced LV filling pressures, such as elevated pulmonary vascular resistance (PVR), whereas increased pulmonary vein area would favor a mechanism of intrinsic dysfunction of the LV. We also assessed the relationship of pulmonary vein dimen-

sions to emphysema on CT scans, given that we previously observed a stronger relationship of LV filling to emphysema than to lung function in the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study.²⁶

MATERIALS AND METHODS

See e-Appendix 1 for a complete description of the methods. The MESA COPD Study recruited patients with COPD and control subjects predominantly from MESA, a population-based, prospective cohort study of subclinical atherosclerosis,²⁷ and the Emphysema and Cancer Action Project, a separate, nonoverlapping lung cancer screening study,²⁸ and also from the outpatient community at Columbia University Medical Center. Included participants were 50 to 79 years of age with a ≥ 10 pack-year smoking history. Exclusion criteria were clinical cardiovascular disease, stage 3B to 5 chronic kidney disease, asthma prior to age 45 years, prior lung resection, contraindication to MRI, and pregnancy. The current report includes participants from one site where three-dimensional, contrast-enhanced MRI of the pulmonary veins was performed.

Protocols for this study were approved by the institutional review board of Columbia University Medical Center and by the National Heart, Lung, and Blood Institute (approval numbers AAAA7791 and AAAD6395). Written informed consent was obtained from all participants.

MRI

The cardiac MRI protocol was from the fifth examination of MESA modified to include assessment of pulmonary vasculature.²⁹ Images were obtained using a 1.5 Tesla, whole-body magnetic resonance (MR) system (Signa LX; GE Healthcare LLC) with phased-array coil for signal reception. Pulmonary veins were assessed by MR angiography with a three-dimensional, vascular, spoiled gradient-recalled imaging sequence with 5-mm slice thickness interpolated to 2.5 mm to obtain an anatomic view of the entire thorax in the coronal plane.

Ventricular Assessment: To measure LV function, the heart was imaged in short-axis orientation with ≥ 12 slices. Cine images were reconstructed at intervals of 20 to 35 milliseconds over the cardiac cycle with 40 phases. In a subset of participants, phase-contrast images were obtained using a segmented fast gradient-echo sequence without breathhold. The mitral inflow pattern was assessed using phase-contrast images to estimate blood flow across the mitral valve. All images were analyzed quantitatively using dedicated software for LV function (Cardiac Image Modeler; Auckland MRI Research Group), in addition to right ventricular (RV) parameters and phase-contrast images using QFLOW 7.2 (Medis Medical Imaging Systems BV).³⁰

Pulmonary Vein Assessment: Pulmonary vein area was assessed by a single reader using multiplanar reformation software (Volume Viewer Plus Suite 15.10.4; General Electric Co). Pulmonary vein ostia were defined by the signal intensity reflection between the planes of the left atrium and pulmonary vein.³¹ Cross-sectional area was determined by manual edge tracing on the reformatted orthogonal image. Total cross-sectional pulmonary vein area was reported as the sum of all pulmonary veins. The coefficient of variation of vein area measurements on blinded duplicate reading was 3.7%.

COPD Case Status

We used the standard clinical definition of COPD to define case status: a postbronchodilator FEV₁/FVC ratio < 0.70 .^{2,32} See e-Appendix 1 for more details.

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Participants underwent full-lung thoracic CT scan on a General Electric 64-slice helical scanner (120 kVp, 200 mA at 0.5 s; General Electric Co) with 0.75-mm slice thickness. Image attenuation was assessed at a single reading center by trained readers without knowledge of other participant information (VIDA Diagnostics Inc). Percent of emphysema-like lung (also known as percent low-attenuation area and hereafter referred to as percent emphysema) was defined as the percentage of total voxels within the lung field that was < -910 Hounsfield units (HU).³³

Anthropometry, Smoking Status, and Other Covariates

Age, sex, race/ethnicity, smoking status, and number of pack-years smoked were self reported. Study participants who reported smoking at least one cigarette in the 30 days prior to assessment were classified as current smokers. Height, weight, and seated BP were measured using standard techniques.³⁴

Statistical Analysis

The sample was stratified by COPD status with dichotomous variables presented as proportions and continuous variables as means with SD, unless otherwise indicated. Multiple linear regression models were used to adjust for participant age, sex, race/ethnicity, height, weight, cohort, smoking status, and pack-years smoked. Alternate adjustments for body size were performed using body surface area and height squared. Additional sensitivity analyses included adjustments for variant vein anatomy, ventricular function, and systolic BP. A two-tailed P value $< .05$ was considered to indicate statistical significance. Analyses were performed using SAS version 9.3 (SAS Institute Inc) statistical software.

RESULTS

Of 201 participants enrolled at one site where pulmonary vein quantification was performed, 165 completed spirometry, thoracic CT scans, and cardiac MRI with pulmonary vein quantification (e-Fig 1). Participants enrolled but not completing all components of the pulmonary vein study had lower lung function, smaller LV dimensions, and were less likely to report current smoking (e-Table 1).

The mean age of the study patients was 68 ± 7 years, and 60% were men. Fifty-three percent had COPD, and 32% were current smokers. Table 1 summarizes the clinical characteristics according to COPD status. Height and Hispanic ethnicity differed by COPD status. The extent of emphysema on CT scan was greater among participants with COPD (Table 1). LV end-diastolic volume (EDV) was smaller in patients with COPD than in control subjects when adjusted for age, sex, race/ethnicity, and body size ($P = .04$) (e-Table 2).

Pulmonary Vein Area in COPD

The mean total pulmonary vein cross-sectional area was 558 ± 159 mm² in COPD cases compared with 623 ± 145 mm² in control subjects ($P = .006$), for a mean difference of -65 mm² (95% CI, -111 to -18 mm²),

Table 1—Characteristics of Participants With Pulmonary Vein Measurements in the MESA COPD Study

Characteristic	COPD (n = 88)	No COPD (n = 77)
Age, y	67 ± 8	69 ± 6
Male patients, %	64	56
Race/ethnicity, %		
White	63	53
Black	28	26
Hispanic	8	17
Asian	1	4
Height, cm	170 ± 9	167 ± 9
Weight, kg	77 ± 17	80 ± 16
BMI, kg/m ²	26 ± 4	29 ± 5
Current smoker, %	35	27
Pack-y smoked, median (IQR)	40 (30)	32 (27)
FEV ₁ % predicted	72 ± 21	100 ± 18
FEV ₁ /FVC, %	56 ± 12	77 ± 4
COPD severity, %		
FEV ₁ $\geq 80\%$ predicted	38	...
$50\% \geq$ FEV ₁ $< 80\%$ predicted	45	...
FEV ₁ $< 50\%$ predicted	17	...
Total lung capacity, ^a L	6.0 ± 1.2	5.2 ± 1.0
% predicted total lung capacity ^a	105 ± 13	98 ± 13
Emphysema -910 HU, median (IQR)	24 (22)	12 (14)
Emphysema -950 HU, median (IQR)	3.0 (6.7)	1.0 (1.1)
LV EDV, mL	117 ± 31	121 ± 27
LV end-systolic volume, mL	48 ± 17	48 ± 18
LV stroke volume, mL	69 ± 18	73 ± 13
LV EDV index, mL/m ²	61 ± 15	63 ± 12
LV end-systolic volume index, mL/m ²	25 ± 9	25 ± 8
LV stroke-volume index, mL/m ²	36 ± 9	38 ± 7
LV ejection fraction, %	60 ± 8	61 ± 7

Data are given as mean $\pm$ SD unless otherwise indicated. EDV = end-diastolic volume; HU = Hounsfield units; IQR = interquartile range; LV = left ventricle; MESA = Multi-Ethnic Study of Atherosclerosis.

^aBody plethysmography was attempted only on participants recruited from the Emphysema and Cancer Action Project and the local outpatient community (n = 106).

or about 10.4% smaller in patients with COPD compared with control subjects. This difference persisted with similar magnitude in the fully adjusted model (Table 2).

Pulmonary Vein Area and Percent Emphysema

Percent emphysema on CT scan was associated with significant reduction in total pulmonary vein area (Table 3). The decrement was monotonic across quartiles of percent emphysema, with a 19% decrement between lowest and highest quartiles of percent emphysema in fully adjusted models. The continuous relationship of percent emphysema to total pulmonary vein area was nonlinear, with a flattening in the relationship at higher levels of percent emphysema (Fig 1).

Table 2—Predicted Values and Mean Difference in Total Cross-Sectional Pulmonary Vein Area Among Patients With and Without COPD

Pulmonary Vein Area	COPD (n = 88)	No COPD (n = 77)	Mean Difference in Total Pulmonary Vein Area (95% CI)	P Value
Total pulmonary vein area, mm ²	558	623	−65 (−111 to −18)	.006
Predicted total pulmonary vein area, mm ²				
Base model ^a	562	618	−57 (−105 to −8)	.02
Base model with smoking terms	562	618	−57 (−106 to −7)	.03

^aPredicted values and mean differences in the base model adjusted for age, sex, race/ethnicity, height, weight, and cohort. Smoking terms refer to smoking status (current vs former) and pack-y smoked.

Pulmonary Vein Area in COPD and Emphysema

Examination of the joint relationship of COPD and percent emphysema to total pulmonary vein area revealed a significant, subadditive interaction term between COPD and percent emphysema ($P = .03$). Participants, therefore, were stratified into control subjects with neither COPD nor emphysema, COPD without emphysema, COPD with emphysema, and emphysema without COPD. The characteristics of participants according to these categories are shown in e-Table 3.

Participants with COPD with, and without, emphysema had large and statistically significant reductions in total pulmonary vein area compared with control subjects (Table 4). The magnitude of the decrement was similar in both groups without evidence of an additive effect. Participants with only emphysema also had a large and statistically significant decrement in total pulmonary vein area compared with control subjects. The magnitude of this decrement was similar to that observed with COPD (Fig 2).

E/A RatioMR in COPD

Of 329 participants enrolled in the multicenter MESA COPD Study, E/A ratioMR measures were available for 194. Adjusting for age, sex, race/ethnicity,

body size, LV mass, systolic BP, and diabetes, the presence of COPD was associated with increased odds of an abnormal E/A ratioMR (OR, 2.6; 95% CI, 1.3-5.4; $P = .01$) (e-Table 4). Among 69 participants with both E/A ratioMR and pulmonary vein measures, pulmonary vein area was reduced among patients with COPD with and without an abnormal E/A ratioMR, but was elevated among control subjects without COPD who had an abnormal E/A ratioMR; however, none of these differences were statistically significant (e-Table 5).

Sensitivity Analyses

Primary analysis was based on MR sequences acquired at full inspiration to minimize artifact from respiratory motion. To ensure the observed relationship between pulmonary vein area and chronic lower respiratory disease was not solely determined by lung volume attained at full inspiration, we analyzed a subset of scans at end expiration and found similar associations between COPD, percent emphysema, and reduced pulmonary vein area (e-Figs 2, 3).

Sensitivity analyses using alternative metrics of body size and emphysema, as well as adjustment for oxygen saturation and physician-diagnosed sleep apnea, yielded consistent findings (e-Figs 2, 3). The association between COPD, emphysema, and total pulmonary

Table 3—Predicted Values and Mean Difference in Total Cross-Sectional Pulmonary Vein Area According to Percent Emphysema on CT Scan

Pulmonary Vein Area	Quartiles of Percent Emphysema −910 HU				Mean Difference in Total Pulmonary Vein Area per 10 Percentage-Point Increase in Emphysema −910 HU (95% CI)	P Value
	4.6% (n = 41)	13% (n = 41)	23% (n = 42)	40% (n = 41)		
Total pulmonary vein area, mm ²	635	588	545	586	...	.01
Predicted total pulmonary vein area, mm ²						
Base model ^a	647	609	573	532	−28 (−44 to −12)	< .001
Base model with smoking terms	652	610	571	526	−30 (−47 to −14)	< .001

See Table 1 legend for expansion of abbreviations.

^aPredicted values and mean differences in the base model adjusted for age, sex, race/ethnicity, height, weight, and cohort. Mean differences were back-transformed to represent a 10 percentage-point increase in emphysema −910 HU above study population mean. Smoking terms refer to smoking status (current vs former) and pack-y smoked.

FIGURE 1. Generalized additive model of total cross-sectional pulmonary vein area. Results of multivariate analysis of the relationship between total pulmonary vein cross-sectional area and percent emphysema (< −910 Hu on CT scan) are shown. Tick marks above the x axis represent observed emphysema measures. The predicted total pulmonary vein area is represented by the solid line and was obtained from a smoothed regression model adjusted for age, sex, height, weight, race/ethnicity, current smoking status, number of pack-y smoked, and cohort. The dashed lines represent the 95% confidence boundary. Test for nonlinearity of emphysema term: $P = .001$. Hu = Hounsfield units.

vein area also remained significant following addition of terms for LV or RV structure (e-Figs 2, 3). In these models, both RV EDV and LV EDV were significantly associated with total pulmonary vein area ($P < .01$). Results of stratified analyses presented in Table 4 were similar when using alternate definitions of emphysema (e-Table 6).

Plethysmography was performed in a subset of participants recruited from the Emphysema and Cancer Action Project and the local outpatient community ($n = 106$). Higher % predicted total lung capacity was associated with significantly smaller pulmonary vein area and a trend toward reduced LV EDV (e-Table 7).

Participants with predominantly mild to moderate COPD had reduced total pulmonary vein cross-sectional area as assessed by contrast-enhanced MRI compared with control subjects without COPD. In addition, pulmonary vein size was inversely associated with percent emphysema and was significantly reduced among participants with emphysema on CT scan who did not have clinical COPD. These findings suggest reduced LV preload in both clinical COPD and in patients with emphysema on CT scan.

To our knowledge, this study is the first to report pulmonary vein dimensions in COPD and emphysema. It is potentially clinically relevant for two reasons. First, among patients with COPD, LV diastolic dysfunction based on E/A ratio is common^{14-16,26,35}; however, these mitral inflow abnormalities can reflect increased stiffness of the LV or states of low LV filling pressure.¹⁷⁻¹⁹ Our findings suggest low LV distending pressure resulting from upstream pulmonary causes rather than intrinsic cardiac dysfunction may contribute significantly to impaired LV filling in COPD. Second, since emphysema on CT scan is not usually assessed clinically, patients with emphysema but normal lung function presenting with dyspnea may appear to have diastolic dysfunction on echocardiography that may, in fact, be due to emphysema-related low LV preload. This underrecognized subgroup of chronic lower respiratory disease represented 13% of smokers in the present study.

Potential mechanisms of reduced pulmonary vein size in COPD and emphysema, while not the primary focus of this study, include altered intrathoracic pressure and PVR. Intrathoracic pressure may impair venous return to the right side of the heart, resulting in underfilling of the pulmonary veins.^{36,37} In support of this mechanism, smaller total pulmonary vein area was associated with reduced RV EDV. Prior studies have also demonstrated reduced RV dimensions in severe emphysema with COPD, as well as improvements in LV filling following lung volume reduction

Table 4—Predicted Values for and Mean Difference in Total Cross-Sectional Pulmonary Vein Area by Strata of COPD and Emphysema

Pulmonary Vein Area	No COPD or Emphysema (n = 54)	COPD Without Emphysema (n = 29)	COPD With Emphysema (n = 59)	Emphysema Without COPD (n = 23)
Total pulmonary vein area, mm ²	637	563	556	590
Predicted total pulmonary vein area, mm ²				
Base model ^a	641	571	556	570
Mean difference (95% CI)	Reference	−70 (−135 to −5)	−85 (−145 to −25)	−71 (−140 to −1)
Base model with smoking terms	641	569	556	570
Mean difference (95% CI)	Reference	−72 (−138 to −6)	−85 (−146 to −25)	−71 (−140 to −1)

^aPredicted values in the base model were adjusted for age, sex, race/ethnicity, height, weight, and cohort. Smoking terms refer to smoking status (current vs former) and pack-y smoked. No emphysema was defined as less than median percent emphysema—910 Hounsfield units in the entire study population. Predicted mean differences are relative to stratum with no COPD or emphysema.

FIGURE 2. Predicted total cross-sectional pulmonary vein area by strata of COPD and emphysema. Predicted values in the model were adjusted for age, sex, race/ethnicity, height, weight, smoking status, and number of pack-y smoked. No emphysema was defined as less than median percent emphysema (<-910 Hounsfield units on CT scan) in the entire study population.

surgery.³⁸⁻⁴⁰ Alternatively, hyperinflation-associated increase in intrathoracic pressure may act directly at the LV to impair filling. However, we believe this mechanism unlikely because upstream intrathoracic structures would also be exposed to this augmented pressure.⁴¹ Indeed, higher % predicted total lung capacity was associated with both smaller pulmonary veins and a trend toward smaller LV EDV.

Classic descriptions of cor pulmonale attribute increased PVR to emphysematous disruption of the vascular bed, hypoxic vasoconstriction, vascular remodeling, thrombosis, and left-sided heart dysfunction.^{15,42} In addition, hyperinflation-associated increases in PVR may result from compression, or lengthening and narrowing of alveolar vessels.^{43,44} While PVR and intrathoracic pressure were not assessed in the present study, these mechanisms may both contribute to impaired flow to the pulmonary veins and reductions in their dimensions. Given that the associations of COPD and emphysema to pulmonary vein area were independent of RV EDV, it is likely that, in addition to RV underfilling, an additional mechanism, such as increased PVR, likely contributes to reduced pulmonary vein dimensions.

Diastolic dysfunction is characterized by myocardial stiffening and fibrosis.⁴⁵ An alternative explanation for our observation is that such fibrosis may extend to the left atrium and pulmonary veins. We think this explanation unlikely, however, given that the left atrium is typically enlarged in diastolic dysfunction with high, LV end-diastolic pressure.^{25,46-48} RV dilation with impingement on the LV is also an important consideration in states of very high pulmonary artery pressure,¹⁵ which is unlikely in the present study of predominantly mild to moderate COPD. Smaller pulmonary vein dimensions were associated with reduced RV EDV. Furthermore, adjustment for RV dimensions in the

present study did not alter the associations of COPD and emphysema with smaller total pulmonary vein area. Hence, our findings of reduced pulmonary vein dimensions in COPD and emphysema support an upstream mechanism that is independent of impaired LV relaxation.

Nonetheless, cardiopulmonary interactions in COPD and emphysema are complex.²⁰ It is likely that intrinsic LV dysfunction is more common in patients with COPD,¹⁵ particularly since the present study excluded patients with clinical cardiovascular disease and atrial fibrillation. The significant increase in odds of an abnormal E/A ratioMR in the presence of COPD was associated with a nonsignificant reduction in total pulmonary vein area. While this may have been due to inadequate power or misclassification of pseudonormal mitral inflow velocities, residual confounding by unaccounted causes of intrinsic LV dysfunction is possible. Further, there is evidence to support accelerated aging in the pathogenesis of COPD and emphysema^{49,50} and similar mechanisms have been proposed for diastolic dysfunction.^{51,52} In addition, LV myocardial fibrosis has been demonstrated in patients with COPD and cor pulmonale.⁵³

There are several limitations to the current study. We did not validate pulmonary vein area as a surrogate for LV end-diastolic pressure. However, in the context of chronic lower respiratory diseases, changes in lung mechanics alter juxtacardiac pressures.⁵⁴ Whereas the volume (and cross-sectional area) of intrathoracic cardiovascular structures reflect their transmural pressure difference, direct quantification of transmural cardiac pressures would require invasive measurements of both intracardiac and pericardial/pleural pressures.^{54,55} Such procedures were too invasive to perform in 165 patients with mild to moderate lung disease who were free of clinical cardiac disease. MRI was performed instead of echocardiography to minimize potential bias from inadequate acoustic windows among patients with hyperinflation.¹⁷ Phase-contrast MR evaluation of E/A ratio, as was done in the present study, has been shown to correlate well with transthoracic echocardiography.^{56,57} These studies were small, however, and our secondary findings related to E/A ratioMR should be interpreted in light of this relatively novel method of assessing LV filling.

Vein measurements were performed on nongated MR images to reduce sequence acquisition time during breathhold. While this may have introduced motion artifact, only a minority of scans could not be quantified. To minimize respiratory artifact, pulmonary vein MR images were acquired at suspended inspiration, which may have affected pulmonary blood flow. Pulmonary veins were also assessed in a subset of participants with dedicated pulmonary vein sequences at end expiration and similar results were obtained.

COPD was defined by standard criteria²; however, there are currently no standard criteria to define emphysema on CT scan. We assessed emphysema quantitatively, which has much greater precision than radiologist assessment but for which a standard threshold of normality is currently lacking.^{58,59} Therefore, we used an arbitrary but reasonable threshold of the median value of percent emphysema. Sensitivity analyses showed that results were similar using a 25th percentile threshold and using a −950 HU definition (median or 25th percentile) to define percent emphysema.

The observational design of the study limits inference that COPD or emphysema reduced pulmonary vein area, although it seems unlikely that pulmonary vein size contributed to COPD and emphysema. Selection bias can affect the validity of case-control studies; however, the study was predominantly nested in two cohort studies and secondary analyses restricted to participants selected from those cohorts yielded consistent results, which makes selection bias an unlikely explanation for our results. Confounding is always of potential concern in observational studies; however, adjustment for multiple, precisely measured confounders had little impact on effect estimates. Finally, the study sample size was relatively small, particularly in stratified analyses, hence, effect estimates may be relatively imprecise.

In summary, COPD and emphysema on CT scan were associated with reduced pulmonary vein cross-sectional area. These findings suggest that impaired LV filling in COPD, and also in emphysema in the absence of clinical COPD, may be predominantly due to reduced LV preload from upstream pulmonary causes rather than intrinsic diastolic dysfunction, although cardiopulmonary interactions are likely complex.

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Dr Smith: contributed to study concept and design; data analysis and interpretation; and drafting, revising, and final approval of the manuscript and served as principle author.

Dr Prince: contributed to study concept and design, data interpretation, and revision and final approval of the manuscript.

Dr Hoffman: contributed to study concept and design, data analysis, and revision and final approval of the manuscript.

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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the "Supplemental Materials" area of the online article.

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