

ORIGINAL ARTICLE

Percent Emphysema, Airflow Obstruction, and Impaired Left Ventricular Filling

R. Graham Barr, M.D., Dr.P.H., David A. Bluemke, M.D., Ph.D.,
Firas S. Ahmed, M.D., M.P.H., J. Jeffery Carr, M.D., Paul L. Enright, M.D.,
Eric A. Hoffman, Ph.D., Rui Jiang, M.D., Dr.P.H., Steven M. Kawut, M.D.,
Richard A. Kronmal, Ph.D., João A.C. Lima, M.D., Eyal Shahar, M.D., M.P.H.,
Lewis J. Smith, M.D., and Karol E. Watson, M.D., Ph.D.

ABSTRACT

BACKGROUND

Very severe chronic obstructive pulmonary disease causes cor pulmonale with elevated pulmonary vascular resistance and secondary reductions in left ventricular filling, stroke volume, and cardiac output. We hypothesized that emphysema, as detected on computed tomography (CT), and airflow obstruction are inversely related to left ventricular end-diastolic volume, stroke volume, and cardiac output among persons without very severe lung disease.

METHODS

We measured left ventricular structure and function with the use of magnetic resonance imaging in 2816 persons who were 45 to 84 years of age. The extent of emphysema (expressed as percent emphysema) was defined as the percentage of voxels below -910 Hounsfield units in the lung windows on cardiac computed tomographic scans. Spirometry was performed according to American Thoracic Society guidelines. Generalized additive models were used to test for threshold effects.

RESULTS

Of the study participants, 13% were current smokers, 38% were former smokers, and 49% had never smoked. A 10-point increase in percent emphysema was linearly related to reductions in left ventricular end-diastolic volume (-4.1 ml; 95% confidence interval [CI], -3.3 to -4.9 ; $P < 0.001$), stroke volume (-2.7 ml; 95% CI, -2.2 to -3.3 ; $P < 0.001$), and cardiac output (-0.19 liters per minute; 95% CI, -0.14 to -0.23 ; $P < 0.001$). These associations were of greater magnitude among current smokers than among former smokers and those who had never smoked. The extent of airflow obstruction was similarly associated with left ventricular structure and function, and smoking status had similar modifying effects on these associations. Percent emphysema and airflow obstruction were not associated with the left ventricular ejection fraction.

CONCLUSIONS

In a population-based study, a greater extent of emphysema on CT scanning and more severe airflow obstruction were linearly related to impaired left ventricular filling, reduced stroke volume, and lower cardiac output without changes in the ejection fraction.

From the Department of Medicine, College of Physicians and Surgeons (R.G.B., F.S.A., R.J.), and the Department of Epidemiology, Mailman School of Public Health (R.G.B., R.J.), Columbia University, New York; the Department of Radiology and Imaging Sciences, National Institutes of Health Clinical Center, Bethesda, MD (D.A.B.); the Department of Radiology, Wake Forest University, Winston-Salem, NC (J.J.C.); the Division of Epidemiology and Biostatistics, University of Arizona, Tucson (P.L.E., E.S.); the Department of Radiology, University of Iowa, Iowa City (E.A.H.); the Penn Cardiovascular Institute, the Center for Clinical Epidemiology and Biostatistics, and Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia (S.M.K.); the Department of Biostatistics, University of Washington, Seattle (R.A.K.); the Departments of Medicine and Radiology, Johns Hopkins University, Baltimore (J.A.C.L.); the Department of Medicine, Northwestern University, Chicago (L.J.S.); and the Department of Medicine, University of California, Los Angeles, Los Angeles (K.E.W.). Address reprint requests to Dr. Barr at the Division of General Medicine, Columbia University Medical Center, 630 W. 168th St., PH 9 East, Rm. 105, New York, NY 10032, or at rgb9@columbia.edu.

A full list of investigators and institutions participating in the Multi-Ethnic Study of Atherosclerosis (MESA) can be found at www.mesa-nhlbi.org.

N Engl J Med 2010;362:217-27.

Copyright © 2010 Massachusetts Medical Society.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD), defined as airflow obstruction that is not fully reversible,¹ is currently the fourth leading cause of death in the United States.² COPD overlaps partially with emphysema, which is characterized by the destruction of alveolar walls and the permanent enlargement of air spaces distal to the terminal bronchioles.^{1,3}

Cor pulmonale, which can occur in very severe COPD, is characterized by elevated pulmonary vascular resistance and right heart failure, with associated reductions in left ventricular filling, left ventricular stroke volume, and cardiac output, although left ventricular ejection fraction is generally preserved.⁴⁻⁷ This disorder may occur as a result of various mechanisms, including loss of pulmonary vascular capacity due to parenchymal destruction,⁸ hypoxic pulmonary arterial vasoconstriction,⁹ and pulmonary hyperinflation with elevated intrathoracic pressure.¹⁰ Whether similar changes occur in milder chronic lung disease, however, remains unknown.

We therefore examined the relationships between the extent of emphysema (as measured quantitatively on computed tomography [CT]) and of airflow obstruction (as measured on spirometry) and cardiac structure and function (as measured on magnetic resonance imaging [MRI]) in a large, population-based cohort. We hypothesized that a greater extent of CT-defined emphysema and more severe airflow obstruction would be associated with decrements in left ventricular end-diastolic volume, left ventricular stroke volume, and cardiac output; that these relationships would be linear across a spectrum from normal lung structure and function to severe emphysema and airflow obstruction; and that the magnitude of the associations would be modified by smoking status.

METHODS

STUDY PARTICIPANTS

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter, prospective cohort study of the prevalence, correlates, and progression of subclinical cardiovascular disease in whites, blacks, Hispanics, and Asians without clinical cardiovascular disease.¹¹ Between 2000 and 2002, MESA recruited 6814 men and women 45 to 84 years of age from six U.S. communities: Forsyth County, North Carolina; New York City; Baltimore; St. Paul,

Minnesota; Chicago; and Los Angeles. Exclusion criteria were clinical cardiovascular disease, weight exceeding 136 kg (300 lb), pregnancy, and impediments to long-term participation. Written informed consent was obtained from all participants.

The MESA Lung Study enrolled MESA participants who were sampled from those who underwent baseline measurements of endothelial function, consented to genetic analyses, and underwent an examination during the MESA Lung Study recruitment period between 2004 and 2006 (see Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Asians were oversampled. We excluded participants who had a restrictive pattern on spirometry — defined here as a forced vital capacity (FVC) below the lower limit of normal¹² with a ratio of forced expiratory volume in 1 second (FEV₁) to FVC above 0.70 — in order to exclude participants with a mixed ventilatory defect and because our primary hypothesis was related to obstructive lung disease.

STUDY OVERSIGHT

MESA and the MESA Lung Study were funded by the National Heart, Lung, and Blood Institute (NHLBI). The MESA Lung Study was designed by the study investigators. The protocols were approved by the institutional review boards of all collaborating institutions and by the NHLBI. The authors, together with other MESA investigators, collected and analyzed the data, vouch for the data and analysis, and wrote and submitted the manuscript for publication. NHLBI staff monitored study performance routinely and participated in the internal review of the manuscript before submission.

MEASUREMENTS OF LEFT VENTRICULAR STRUCTURE AND FUNCTION

Participants underwent cardiac MRI between 2000 and 2002. The protocol, its reliability, and the characteristics of MESA participants with and without MRI measurements have been described previously.^{13,14} All imaging was performed on 1.5-T magnets with a four-element, phased-array surface coil positioned anteriorly and posteriorly and with electrocardiographic gating. Imaging consisted of fast gradient-echo cine images of the left ventricle, with a temporal resolution of 50 msec or less. Left ventricular volumes and mass were determined by the summation-of-disks method.^{15,16} Im-

aging data were read with the use of MASS software, version 4.2 (Medis), at a single reading center by trained readers with no knowledge of other information about the participants. Cardiac output was calculated as the left ventricular stroke volume (i.e., end-diastolic volume minus end-systolic volume) times the heart rate. The left ventricular ejection fraction was calculated as the stroke volume divided by the end-diastolic volume.

ASSESSMENT OF EMPHYSEMA

The extent of emphysema was measured quantitatively on the lung fields of cardiac CT scans, which included approximately 70% of the lung volume from the carina to the lung bases. Cardiac CT scans were obtained at full inspiration on multidetector and electron-beam CT scanners between 2000 and 2002 according to a standardized protocol.¹⁷ Two scans were obtained for each participant, and the scan with the greater volume of lung air was used for analyses, except in cases of discordant scan quality, when the higher-quality scan was analyzed.¹⁸

Image attenuation was assessed with the use of a modified version of the Pulmonary Analysis Software Suite¹⁹⁻²² at a single reading center by trained readers without knowledge of other information about the study participants. Attenuation of air outside the chest was measured on all scans to confirm scanner calibration at -1000 Hounsfield units. The percentage of lung volume with emphysematous features (hereafter referred to as percent emphysema) was defined as the percentage of the total voxels in the lung that showed attenuation of less than -910 Hounsfield units. This threshold was chosen on the basis of quantitative histologic comparisons²³ and the generally mild degree of emphysema in the study. Emphysema measurements from the cardiac scans correlated closely with those from full-lung scans in the same study participants.¹⁸

SPIROMETRY

Spirometric assessments were conducted between 2004 and 2006 in accordance with the American Thoracic Society-European Respiratory Society guidelines.²⁴ All study participants performed at least three acceptable maneuvers on a dry rolling seal spirometer with automated quality checks (Occupational Marketing). All spirometric examinations were reviewed by a single investigator, and each test was graded for quality.²⁵

SMOKING STATUS AND OTHER COVARIATES

Age, sex, race or ethnic group, educational level, number of pack-years of smoking, medical history, and level of physical activity²⁶ were self-reported. Height, weight, resting blood pressure, serum glucose level, C-reactive protein level, and fibrinogen level were measured with the use of standard techniques.²⁷ Study participants who reported having smoked at least 1 cigarette in the 30 days before the CT examination or who had a urinary cotinine level greater than 100 ng per milliliter on the day of the CT examination were classified as current smokers. Participants with a lifetime smoking history of fewer than 100 cigarettes, a urinary cotinine level of 100 ng per milliliter or less on the day of the CT examination, and a report of "never smoking" on multiple examinations were classified as never having smoked.

STATISTICAL ANALYSIS

Initial analyses in generalized additive models involved the regression of left ventricular volumes, cardiac output, ejection fraction, and mass on percent emphysema and the FEV₁:FVC ratio after adjustment for age, sex, race or ethnic group, and body-surface area. A priori, effect modification of the relationships of the pulmonary measures to left ventricular end-diastolic volume and stroke volume according to smoking status was anticipated. The presence of such effect modification was tested with the -2 log-likelihood test of nested models with and without interaction terms.

Multivariate models were adjusted for the following additional potential confounders: number of pack-years of smoking, urinary cotinine level, educational level, presence or absence of diabetes mellitus, fasting blood glucose level, presence or absence of hypertension, systolic and diastolic blood pressure, C-reactive protein level, and fibrinogen level. Analyses of percent emphysema were further adjusted for body-mass index, CT scanner type, and tube current in milliamperes, all of which affect attenuation. Lung-function analyses were further adjusted for height, since lung function is correlated with height. Age, number of pack-years of smoking, and other continuous variables that were potential confounders were fit with locally weighted scatterplot smoothing (LOWESS) functions to minimize model misspecification.

The tests of the primary hypothesis, 95% confidence intervals, and P values were estimated

Table 1. Baseline Characteristics of Study Participants Included in the Analysis.*

Characteristic	Study Participants (N = 2816)
Age — yr	61±10
Male sex — no. (%)	1383 (49)
Race or ethnic group — no. (%)†	
White	1005 (36)
Black	701 (25)
Hispanic	616 (22)
Asian	494 (18)
Educational level — no. (%)	
No high-school degree	440 (16)
High-school degree	505 (18)
Some college	762 (27)
College degree	534 (19)
Higher than bachelor's degree	575 (20)
Height — cm	166±10
Body-surface area — m ²	1.84±0.22
Body-mass index‡	27.4±4.8
Cigarette-smoking status — no. (%)	
Never smoked	1379 (49)
Former smoker	1067 (38)
Current smoker	370 (13)
Pack-years of smoking among current or former smokers — no.	
Median	17
Interquartile range	6–35
Hypertension — no. (%)	1001 (36)
Blood pressure — mm Hg	
Systolic	124±20
Diastolic	72±10
Diabetes mellitus — no. (%)	249 (9)
Fasting plasma glucose — mg/dl§	
Median	96
Interquartile range	89–104
C-reactive protein — mg/liter	
Median	1.6
Interquartile range	0.7–3.8
Fibrinogen — mg/dl	
Median	332
Interquartile range	292–382
Family history of emphysema — no. (%)	120 (4)
Asthma before age of 45 yr — no. (%)	202 (7)
MRC-defined chronic bronchitis — no. (%)¶	221 (8)
Obstructive sleep apnea — no. (%)	79 (3)
Self-reported COPD, emphysema, or chronic bronchitis — no. (%)	205 (7)

* Plus-minus values are means ±SD. COPD denotes chronic obstructive pulmonary disease, and MRC Medical Research Council.

† Race or ethnic group was self-reported.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ To convert the values for glucose to millimoles per liter, multiply by 0.05551.

¶ The Medical Research Council's definition of chronic bronchitis is a cough productive of phlegm on most days for at least 3 months in at least 2 consecutive years.³

from generalized additive models. A P value of less than 0.05 was considered to indicate statistical significance. Analyses were performed with the use of R statistical software, version 2.6 (R Foundation for Statistical Computing, Vienna).

RESULTS

STUDY PARTICIPANTS

Of the 6814 MESA participants, 3965 were enrolled in the MESA Lung Study. Of these, 322 were excluded because of restriction detected on spirometry, and 827 were excluded because cardiac MRI measurements were not obtained (Fig. 1 in the Supplementary Appendix). There were small differences between the remaining 2816 participants included in the analyses and the 827 without MRI measurements, with respect to age, race or ethnic group, body size, and smoking history (Table 1 in the Supplementary Appendix).

Among the participants included in the analysis, the mean age was 61 years, and 49% were men (Table 1). Thirteen percent currently smoked cigarettes, 38% had smoked in the past, and 49% had never smoked. As compared with participants who had never smoked, those who were current or former smokers were more likely to be men, to be white, to have a lower educational level, and to have a greater body-surface area (Table 2 in the Supplementary Appendix).

Mean spirometric measures were within the normal range, as were MRI measures of left ventricular structure and function (Table 2). The median value for percent emphysema was 15%. Mean values for lung function and the left ventricular ejection fraction were lower and left ventricular mass was greater among current smokers than among those who had never smoked (Table 3 in the Supplementary Appendix).

EMPHYSEMA AND CARDIAC FUNCTION

Significant associations were found between percent emphysema and left ventricular measures (Table 3). After multivariate adjustment, an increase of 10 percentage points in percent emphysema was associated with a 4.1-ml decrement in left ventricular end-diastolic volume, a 2.7-ml decrement in stroke volume, and a decrement of 0.19 liter per minute in cardiac output. In contrast, there was no evidence of an association between percent emphysema and the left ventricular ejection fraction.

Table 2. Percent Emphysema on CT, Lung Function, and Left Ventricular Structure and Function.*

Variable	Study Participants (N = 2816)
Percent emphysema — median (IQR)	15 (7.8–24.9)
Lung function	
FEV ₁ — percent of predicted†	96.2±17.1
FVC — percent of predicted†	98.3±14.6
FEV ₁ :FVC ratio — %‡	74.6±8.6
Left ventricular measures	
End-diastolic volume — ml	126.7±31.4
End-systolic volume — ml	39.7±16.7
Stroke volume — ml	87.0±19.8
Stroke volume index§	41.7±7.2
Cardiac output — liter/min	5.7±1.5
Cardiac index§	2.6±0.3
Ejection fraction — %	69.3±7.2
Mass — g	144.0±38.6

* Plus-minus values are means ±SD. FEV₁ denotes forced expiratory volume in 1 second, FVC forced vital capacity, and IQR interquartile range.

† Predicted values were calculated with the use of the National Health and Nutrition Examination Survey III reference equations for whites, blacks, and Hispanics, with a correction factor of 0.88 for Asians.^{12,25}

‡ The FEV₁:FVC ratio was calculated by dividing the FEV₁ by the FVC and then multiplying by 100 to express as a percentage.

§ The stroke volume and cardiac output were indexed by dividing by body-surface area.

Figure 1 shows the relationships of percent emphysema to left ventricular end-diastolic volume and to stroke volume. These relationships were linear across the spectrum of lung structure from normal to severe emphysema, without evidence of a threshold effect.

Smoking status modified the associations of percent emphysema with left ventricular end-diastolic volume (P<0.001 for interaction) and stroke volume (P=0.008 for interaction). The magnitude of the associations was greater among current smokers than among former smokers and among former smokers than among study participants who had never smoked (Table 4 in the Supplementary Appendix). For example, an increase of 10 percentage points in percent emphysema was associated with a 9.2-ml decrement in left ventricular end-diastolic volume in current smokers, a 4.2-ml decrement in former smokers, and a 2.6-ml decrement in those who had never smoked. The results were similar for the relationship of percent emphysema to stroke volume and to car-

Table 3. Predicted Values for and Mean Change in Left Ventricular Structure and Function According to Percent Emphysema on CT.*

Variable	Percent Emphysema					Mean Change in LV Measure per 10-Percentage-Point Increase in Emphysema (95% CI)	P Value
	3.5% (N=563)	9.1% (N=563)	15.0% (N=564)	22.5% (N=564)	34.5% (N=562)		
LV end-diastolic volume — ml	124.9	121.8	118.8	115.8	111.2	-4.1 (-4.9 to -3.3)	<0.001
LV end-systolic volume — ml	37.8	36.7	35.4	34.3	32.9	-1.4 (-1.9 to -0.9)	<0.001
LV stroke volume — ml	87.1	85.1	83.4	81.5	78.3	-2.7 (-3.3 to -2.2)	<0.001
Cardiac output — liters/min	5.90	5.72	5.61	5.45	5.27	-0.19 (-0.23 to -0.14)	<0.001
LV ejection fraction — %	70.4	70.5	70.8	70.7	70.7	0.02 (-0.22 to 0.25)	0.89
LV mass — g	138.3	134.7	134.2	131.9	129.3	-2.5 (-3.4 to -1.6)	<0.001

* Predicted values and mean differences were adjusted for age, race or ethnic group, sex, body-surface area, number of pack-years of smoking, urinary cotinine level, educational level, presence or absence of diabetes mellitus, fasting plasma glucose level, body-mass index, presence or absence of hypertension, systolic and diastolic blood pressure, C-reactive protein level, fibrinogen level, CT scanner type, and tube current in milliamperes. Predicted values and mean differences, along with 95% confidence intervals and P values for the linear term for percent emphysema, were estimated in generalized additive models. LV denotes left ventricular.

diac output. These relationships were linear among current smokers, former smokers, and those who had never smoked (Fig. 2 in the Supplementary Appendix). Effect modification by pack-years of smoking was similar to that by smoking status.

AIRFLOW OBSTRUCTION AND CARDIAC FUNCTION

Significant associations were also observed between the FEV₁:FVC ratio and left ventricular measures (Table 4). In fully adjusted analyses, a decrease of 10 percentage points in the FEV₁:FVC ratio was associated with decrements of 1.7 ml in left ventricular end-diastolic volume, 1.5 ml in stroke volume, and 0.10 liters per minute in cardiac output. There was no significant association between the FEV₁:FVC ratio and left ventricular ejection fraction.

Figure 2 shows the relationship of the FEV₁:FVC ratio to left ventricular end-diastolic volume and to stroke volume. The relationship of the FEV₁:FVC ratio to left ventricular end-diastolic volume was nonlinear, whereas the relationship to stroke volume was linear across the spectrum of lung function from normal to moderately severe airflow obstruction.

Smoking status modified the associations of the FEV₁:FVC ratio with left ventricular end-diastolic volume (P=0.002 for interaction) and stroke volume (P=0.02 for interaction), in that there were stronger associations among current smokers than among former smokers, but there was no evidence of associations among study participants who had

never smoked (Table 5 in the Supplementary Appendix). Relationships for both left ventricular end-diastolic volume and stroke volume were linear among current smokers and former smokers (Fig. 3 in the Supplementary Appendix). Effect modification by pack-years of smoking was similar to that by smoking status.

A similar pattern of relationships with left ventricular measures was observed for FEV₁ (Table 6 in the Supplementary Appendix), although effect modification by smoking status was not significant. FVC was not modified by smoking status and was associated with left ventricular end-diastolic volume (P=0.005), end-systolic volume (P=0.02), and stroke volume (P=0.03) but not with cardiac output (P=0.15).

ADDITIONAL ANALYSES

There was no evidence of effect modification by sex, race or ethnic group, Medical Research Council-defined chronic bronchitis, or obesity, and analyses were not sensitive to additional adjustments for left ventricular end-systolic volume, left ventricular mass, sleep-disordered breathing, and physical activity. Associations between percent emphysema and left ventricular measures were similar when percent emphysema was defined at a threshold of -950 Hounsfield units and when the threshold was corrected for variation in attenuation of air outside the body or inside the trachea. (See Tables 7, 8, and 9 in the Supplementary Appendix.)

DISCUSSION

A greater extent of emphysema as measured by CT and greater airflow obstruction as measured by spirometry were associated with smaller left ventricular end-diastolic volumes and concomitant reductions in stroke volume and cardiac output in this large, population-based cohort that was free of clinical cardiovascular disease. Relationships were linear across a spectrum from normal lung structure and function to moderately severe airflow obstruction and emphysema. In contrast, the left ventricular ejection fraction was preserved. These findings indicate that subclinical hemodynamic changes occur with mild emphysema and airflow obstruction.

The apparent effect of emphysema on left ventricular end-diastolic volume and cardiac output was similar to that of traditional cardiac risk factors previously reported in MESA and, among smokers, was greater than that of traditional cardiac risk factors.¹⁴ For comparison, a 1-SD change in systolic blood pressure of 21 mm Hg was associated with a change of 4.3 ml in left ventricular end-diastolic volume and a change of 0.26 liters per minute in cardiac output.

The effects of COPD and emphysema on the heart have long been recognized but have been studied principally in very severe COPD.²⁸⁻³⁶ Clinical data on pulmonary hypertension in milder lung disease are limited owing to the invasiveness of the usual reference measure — that is, right heart catheterization. The one study involving patients with mild-to-moderate COPD that used right heart catheterization showed increases in pulmonary-artery pressure with exercise.³⁷ Anatomical studies show proliferation of smooth-muscle cells in pulmonary arteries from patients with mild-to-moderate COPD^{38,39} and from smokers without COPD,⁴⁰ which suggests subclinical increases in pulmonary vascular resistance in patients with mild-to-moderate COPD and in smokers without spirometrically defined COPD. Consistent with our results were those of a small case-control study, which showed reductions in left ventricular end-diastolic volume and stroke volume on MRI in 25 patients who had moderate COPD without clinically significant hypoxemia (defined as a partial pressure of oxygen in arterial blood of less than 60 mm Hg), as compared with controls.⁴¹

Mechanisms of impaired left ventricular filling in very severe COPD include alveolar hypoxia and related pulmonary vascular changes, pulmo-

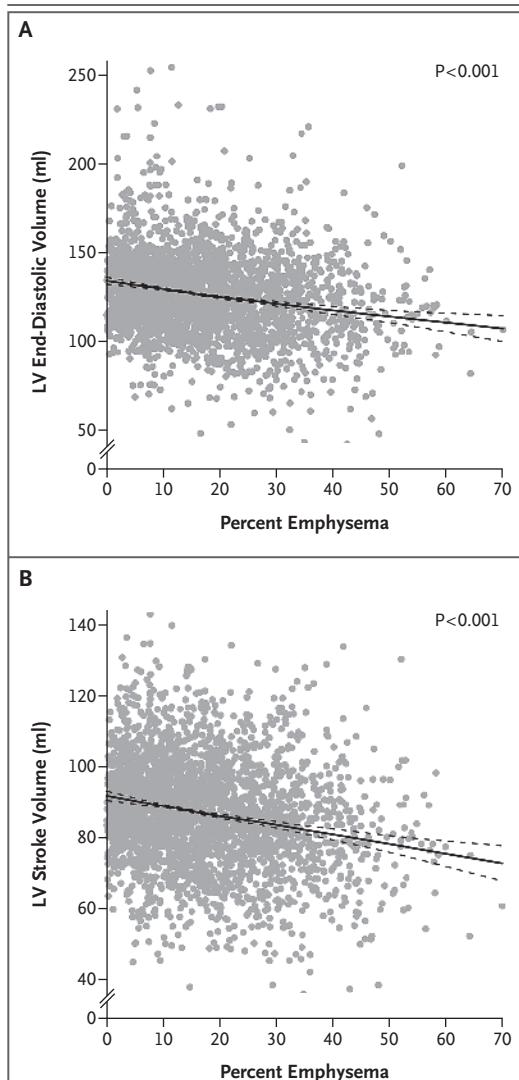


Figure 1. Relationship between Percent Emphysema and Left Ventricular (LV) End-Diastolic and Stroke Volumes.

Results of multivariate analyses of the relationship between percent emphysema and left ventricular end-diastolic volume (Panel A) and stroke volume (Panel B) are shown. Solid lines indicate smoothed regression lines adjusted for age, race or ethnic group, sex, body-surface area, number of pack-years of smoking, urinary cotinine level, educational level, presence or absence of diabetes mellitus, fasting plasma glucose level, body-mass index, presence or absence of hypertension, systolic and diastolic blood pressure, C-reactive protein level, fibrinogen level, CT scanner type, and tube current in milliamperes. Dashed lines indicate 95% confidence intervals. Dots represent predicted plus residual values. The smoothing functions did not improve the model fit as compared with linear terms for LV end-diastolic volume or LV stroke volume, which implies that thresholds in the relationship of percent emphysema to LV end-diastolic volume and to stroke volume could not be demonstrated.

Table 4. Predicted Values for and Mean Change in Left Ventricular Structure and Function According to FEV₁:FVC Ratio.*

Variable	FEV ₁ :FVC Ratio					Mean Change in LV Measure (95% CI) per 10-Percentage-Point Increase in FEV ₁ :FVC Ratio	P Value
	64.6% (N=545)	71.8% (N=545)	75.9% (N=546)	79.3% (N=545)	83.6% (N=545)		
LV end-diastolic volume — ml	126.5	127.7	127.7	129.0	128.3	1.7 (0.5 to 2.8)	0.005
LV end-systolic volume — ml	40.9	41.1	40.8	41.3	40.3	0.1 (–0.5 to 0.8)	0.72
LV stroke volume — ml	85.6	86.6	86.9	87.7	88.0	1.5 (0.8 to 2.3)	<0.001
Cardiac output — liters/min	5.57	5.58	5.67	5.67	5.74	0.10 (0.04 to 0.17)	0.002
LV ejection fraction — %	68.6	68.6	68.8	68.7	69.2	0.2 (–0.1 to 0.5)	0.22
LV mass — g	151.0	149.0	149.2	148.7	149.2	–0.7 (–1.9 to 0.5)	0.24

* Predicted values and mean differences were adjusted for age, race or ethnic group, sex, body-surface area, pack-years of smoking, urine cotinine level, educational level, height, presence or absence of diabetes mellitus, fasting plasma glucose level, presence or absence of hypertension, systolic and diastolic blood pressure, C-reactive protein level, and fibrinogen level. Predicted values and mean differences, along with 95% confidence intervals (CI) and P values for the linear term for FEV₁:FVC, were estimated in generalized additive models. The FEV₁:FVC ratio was calculated by dividing the FEV₁ by the FVC and then multiplying by 100 to express as a percentage. FEV₁ denotes forced expiratory volume in 1 second, FVC forced vital capacity, and LV left ventricular.

nary hyperinflation, and ventricular interdependence. Alveolar hypoxia causes pulmonary-artery vasoconstriction and vascular remodeling,⁹ with increased pulmonary vascular resistance and impaired left ventricular filling. Its relevance in milder disease, however, is unclear, since alveolar hypoxia does not account for changes in the transit time of pulmonary blood flow observed in patients with mild-to-moderate COPD.⁴² Hyperinflation in very severe COPD can cause intrathoracic pressure to exceed venous pressure, with reductions in the blood volumes of both ventricles.¹⁰ The effect of hyperinflation on hemodynamics, however, is debated,⁴³ and the absence of an association between the severity of airflow obstruction and left ventricular filling in study participants who had never smoked suggests that our findings with respect to emphysema were not simply due to hyperinflation. Ventricular interdependence can impair left ventricular filling in patients with severe COPD^{44,45} and pulmonary arterial hypertension⁴⁶ but is of unclear relevance to this generally healthy cohort in which we observed inconsistent relationships with left ventricular end-systolic volume.

A more likely mechanism in early, mild emphysema may be the subclinical loss of lung parenchyma and the pulmonary capillary bed.⁸ Since the pulmonary circulation is a low-pressure but high-flow system, relatively modest reductions in

the pulmonary capillary cross-sectional area may result in substantially limited flow with only small increases in pulmonary-artery pressure. Studies of the pathogenesis of emphysema suggest that smoking causes apoptosis of the pulmonary endothelium⁴⁷⁻⁴⁹ and endothelial dysfunction,⁵⁰ which may simultaneously decrease pulmonary vascular cross-sectional area and capacitance, increase pulmonary vascular resistance, and lead to emphysema. This endothelial hypothesis of emphysema is relevant to our findings in this cohort of patients who had relatively mild, mostly subclinical emphysema and is consistent with the stronger associations that we observed among smokers than among former smokers or those who had never smoked.

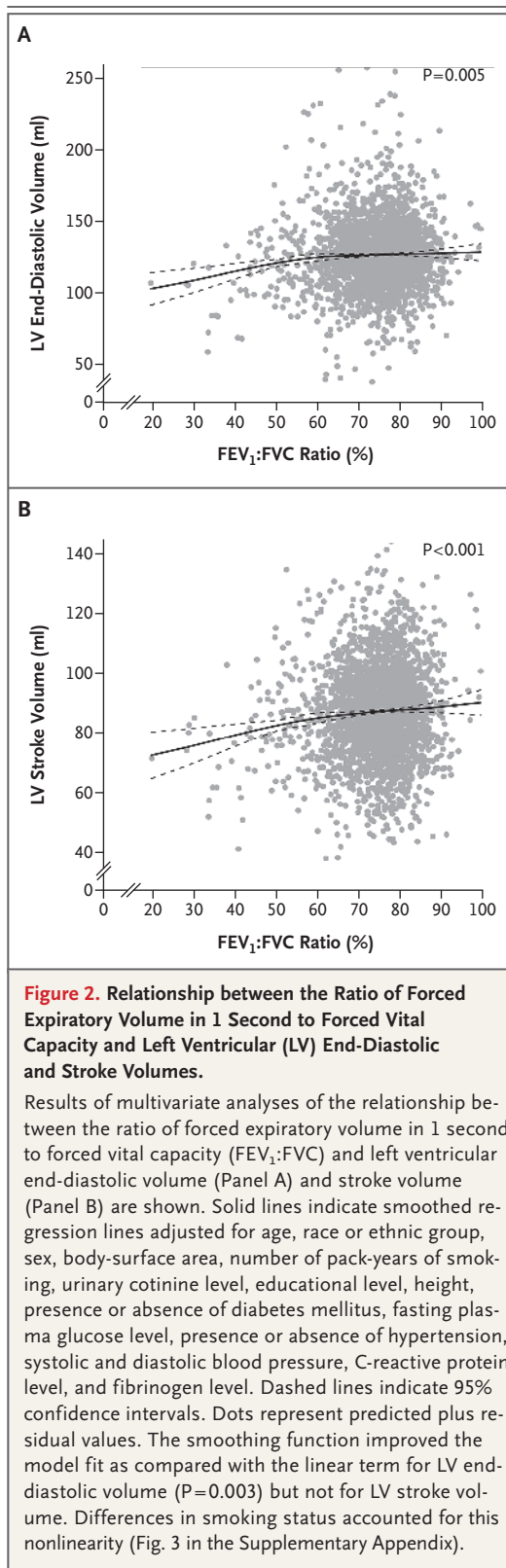
Although smoking itself may cause subclinical changes in left ventricular function,⁵¹ it is probably not a confounder of the observed associations for several reasons. First, the results of multivariate analyses changed little before and after the adjustment for multiple measures of smoking (data not shown). Second, it is not likely that current smokers were misclassified, since this status was confirmed by means of urinary cotinine levels. Third, the number of pack-years of smoking was not associated with left ventricular measures¹⁴ and was therefore not likely to have confounded the observed associations even if we had not adjusted for it. Finally, the association of percent emphy-

sema with left ventricular measures was also observed among the study participants who had never smoked.

One limitation of our study is that percent emphysema was measured on partial-lung rather than full-lung CT scans. However, we have previously found the percent emphysema on MESA cardiac scans to be valid as compared with full-lung measures.¹⁸ The use of cardiac scans limited the assessment of apical emphysema; however, pulmonary blood flow in both the upright and supine positions is greatest in the lower and central regions of the lung, which were included in the cardiac-scan field of view.^{52,53} Lung function was assessed approximately 4 years after the other measures; however, the expected mean change in the FEV₁:FVC ratio over a period of 4 years in a population-based study such as MESA is small (approximately 1%⁵⁴) relative to the standard deviation of the FEV₁:FVC ratio (9%). Therefore, misclassification due to the 4-year interval is unlikely to explain the observed associations.

Cross-sectional studies are potentially subject to reverse causality and selection bias. Cardiogenic pulmonary edema can occasionally cause bronchial hyperresponsiveness (i.e., “cardiac asthma”)⁵⁵; however, pulmonary edema typically results in a restrictive pattern on spirometry^{56,57} and increased attenuation on CT images, decreasing rather than increasing the percent emphysema. Selection bias is also not likely to explain the observed results, since the study was population-based, participants were not selected on the basis of the presence or absence of lung disease, the effect estimates were relatively large, and sensitivity analyses that were weighted according to the probability of undergoing the MRI examination yielded consistent results. Finally, direct measures of pulmonary-artery pressures, right ventricular and left atrial volumes, and alveolar hypoxia were not available in the current study. Measures of pulmonary pressures, however, are impractical in a study of this size. Findings from much smaller studies with right ventricular and left atrial volumes are consistent with our results.^{41,45} Hypoxia may be in the causal pathway between emphysema and left ventricular filling and therefore should not confound the observed results.

In conclusion, in this population-based study of subjects without very severe COPD, percent emphysema and the severity of airflow obstruction



were associated with significant decrements in left ventricular filling and cardiac output. The magnitude of these associations was greater among participants with a history of smoking, but the associations with percent emphysema were also present among participants who had never smoked.

Supported by grants (R01-HL077612, R01-HL075476, and R01-HL093081) and contracts (N01-HC95159 through N01-HC95169) from the National Heart, Lung, and Blood Institute, with additional support from UL1-RR02415.

Dr. Enright reports receiving consulting fees from Pfizer and Gilead; Dr. Hoffman, having equity ownership in and being a founder of VIDA Diagnostics and receiving lecture fees from Sanofi-Aventis, AstraZeneca, and Chiesi Pharmaceuticals; Dr. Kawut, receiving grant support from Pfizer; Dr. Lima, receiving grant support from Toshiba Medical Systems and General Electric; and Dr. Smith, receiving consulting fees from Merck and KarmelSonix. No other potential conflict of interest relevant to this article was reported.

We thank the other investigators, staff, and participants of MESA and the MESA Lung Study for their valuable contributions.

REFERENCES

- Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176:532-55.
- Jemal A, Ward E, Hao Y, Thun M. Trends in the leading causes of death in the United States, 1970-2002. *JAMA* 2005; 294:1255-9.
- Celli BR, MacNee W, ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932-46.
- Frank MJ, Weisse AB, Moschos CB, Levinson GE. Left ventricular function, metabolism and blood flow in chronic cor pulmonale. *Circulation* 1973;47:798-806.
- Steele P, Ellis JH, Van Dyke D, Sutton F, Creagh E, Davies H. Left ventricular ejection fraction in severe chronic obstructive airways disease. *Am J Med* 1975;59: 21-8.
- Fishman AP. Chronic cor pulmonale. *Am Rev Respir Dis* 1976;114:775-94.
- MacNee W. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1994;150:833-52.
- Leibow AA. Pulmonary emphysema with special reference to vascular change. *Am Rev Respir Dis* 1959;80:67-93.
- Barberà JA, Peinado VI, Santos S. Pulmonary hypertension in chronic obstructive pulmonary disease. *Eur Respir J* 2003; 21:892-905.
- Jørgensen K, Müller MF, Nel J, Upton RN, Houlz E, Rickstein SE. Reduced intrathoracic blood volume and left and right ventricular dimensions in patients with severe emphysema: an MRI study. *Chest* 2007;131:1050-7.
- Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol* 2002; 156:871-81.
- Hankinson J, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179-87.
- Natori S, Lai S, Finn JP, et al. Cardiovascular function in the Multi-Ethnic Study of Atherosclerosis: normal values by age, sex, and ethnicity. *AJR Am J Roentgenol* 2006;186:Suppl 2:S357-S365.
- Heckbert SR, Post W, Pearson GDN, et al. Traditional cardiovascular risk factors in relation to left ventricular mass, volume, and systolic function by cardiac magnetic resonance imaging: the Multi-Ethnic Study of Atherosclerosis. *J Am Coll Cardiol* 2006;48:2285-92.
- Katz J, Milliken MC, Stray-Gundersen J, et al. Estimation of human myocardial mass with MR imaging. *Radiology* 1988; 169:495-8.
- Keller AM, Peshock RM, Malloy CR, et al. In vivo measurement of myocardial mass using nuclear magnetic resonance imaging. *J Am Coll Cardiol* 1986;8:113-7.
- Carr JJ, Nelson JC, Wong ND, et al. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. *Radiology* 2005;234:35-43.
- Hoffman EA, Jiang R, Baumhauer HA, et al. Reproducibility and validation of lung density measures from cardiac CT scans — the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study. *Acad Radiol* 2009;16:689-99.
- Guo J, Reinhardt JM, Kitaoka H, Zhang L, McLennan G, Hoffman EA. Integrated system for CT-based assessment of parenchymal lung disease. In: Proceedings of IEEE International Symposium on Biomedical Imaging. New York: Institute of Electrical and Electronics Engineers, 2002:871-4.
- Tschirren J, McLennan G, Palágyi K, Hoffman EA, Sonka M. Matching and anatomical labeling of human airway tree. *IEEE Trans Med Imaging* 2005;24: 1540-7.
- Hu S, Hoffman EA, Reinhardt JM. Automatic lung segmentation for accurate quantitation of volumetric X-ray CT images. *IEEE Trans Med Imaging* 2001;20: 490-8.
- Zhang L, Hoffman EA, Reinhardt JM. Atlas-driven lung lobe segmentation in volumetric X-ray CT images. *IEEE Trans Med Imaging* 2006;25:1-16.
- Coxson HO, Mayo JR, Behzad H, et al. Measurement of lung expansion with computed tomography and comparison with quantitative histology. *J Appl Physiol* 1995; 79:1525-30.
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
- Hankinson JL, Kawut SM, Shahar E, Smith LJ, Stukovsky KH, Barr RG. Performance of ATS-recommended spirometry reference values in a multiethnic sample of adults: the MESA Lung Study. *Chest* 2010;137:138-45.
- Bertoni AG, Whitt-Glover MC, Chung H, et al. The association between physical activity and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis. *Am J Epidemiol* 2008;169:444-54.
- MESA Manual of Operations. Field center and laboratory procedures. Seattle: University of Washington, 2008. (Accessed December 23, 2009, at <http://www.mesa-nhlbi.org/manuals.aspx>.)
- Harvey RM, Ferrer MI, Richards DW Jr, Cournaud A. Influence of chronic pulmonary disease on the heart and circulation. *Am J Med* 1951;10:719-38.
- Bristow JD, Morris JF, Kloster FE. Hemodynamics of cor pulmonale. *Prog Cardiovasc Dis* 1966;9:239-58.
- Baum GL, Schwartz A, Llamas R, Castillo C. Left ventricular function in chronic obstructive lung disease. *N Engl J Med* 1971;285:361-5.
- Kline LE, Crawford MH, MacDonald WJ, Schelbert H, O'Rourke RA, Moser KM. Noninvasive assessment of left ventricular performance in patients with chronic obstructive pulmonary disease. *Chest* 1977;72:558-64.
- Buda AJ, Pinsky MR, Ingels NB Jr, Daughters GT II, Stinson EB, Alderman EL. Effect of intrathoracic pressure on left ventricular performance. *N Engl J Med* 1979;301:453-9.
- Burrows B, Kettel LJ, Niden AH, Rabinowitz M, Diener CF. Patterns of cardiovascular dysfunction in chronic obstructive pulmonary disease. *N Engl J Med* 1972;286:912-8.
- Chaouat A, Bugnet A-S, Kadaoui N, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;172:189-94.

35. Scharf SM, Iqbal M, Keller C, et al. Hemodynamic characterization of patients with severe emphysema. *Am J Respir Crit Care Med* 2002;166:314-22.
36. Thabut G, Dauriat G, Stern JB, et al. Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. *Chest* 2005;127:1531-6.
37. Marzluft BA, Burian B, Vonbank K, Stiebellehner L, Mosgoeller W, Petkov V. Relevance of pulmonary hypertension in COPD: prevalence of resting and exercise-induced pulmonary hypertension at different stages of COPD. *Eur Respir J* 2007; 30:Suppl:608s. abstract.
38. Barberà JA, Riverola A, Roca J, et al. Pulmonary vascular abnormalities and ventilation-perfusion relationships in mild chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1994;149:423-9.
39. 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.
40. Santos S, Peinado VI, Ramirez J, et al. Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD. *Eur Respir J* 2002;19:632-8.
41. Vonk-Noordegraaf A, Marcus JT, Holverda S, Roseboom B, Postmus PE. Early changes of cardiac structure and function in COPD patients with mild hypoxemia. *Chest* 2005;127:1898-903.
42. Capderou A, Aurengo A, Derenne JP, Similowski T, Zelter M. Pulmonary blood flow distribution in stage 1 chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;162:2073-8.
43. Macklem PT. Circulatory effects of expiratory flow-limited exercise, dynamic hyperinflation and expiratory muscle pressure. *Eur Respir Rev* 2006;15:80-4.
44. Vonk Noordegraaf A, Marcus JT, Roseboom B, Postmus PE, Faes TJ, de Vries PM. The effect of right ventricular hypertrophy on left ventricular ejection fraction in pulmonary emphysema. *Chest* 1997;112:640-5.
45. Boussuges A, Pinet C, Molenat F, et al. Left atrial and ventricular filling in chronic obstructive pulmonary disease: an echocardiographic and Doppler study. *Am J Respir Crit Care Med* 2000;162:670-5.
46. Gan CT, Lankhaar J-W, Marcus JT, et al. Impaired left ventricular filling due to right-to-left ventricular interaction in patients with pulmonary arterial hypertension. *Am J Physiol Heart Circ Physiol* 2006;290:H1528-H1533.
47. Kasahara Y, Tudor RM, Cool CD, Lynch DA, Flores SC, Voelkel NE. Endothelial cell death and decreased expression of vascular endothelial growth factor and vascular endothelial growth factor receptor 2 in emphysema. *Am J Respir Crit Care Med* 2001;163:737-44.
48. Demedts IK, Demoor T, Bracke KR, Joos GF, Brusselle GG. Role of apoptosis in the pathogenesis of COPD and pulmonary emphysema. *Respir Res* 2006;7:53.
49. Petrache I, Natarajan V, Zhen L, et al. Ceramide upregulation causes pulmonary cell apoptosis and emphysema-like disease in mice. *Nat Med* 2005;11:491-8.
50. Barr RG, Mesia-Vela S, Austin JHM, 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;176:1200-7.
51. Lichodziejewska B, Kurnicka K, Grudzka K, Malysz J, Ciurzynski M, Liszewska-Pfeffer D. Chronic and acute effects of smoking on left and right ventricular relaxation in young healthy smokers. *Chest* 2007;131:1142-8.
52. Hakim TS, Lisbona R, Dean GW. Gravity-independent inequality in pulmonary blood flow in humans. *J Appl Physiol* 1987;63:1114-21.
53. Glenn RW, Lamm WJ, Albert RK, Robertson HT. Gravity is a minor determinant of pulmonary blood flow distribution. *J Appl Physiol* 1991;71:620-9.
54. Jiang R, Burke GL, Enright PL, et al. Inflammatory markers and longitudinal lung function decline in the elderly. *Am J Epidemiol* 2008;168:602-10.
55. Cabanes LR, Weber SN, Matran R, et al. Bronchial hyperresponsiveness to methacholine in patients with impaired left ventricular function. *N Engl J Med* 1989; 320:1317-22.
56. Carmo MM, Ferreira T, Lousada N, et al. The repercussions of pulmonary congestion on ventilatory volumes, capacities and flows. *Rev Port Cardiol* 1994;13:763-8. (In Portuguese.)
57. Faggiano P, Lombardi C, Sorgato A, Ghizzoni G, Spedini C, Rusconi C. Pulmonary function tests in patients with congestive heart failure: effects of medical therapy. *Cardiology* 1993;83:30-5.

Copyright © 2010 Massachusetts Medical Society.

PERSONAL ARCHIVES IN THE JOURNAL ONLINE

Individual subscribers can store articles and searches using a feature on the *Journal's* Web site (NEJM.org) called "Personal Archive." Each article and search result links to this feature. Users can create personal folders and move articles into them for convenient retrieval later.