In Vivo Detection of Acinar Microstructural Changes in Early Emphysema with ^3He Lung Morphometry¹

James D. Quirk, PhD
Barbara A. Lutey, MD
David S. Gierada, MD
Jason C. Woods, PhD
Robert M. Senior, MD
Stephen S. Lefrak, MD
Alexander L. Sukstanskii, PhD
Mark S. Conradi, PhD
Dmitriy A. Yablonskiy, PhD

Purpose:

To quantitatively characterize early emphysematous changes in the lung microstructure of current and former smokers with noninvasive helium 3 (^3He) lung morphometry and to compare these results with the clinical standards, pulmonary function testing (PFT) and low-dose computed tomography (CT).

Materials and Methods:

This study was approved by the local institutional review board, and all subjects provided informed consent. Thirty current and former smokers, each with a minimum 30-pack-year smoking history and mild or no abnormalities at PFT, underwent ^3He lung morphometry. This technique is based on diffusion MR imaging with hyperpolarized ^3He gas and yields quantitative localized in vivo measurements of acinar airway geometric parameters, such as airway radii, alveolar depth, and number of alveoli per unit lung volume. These measurements enable calculation of standard morphometric characteristics, such as mean linear intercept and surface-to-volume ratio.

Results:

Noninvasive ^3He lung morphometry was used to detect alterations in acinar structure in smokers with normal PFT findings. When compared with smokers with the largest forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio, those with chronic obstructive pulmonary disease had significantly reduced alveolar depth (0.07 mm vs 0.13 mm) and enlarged acinar ducts (0.36 mm vs 0.3 mm). The mean alveolar geometry measurements in the healthiest subjects were in excellent quantitative agreement with literature values obtained by using invasive techniques (acinar duct radius, 0.3 mm; alveolar depth, 0.14 mm at 1 L above functional residual capacity). ^3He lung morphometry depicted greater abnormalities than did PFT and CT. No adverse events were associated with inhalation of ^3He gas.

Conclusion:

^3He lung morphometry yields valuable noninvasive insight into early emphysematous changes in alveolar geometry with increased sensitivity compared with conventional techniques.

© RSNA, 2011

Supplemental material: <http://radiology.rsna.org/lookup/suppl/doi:10.1148/radiol.11102226/-/DC1>

¹From the Mallinckrodt Institute of Radiology, Washington University School of Medicine, 4525 Scott Ave, Campus Box 8227, St Louis, MO 63110 (J.D.Q., D.S.G., J.C.W., A.L.S., M.S.C., D.A.Y.); Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine (B.A.L., R.M.S., S.S.L.); and Department of Physics (J.C.W., M.S.C., D.A.Y.), Washington University, St Louis, Mo. Received November 10, 2010; revision requested December 28; revision received March 18, 2011; accepted April 14; final version accepted May 2. Supported by an equipment loan from GE Healthcare. Address correspondence to J.D.Q. (e-mail: jquirk@wustl.edu).

Techniques that are sensitive to local lung structure at the alveolar level are required to understand the pathophysiology of early emphysema. Direct measurement of lung morphometry currently requires invasive collection of specimens via biopsy or lung resection and is therefore limited by safety concerns. Current noninvasive clinical measurements lack sufficient sensitivity to enable identification of early emphysematous changes, which are typically heterogeneously distributed throughout the lung. Pulmonary function testing (PFT) is used to measure only net lung function; it is considered insensitive to early chronic obstructive pulmonary disease (1), and it correlates poorly with clinical outcome in individual subjects (2). Computed tomography (CT) has greater value in the evaluation of emphysema (3,4). In patients with emphysema, enlargement of airspaces and destruc-

tion of alveolar walls reduces x-ray attenuation, particularly in patients with advanced disease (5,6). Although correlations have been found between the amount of emphysema seen at CT and the amount of emphysema found in pathologic specimens (6–8), the microstructural alterations that cause this attenuation loss cannot be distinguished. Importantly, the use of CT in healthy subjects and longitudinal studies is limited because of exposure to ionizing radiation.

In this study, we characterized emphysema by using helium 3 (^3He) lung morphometry, which is a noninvasive technique based on in vivo magnetic resonance (MR) measurement of inhaled hyperpolarized ^3He gas diffusivity in the lungs (9–13). This technique is a safe (14) and highly sensitive method with which to characterize the severity and distribution of alveolar structural abnormalities. In this approach, the lung acini are treated—in the framework proposed by Haefeli-Bleuer and Weibel (15) and Rodriguez et al (16)—as networks of cylindrical airways covered with alveoli, as shown in Figure 1. ^3He diffusion measurements are used to determine values for acinar duct radii (R) and airway lumen radii (r) and to determine the depth of the alveolar sleeve (h) in each image pixel with the following equation: $h = R - r$. From these estimates, we can calculate standard morphometric parameters such as the number of alveoli per unit lung volume, mean chord length, and surface-to-volume ratio (9). Measurements in explanted human lungs (9) and in vivo (17) and ex vivo (13) measurements in mouse lungs have shown that the mean chord length determined with ^3He MR imaging agrees well with histologic measurements in the same

lungs and with literature values. We anticipate that the ^3He lung morphometry technique will enable us to identify localized morphologic changes in acinar airways of subjects without clinically detectable abnormalities and with improved sensitivity over low-dose CT.

The purpose of this study was to quantitatively characterize early emphysematous changes in lung microstructure of current and former smokers with noninvasive ^3He lung morphometry and to compare the results obtained with this modality with those obtained with the clinical standards, PFT and low-dose CT.

Materials and Methods

Subject Selection

All subjects provided informed consent, and procedures were performed with approval from the local institutional review board and under a Food and Drug Administration Investigational New Drug exemption (no. 59269). Thirty current and former smokers (mean age, 62 years

Advances in Knowledge

- Noninvasive helium 3 (^3He) lung morphometry, which is based on hyperpolarized ^3He diffusion MR imaging, yields quantitative in vivo measurements of acinar airways and alveoli microgeometry across the lung, with results that are in good agreement with invasive histologic measurements reported in the literature.
- A significant 9% average expansion of the acinar ducts and a 30% average loss of alveolar depth were identified noninvasively in smokers with a 30-pack-year smoking history but without clinical emphysema ($P = .017$ and $P = .039$, respectively); ^3He lung morphometry measurements correlated significantly with multiple pulmonary function testing (PFT) results.
- In smokers without emphysema, low-dose CT trended toward an increased emphysema index (5%), however, this increase was not significant ($P = .34$); no significant correlations between PFT and low-dose CT were detected.

Implication for Patient Care

- Because of its safety and sensitivity, ^3He lung morphometry is well suited for improving our understanding of the mechanisms and development of early emphysematous disease and has the potential to be used to monitor the efficacy of therapeutic interventions in smaller clinical trials.

Published online before print

10.1148/radiol.11102226 Content code: CH

Radiology 2011; 260:866–874

Abbreviations:

El₋₉₅₀ = CT emphysema index at −950 HU
 FEV₁ = forced expiratory volume in 1 second
 FVC = forced vital capacity
 GOLD = Global Initiative for Obstructive Lung Disease
 PFT = pulmonary function testing
 TLC = total lung capacity

Author contributions:

Guarantors of integrity of entire study, J.D.Q., D.A.Y.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, J.D.Q., J.C.W., R.M.S., S.S.L., A.L.S., D.A.Y.; clinical studies, J.D.Q., B.A.L., J.C.W., S.S.L.; statistical analysis, J.D.Q., A.L.S.; and manuscript editing, J.D.Q., D.S.G., J.C.W., R.M.S., S.S.L., A.L.S., M.S.C., D.A.Y.

Funding:

This research was supported by the National Institutes of Health (grants R01HL70037, R01HL72369, and IP50HL084922).

Potential conflicts of interest are listed at the end of this article.

± 3 [standard deviation]; mean smoking history, 50 pack-years ± 20) were recruited from the CT screening arm of the local cohort of the National Lung Screening Trial, in which subjects aged 55–74 years with a minimum 30-pack-year smoking history were enrolled. Recruitment criteria for the current study included a National Lung Screening Trial CT examination that was negative for lung cancer, no pulmonary abnormalities other than chronic obstructive pulmonary disease, no known cardiac disease (including evidence of coronary artery calcification at CT that might predispose subjects to increased risks from desaturation during anoxic breath holding), and no contraindications to MR imaging. Study physicians recruited all subjects from the CT screening arm of the National Lung Screening Trial who met these criteria and were willing to participate in this study.

^3He Lung Morphometry

^3He gas was hyperpolarized to approximately 40% polarization with either a custom spin-exchange optical pumping polarizer or a commercial polarizer (IGL9600.He; GE Healthcare, Durham, NC). Gradient-echo diffusion ^3He MR images were acquired with a 1.5-T imager (Siemens Sonata; Siemens Medical Systems, Iselin, NJ) and use of a custom birdcage transmit coil and an eight-channel ^3He phased-array receiver coil (Stark Contrast MRI Coils Research, Erlangen, Germany) with 7×7 -mm resolution over three 30-mm axial sections (repetition time msec/echo time msec, 13/8.3; flip angle, 5.5° ; b values, 0, 2, 4, 6, 8, and 10 sec/cm 2) (18). The diffusion gradient pair (1.8-msec duration each, 0.3-msec rise times, no gap between lobes) was oriented perpendicular to the long axis of the body. Subjects inhaled 1 L of a 60:40 mixture of hyperpolarized ^3He gas in nitrogen from functional residual capacity and held their breath for 9 seconds, which constrained the achievable imaging resolution and anatomic coverage. During ^3He imaging, a physician monitored each subject's electrocardiogram, oxygen saturation, and pulse rate for potential adverse effects.

Figure 1

Figure 1: Longitudinal (left) and cross-sectional (right) schematic drawings of acinar airway geometry show the following major geometric parameters in the lung model: alveolar depth (h), acinar duct radius (R), and alveolar lumen radius (r). The assumption of symmetric alveoli fixes the alveolar length (L) at $0.765R$.

For each image voxel, data from all channels in the receiver array were jointly analyzed by using Bayesian probability theory (19–21) and a previously developed mathematic model of ^3He gas diffusion in lung acinar airways (9).

CT Examination

We reviewed each subject's most recent low-dose inspiratory chest CT study, acquired during the National Lung Screening Trial study with a Siemens Sensation 16 imager (Siemens Medical Systems) (120 kVp; 45 mAs; pitch, 1.5; effective tube current, 30 mAs; detector width, 0.75 mm; reconstructed as 2-mm-thick axial sections by using a B30f filter with an average in-plane resolution of $0.85 \text{ mm} \pm 0.2$) less than 1 year prior to the MR examination (22,23). A trained clinical radiology research technologist performed quantitative CT image analysis under the direct supervision of an author (D.S.G.) who has more than 15 years experience in quantitative lung CT densitometry. Segmentation of the lungs was conducted with Emphysema Profiler software (Vida Diagnostics, Iowa City, Iowa), and the emphysema index (EI_{-950}) was expressed as the percentage of pixels with an attenuation lower than -950 HU after large airways were excluded.

Clinical Testing

On the day of ^3He imaging, subjects underwent PFT conducted in accordance with American Thoracic Society standards and performed by certified pulmonary technicians. PFT included measurement of pre- and postbronchodilator spirometry, thoracic gas volumes, and diffusion

capacity of carbon monoxide with a Med-Graphics 1085 System (Medical Graphics, St Paul, Minn). A venous blood sample was also collected from all subjects. Those with a hemoglobin level of less than 12 gm/dL were excluded from the study to limit the potential risk of blood oxygen desaturation during anoxic breath holding. Reductions in the forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio are required to meet the Global Initiative for Obstructive Lung Disease (GOLD) definition of chronic obstructive pulmonary disease (24). Thus, subjects were assigned to one of three groups on the basis of their FEV_1/FVC ratio: the clinically abnormal group (FEV_1/FVC ratio $<70\%$), the normal group (FEV_1/FVC ratio $\geq 80\%$), and the border group, in which patients had an FEV_1/FVC ratio that bordered on abnormal (FEV_1/FVC between 70% and 79%) and in whom progression to clinically important disease appeared most likely.

Statistical Analysis

Nonparametric tests were used, as some parameters were not normally distributed across subjects (Lilliefors test: EI_{-950} , $P = .004$; mean chord length, $P = .07$; acinar duct radii, $P = .26$; depth of alveolar sleeve, $P = .54$). Correlations between metrics were measured with Spearman rank correlation with Holm-Bonferroni correction for multiple comparisons. Differences between FEV_1/FVC ratio groupings were detected with Kruskal-Wallis analysis of variance, followed by a Wilcoxon rank sum test on pairs of groups. All statistical analyses were performed with the R software

Table 1

Subject Characteristics and PFT Results

Characteristic	Overall (<i>n</i> = 30)	Sex		FEV ₁ /FVC Ratio		
		Male (<i>n</i> = 13)	Female (<i>n</i> = 17)	≥80% (<i>n</i> = 4)	70%–79% (<i>n</i> = 21)	<70% (<i>n</i> = 5)
Sex*						
Male	13	NA	NA	0	10	3
Female	17	NA	NA	4	11	2
Race*						
White	27	12	15	3	19	5
Black	3	1	2	1	2	0
Current smokers*	11	6	5	1	9	1
Age (y)	61 ± 3 (58–70)	61 ± 3 (58–68)	61 ± 3 (58–70)	60 ± 2 (58–61)	62 ± 3 (58–70)	60 ± 1 (59–62)
No. of pack years	51 ± 21 (31–105)	53 ± 23 (31–105)	49 ± 20 (32–98)	51 ± 25 (35–88)	53 ± 22 (32–105)	39 ± 6 (31–47)
FEV ₁ (% predicted)	92 ± 14 (59–117)	97 ± 12 (72–117)	88 ± 15 (59–109)	92 ± 8 (81–99)	95 ± 12 (65–117)	77 ± 19 (59–106)
FEV ₁ /FVC (%)	73 ± 7 (56–87)	71 ± 6 (58–78)	75 ± 7 (56–87)	83 ± 3 (80–87)	74 ± 3 (70–78)	62 ± 5 (56–68)
TLC (% predicted)	107 ± 14 (69–138)	113 ± 9 (103–131)	103 ± 16 (69–138)	96 ± 6 (87–101)	107 ± 15 (69–138)	117 ± 11 (106–130)
RV/TLC	0.38 ± 0.08 (0.16–0.57)	0.35 ± 0.04 (0.28–0.45)	0.41 ± 0.09 (0.16–0.57)	109 ± 11 (94–120)	104 ± 20 (38–137)	117 ± 17 (103–147)
DLCO (% predicted)	76 ± 17 (43–112)	83 ± 13 (55–104)	70 ± 17 (43–112)	74 ± 15 (58–92)	77 ± 16 (51–112)	71 ± 21 (43–93)

Note.—Unless otherwise indicated, data are means ± standard deviations. Data in parentheses are ranges. All PFT results are prebronchodilator values. DLCO = diffusing capacity of the lung for carbon monoxide, NA = not applicable, RV = residual volume.

* Data are numbers of patients.

package (version 2.10; R Foundation for Statistical Computing, Vienna, Austria), with $P < .05$ indicating a significant difference.

Results

Subject characteristics and average PFT results are shown in Table 1. These subjects generally had mild or no pulmonary disease at PFT. In the 30 subjects, disease was classified as GOLD 0 in 25, GOLD 1 in three, and GOLD 2 in two. We used the prebronchodilator PFT values in all comparisons for parity with the imaging conditions. Only three subjects responded to the bronchodilator during PFT (>10% change in FEV₁); however, the effect was sufficiently mild (<20% in all subjects), and data from these subjects were retained in this study. The number of pack-years was not significantly associated with any PFT, helium lung morphometry, or CT measurements. Few ventilation defects were observed on ^3He images in this population; therefore, we made no effort to quantify them. No adverse events were associated with inhalation of ^3He gas, and the observed decreases in oxygen saturation were mild (trough PO₂, 93% ± 2; range, 87%–97%)

and transient (duration of PO₂ decrease, 48 seconds ± 10; range, 32–99 seconds). The safety findings in these subjects were incorporated into a 100-subject safety study previously reported in this Journal (14).

Figure 2 shows ^3He MR and CT images in three subjects; there are large abnormalities and heterogeneity in ^3He lung morphometry parameters in the subject with GOLD 0 disease who is a smoker and the subject with GOLD 2 disease who is a former smoker. However, the PFTs were significantly abnormal in only the latter subject, who had emphysematous changes over the majority of the lung. Although the emphysematous regions at CT in these subjects are generally in the same location as abnormal regions on ^3He images, CT depicted an insignificant amount of emphysema (EI_{−950}, 1.6%) in the subject with GOLD 0 disease who is a smoker.

Values of the median acinar duct radius and alveolar depth for each subject are plotted in Figure 3 as functions of FEV₁, FEV₁/FVC ratio, total lung capacity (TLC), and EI_{−950}. Significant correlations are shown with a trend line and 95% confidence intervals. Figure 3b shows that decreasing FEV₁/FVC ratio was

associated with a significant decrease in alveolar depth and a significant increase in acinar duct radius. In contrast, FEV₁, FVC, diffusion capacity of carbon monoxide, and ratio of residual volume after full exhalation to TLC did not significantly correlate with any imaging measurements (only FEV₁ shown). Percentage of EI_{−950} and TLC were correlated with acinar duct radius but not alveolar depth. Figure E1 (online) shows correlation plots for all parameters studied.

Table 2 and Figure 4 summarize the major ^3He MR imaging and CT parameters in subjects stratified by their FEV₁/FVC ratio and enable us to divide subjects in the clinically normal group (24) into deciles. While all imaging measurements vary significantly with FEV₁/FVC ratio (Kruskal-Wallis analysis of variance), for EI_{−950}, the individual comparisons are significant only for subjects in the clinically abnormal group (FEV₁/FVC ratio <70%) (24). In contrast, in subjects with an FEV₁/FVC ratio between 70% and 79%, there were significant differences in acinar duct radii, alveolar depth, and mean chord length compared with subjects with an FEV₁/FVC ratio of 80% or more, indicating that ^3He lung morphometry MR imaging is capable of depicting

Figure 2

Figure 2: Maps of acinar airway geometric parameters obtained with ^3He lung morphometry and CT in a former smoker with GOLD 0 disease (left) (FEV_1 , 93% predicted; FEV_1/FVC , 80%), a smoker with GOLD 0 disease (middle) (FEV_1 , 94% predicted; FEV_1/FVC , 71%), and a former smoker with a GOLD 2 disease (right) (FEV_1 , 62% predicted; FEV_1/FVC , 56%) show heterogeneity of disease across lungs and significant increases in acinar duct radius (R) and mean chord length (L_m) and decreases in alveolar depth (h) and alveolar density (N_a) with chronic obstructive pulmonary disease. Red pixels on CT images indicate regions of emphysema (attenuation less than -950 HU).

changes prior to the accepted threshold of abnormality with PFT.

Discussion

To our knowledge, this report is the first to describe noninvasive in vivo observation of alveolar shallowing and enlargement of alveolar ducts with emphysema progression, a mechanism first proposed by Hartroft (25) and later confirmed in rodent models (26,27) and with ex vivo electron microscopy in patients with emphysema (28).

The distribution of values between the various ^3He lung morphometry mea-

surements in the aforementioned patient with GOLD 0 disease who is a smoker indicates that abnormalities in alveolar depth are larger and more severe than abnormalities in the acinar duct radius, suggesting that retraction of the alveolar walls is more extensive than and potentially preceded gross airway enlargement in this subject.

As ^3He lung morphometry is used to determine the functional acinar geometry, there are multiple potential mechanisms for the observed loss of alveolar depth beyond gross destruction of the septal walls. Emphysematous enlargement of the acinar duct can produce flattening

of the alveolus and retraction of the alveolar septa (25). The loss of elastin in the alveolar mouth could result in a partial collapse of the alveoli (29), as would an abnormality or reduction in surfactant (30) or changes in the proteoglycan and collagen content, organization, or distribution (31,32). The inflammatory processes prevalent in patients with chronic obstructive pulmonary disease (33,34) could thicken the alveolar walls and septa, effectively reducing the alveolar depth. Increases in the number and size of holes in the alveolar walls in emphysematous lungs due to opening of pores of Kohn and fenestrae (35) would allow increased diffusion between adjacent alveoli and acinar ducts, effectively decreasing the apparent alveolar depth and increasing the apparent acinar duct radius.

Our measurements of lung microgeometry are in excellent agreement with ex vivo values in the literature. For example, if the histologic measurements of Haefeli-Bleuer and Weibel (15) and Nagai et al (35) are geometrically scaled to correct for differences in lung inflation level, the acinar duct radius and alveolar depth would become 0.3 mm and 0.14 mm (9), respectively, making them effectively indistinguishable from the values obtained with ^3He lung morphometry in the healthiest smokers (FEV_1/FVC ratio, $\geq 80\%$) in our study. Ochs et al (36) reported alveolar densities between 132 and 178 alveoli per cubic millimeter in healthy lungs intended for transplantation (mean age, 29 years); this is only slightly higher than the alveolar density in the healthiest smokers in our study (130 alveoli per cubic millimeter ± 10), who were significantly older.

As the duct radius is more directly associated with lung volume and density than alveolar depth, we expected that it would correlate more strongly with TLC and CT results. By the GOLD criteria, chronic obstructive pulmonary disease requires a deficit in the FEV_1/FVC ratio, and its severity is then measured by decreases in FEV_1 (24). Since few subjects in our study had a clinically abnormal FEV_1/FVC ratio, a lack of correlation with FEV_1 was not surprising.

Figure 3

Figure 3: Graphs show alveolar depth (h) and acinar duct radius (R) in 30 subjects. Each data point is the median across all imaging voxels for a given subject. Horizontal axis is the prebronchodilator value of (a) FEV_1 percentage predicted, (b) percentage of FEV_1/FVC ratio, (c) TLC percentage predicted, and (d) El_{950} percentage predicted with CT. Solid lines = linear regression results; dashed lines = 95% confidence intervals. Spearman correlation coefficients and P values are given for each line. Trend lines and statistics are given in bold for significant correlations after Holm-Bonferroni correction for multiple comparisons.

Detection of significant pulmonary structural changes in subjects with a clinically normal FEV_1/FVC ratio suggests that the increased sensitivity of ^3He measurements may enable us to determine which subjects have lungs that are approaching this threshold for functional impairment,

thus our focus on classification according to FEV_1/FVC ratio. Interestingly, our correlations held even though the majority of subjects had FEV_1/FVC values within the clinically normal range.

In several previous studies, authors identified correlations between the

FEV_1/FVC ratio and the ^3He apparent diffusion coefficient (37–39), but they differed in detection of correlations with FEV_1 or diffusion capacity of carbon monoxide. The lack of correlation with diffusion capacity of carbon monoxide in this study may be because the subjects

Table 2

Average CT and ^3He Lung Morphometry Results by FEV₁/FVC Ratio

FEV ₁ /FVC Ratio	No. of Patients	^3He Lung Morphometry				No. of Alveoli per Unit Lung Volume (alveoli per cubic millimeter)	EI ₋₉₅₀
		Acinar Duct Radius (mm)	Alveolar Depth (mm)	Chord Length (mm)			
Overall	30	0.330 ± 0.02 (0.328)	0.09 ± 0.03 (0.10)	0.31 ± 0.08 (0.29)		108 ± 30 (104)	5 ± 4 (4)
≥80%	4	0.304 ± 0.005 (0.303)*	0.13 ± 0.02 (0.13)*	0.22 ± 0.02 (0.21)*		130 ± 10 (130)	2.3 ± 0.8 (2.5)
70%–79%	21	0.33 ± 0.02 (0.33) [†]	0.09 ± 0.02 (0.10) [†]	0.31 ± 0.07 (0.29) [†]		109 ± 30 (105)	5 ± 3 (4)
<70%	5	0.36 ± 0.02* [†] (0.36)	0.07 ± 0.02* (0.07)	0.41 ± 0.09* [†] (0.39)		80 ± 10* [†] (80)	9 ± 5* [†] (10)

Note.—Data are means ± standard deviations. Data in parentheses are medians. FEV₁/FVC values were obtained prior to bronchodilator administration.

* $P < .05$ versus FEV₁/FVC ratio of ≥80%.

[†] $P < .05$ versus FEV₁/FVC 70%–79%.

Figure 4

Figure 4: Charts show (a) increase in mean chord length, (b) EI₋₉₅₀, (c) acinar duct radius, and (d) decrease in alveolar depth with decreasing prebronchodilator FEV₁/FVC ratio at PFT. The clinically abnormal group (FEV₁/FVC ratio <70%) differs significantly from all other groups for all measurements shown (*) ($P < .05$). The border group (FEV₁/FVC ratio = 70%–79%) also differs significantly from all other groups for ^3He lung morphometry measurements (*) ($P < .05$), but not on CT-based EI₋₉₅₀. Error bars = standard deviations.

had mild disease and lacked the gross tissue destruction that reduces the gas exchange area sufficiently to alter diffusion capacity of carbon monoxide.

Correlations between CT results and the ^3He apparent diffusion coefficient also have been observed (40,41). Both Diaz et al (40) and van Beek

et al (41) found that PFT measurements correlated more strongly with apparent diffusion coefficient than with CT, which was consistent with our results. Our patient population was unusual in that subjects were relatively healthy in spite of their age and extensive smoking history. The narrow age range of our subjects enabled us to ignore the known influence of age on the apparent diffusion coefficient (42,43).

The increased sensitivity of ^3He lung morphometry compared with that of low-dose CT can be further demonstrated with posthoc power analysis. If we are interested in distinguishing between a population with a currently normal FEV₁/FVC ratio in which deterioration to functional impairment may be most likely (FEV₁/FVC ratio, 70%–79%) and a population in which it is less likely (FEV₁/FVC ratio, ≥80%), our results suggest that a study with 80% power to detect a significant difference at a $P = .05$ level with a two-sided t test would require three times fewer subjects with ^3He lung morphometry (seven or eight subjects per group) than with CT (28 to 35 subjects per group), assuming that means and standard deviations were consistent with those measured here.

Although regions of disease tended to colocalize between low-dose CT and ^3He measurements, there are important differences between the techniques. The spatial resolution in CT is significantly higher than that in ^3He MR imaging, yielding increased sensitivity to small lesions (although still insufficient to resolve pulmonary acini). In contrast, ^3He

lung morphometry is used to determine the average acinar dimensions over a relatively large imaging voxel. However, this technique actually relies on the fact that each voxel contains a random distribution of airway orientations and does not require direct resolution of individual acini. CT depicts only tissue density and generally cannot provide information about the mechanism of density changes, even though acquisition of CT data at multiple inflation volumes can yield limited functional information at the cost of increased radiation dose (44).

Likewise, while measurement of the ^3He apparent diffusion coefficient is sensitive to changes in the mean squared displacement of He atoms resulting from an increased airspace volume in patients with emphysema (10,39,45–49), they do not enable one to distinguish the mechanism of this change. As the apparent diffusion coefficient depends on the parameters of the MR imaging pulse sequence (50), it is not an intrinsic property of the lung. In contrast, ^3He lung morphometry noninvasively yields absolute values for specific geometric changes that occur in the alveolar ducts during emphysema in the same terms as direct lung morphometry.

As there was a delay of up to 1 year between CT imaging and other measurements, disease progression during this time could account for some of the observed sensitivity difference. Since most subjects had normal PFTs and none of them had changed smoking status during the previous year, we expect any changes during this time were minimal (51). To examine this assumption, we measured each subject's emphysema progression by using longitudinal CT data acquired during the National Lung Screening Trial study. Between each subjects' first and last CT examinations (750 days $\pm$ 90), the average yearly change in EL_{-950} was $0.4\% \pm 0.7$ (range, -0.9% to 2.4%). This supports the assumption that disease progression measured with CT was likely insignificant in these subjects during the delay.

An additional source of discrepancy between the CT and ^3He MR imaging experiments was the different inflation

volume used. The CT images were acquired at TLC, whereas the He MR images were acquired at 1 L above functional residual capacity. As TLC is considered the most sensitive inflation level for CT emphysema quantitation with CT, this difference does not explain its reduced sensitivity compared with He MR imaging. The sensitivity of our He MR imaging results could be further improved through customization of the inhalation volume to each subject's TLC instead of using a fixed value for all subjects. The fixed inhalation volume used in our study suggests that subjects with smaller lungs (lower TLC) had a higher relative inflation level than did subjects with larger lungs. However, we detected a significant increase in acinar duct radii with increasing TLC, which suggests that the differences in overall lung size and emphysema severity outweighed these inflation differences in the current subject population.

While we have concentrated on the average values of the ^3He diffusion parameters for the purpose of correlation across modalities, this ignores a major benefit of imaging techniques—the ability to acquire regional information on disease states. The heterogeneity of disease across the lung is clearly shown in Figure 2, and future efforts to analyze this distribution would likely be informative, potentially enabling identification of different emphysema phenotypes based on patterns of lung abnormalities. For example, there was increased intrasubject standard deviation across the lung with increasing FEV_1/FVC ratio for all ^3He measurements; however, this difference was significant for only mean chord length and alveolar density. No trend in intrasubject standard deviation was observed in the CT data (standard deviation data not shown). Sample distributions of CT and major ^3He lung morphometry parameters for two subjects are shown in Appendix E1 and Figures E1 and E2 (online).

In conclusion, ^3He lung morphometry is a sensitive noninvasive biomarker with which to measure acinar geometry. Our results indicate that in vivo ^3He lung morphometry has greater sensitivity to early emphysematous changes than does

low-dose CT or traditional PFTs and that it can be used to detect significant changes in acinar airway geometry, even in individuals with clinically normal PFT results. The safety and sensitivity of this technique suggest that it is well suited to improving our understanding of the mechanisms and development of early emphysematous disease and that it has the potential to be used to monitor the efficacy of therapeutic interventions in smaller clinical trials.

Disclosures of Potential Conflicts of Interest:

J.D.Q. Financial activities related to the present article: institution received an equipment loan from GE Healthcare. Financial activities not related to the present article: has stock/stock options in Pfizer. Other relationships: none to disclose. **B.A.L.** No potential conflicts of interest to disclose. **D.S.G.** No potential conflicts of interest to disclose. **J.C.W.** No potential conflicts of interest to disclose. **R.M.S.** No potential conflicts of interest to disclose. **S.S.L.** No potential conflicts of interest to disclose. **A.L.S.** No potential conflicts of interest to disclose. **M.S.C.** No potential conflicts of interest to disclose. **D.A.Y.** No potential conflicts of interest to disclose.

References

- Thurlbeck WM. Overview of the pathology of pulmonary emphysema in the human. *Clin Chest Med* 1983;4(3):337–350.
- Jones PW, Agusti AG. Outcomes and markers in the assessment of chronic obstructive pulmonary disease. *Eur Respir J* 2006;27(4):822–832.
- Gevenois PA, Yernault JC. Can computed tomography quantify pulmonary emphysema? *Eur Respir J* 1995;8(5):843–848.
- Washko GR. Diagnostic imaging in COPD. *Semin Respir Crit Care Med* 2010;31(3):276–285.
- Gould GA, MacNee W, McLean A, et al. CT measurements of lung density in life can quantitate distal airspace enlargement: an essential defining feature of human emphysema. *Am Rev Respir Dis* 1988;137(2):380–392.
- Müller NL, Staples CA, Miller RR, Abboud RT. “Density mask”: an objective method to quantitate emphysema using computed tomography. *Chest* 1988;94(4):782–787.
- Hayhurst MD, MacNee W, Flenley DC, et al. Diagnosis of pulmonary emphysema by computerised tomography. *Lancet* 1984;2(8398):320–322.
- Coxson HO, Rogers RM, Whittall KP, et al. A quantification of the lung surface area in emphysema using computed tomography. *Am J Respir Crit Care Med* 1999;159(3):851–856.
- Yablonskiy DA, Sukstanskii AL, Woods JC, et al. Quantification of lung microstructure

- with hyperpolarized ^3He diffusion MRI. *J Appl Physiol* 2009;107(4):1258–1265.
10. Yablonskiy DA, Sukstanskii AL, Leawoods JC, et al. Quantitative in vivo assessment of lung microstructure at the alveolar level with hyperpolarized ^3He diffusion MRI. *Proc Natl Acad Sci U S A* 2002;99(5):3111–3116.
 11. Sukstanskii AL, Yablonskiy DA. In vivo lung morphometry with hyperpolarized ^3He diffusion MRI: theoretical background. *J Magn Reson* 2008;190(2):200–210.
 12. Sukstanskii AL, Conradi MS, Yablonskiy DA. ^3He lung morphometry technique: accuracy analysis and pulse sequence optimization. *J Magn Reson* 2010;207(2):234–241.
 13. Osmanagic E, Sukstanskii AL, Quirk JD, et al. Quantitative assessment of lung microstructure in healthy mice using an MR-based ^3He lung morphometry technique. *J Appl Physiol* 2010;109(6):1592–1599.
 14. Lutey BA, Lefrak SS, Woods JC, et al. Hyperpolarized ^3He MR imaging: physiologic monitoring observations and safety considerations in 100 consecutive subjects. *Radiology* 2008;248(2):655–661.
 15. Haefeli-Bleuer B, Weibel ER. Morphometry of the human pulmonary acinus. *Anat Rec* 1988;220(4):401–414.
 16. Rodriguez M, Bur S, Favre A, Weibel ER. Pulmonary acinus: geometry and morphometry of the peripheral airway system in rat and rabbit. *Am J Anat* 1987;180(2):143–155.
 17. Wang W, Nguyen NM, Yablonskiy DA, et al. Imaging lung microstructure in mice with hyperpolarized ^3He diffusion MRI. *Magn Reson Med* 2011;65(3):620–626.
 18. Sukstanskii AL, Bretthorst GL, Chang YV, Conradi MS, Yablonskiy DA. How accurately can the parameters from a model of anisotropic ^3He gas diffusion in lung acinar airways be estimated? Bayesian view. *J Magn Reson* 2007;184(1):62–71.
 19. Bayes T. An essay towards solving a problem in the doctrine of chances: reprinted from *Philosophical Transactions of the Royal Society of London* 1763; 1753:1370–1418. *Biometrika* 1958;45:296–315.
 20. Quirk JD, Sukstanskii AL, Bretthorst GL, Yablonskiy DA. Optimal decay rate constant estimates from phased array data utilizing joint Bayesian analysis. *J Magn Reson* 2009;198(1):49–56.
 21. Bretthorst GL. An introduction to parameter estimation using bayesian probability theory. In: Fougere PF, ed. *Maximum entropy and Bayesian methods*. Dordrecht, the Netherlands: Kluwer Academic Publishers, 1989; 53–79.
 22. Church TR; National Lung Screening Trial Executive Committee. Chest radiography as the comparison for spiral CT in the National Lung Screening Trial. *Acad Radiol* 2003;10(6):713–715.
 23. National Lung Screening Trial Research Team, Aberle DR, Berg CD, et al. The National Lung Screening Trial: overview and study design. *Radiology* 2011;258(1):243–253.
 24. 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(6):532–555.
 25. Hartroft WS. The microscopic diagnosis of pulmonary emphysema. *Am J Pathol* 1945;21(5):889–903.
 26. Kuhn C 3rd, Tavassoli F. The scanning electron microscopy of elastase-induced emphysema: a comparison with emphysema in man. *Lab Invest* 1976;34(1):2–9.
 27. Morris SM, Stone PJ, Snider GL, Albright JT, Franzblau C. Ultrastructural changes in hamster lung four hours to twenty-four days after exposure to elastase. *Anat Rec* 1981;201(3):523–535.
 28. Finlay GA, O'Donnell MD, O'Connor CM, Hayes JP, FitzGerald MX. Elastin and collagen remodeling in emphysema: a scanning electron microscopy study. *Am J Pathol* 1996;149(4):1405–1415.
 29. Gottlieb DJ, Stone PJ, Sparrow D, et al. Urinary desmosine excretion in smokers with and without rapid decline of lung function: the Normative Aging Study. *Am J Respir Crit Care Med* 1996;154(5):1290–1295.
 30. Frerking I, Günther A, Seeger W, Pison U. Pulmonary surfactant: functions, abnormalities and therapeutic options. *Intensive Care Med* 2001;27(11):1699–1717.
 31. Suki B, Bates JH. Extracellular matrix mechanics in lung parenchymal diseases. *Respir Physiol Neurobiol* 2008;163(1-3):33–43.
 32. West JB. Distribution of mechanical stress in the lung, a possible factor in localisation of pulmonary disease. *Lancet* 1971;1(7704):839–841.
 33. Barnes PJ, Chowdhury B, Kharitonov SA, et al. Pulmonary biomarkers in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;174(1):6–14.
 34. Saetta M, Turato G, Maestrelli P, Mapp CE, Fabbri LM. Cellular and structural bases of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;163(6):1304–1309.
 35. Nagai A, Inano H, Matsuba K, Thurlbeck WM. Scanning electronmicroscopic morphometry of emphysema in humans. *Am J Respir Crit Care Med* 1994;150(5 Pt 1):1411–1415.
 36. Ochs M, Nyengaard JR, Jung A, et al. The number of alveoli in the human lung. *Am J Respir Crit Care Med* 2004;169(1):120–124.
 37. Fain SB, Panth SR, Evans MD, et al. Early emphysematous changes in asymptomatic smokers: detection with ^3He MR imaging. *Radiology* 2006;239(3):875–883.
 38. Swift AJ, Wild JM, Fische S, et al. Emphysematous changes and normal variation in smokers and COPD patients using diffusion ^3He MRI. *Eur J Radiol* 2005;54(3):352–358.
 39. Salerno M, de Lange EE, Altes TA, Truwit JD, Brookeman JR, Mugler JP 3rd. Emphysema: hyperpolarized helium 3 diffusion MR imaging of the lungs compared with spirometric indexes—initial experience. *Radiology* 2002;222(1):252–260.
 40. Diaz S, Casselbrant I, Piitulainen E, et al. Validity of apparent diffusion coefficient hyperpolarized ^3He -MRI using MSCT and pulmonary function tests as references. *Eur J Radiol* 2009;71(2):257–263.
 41. van Beek EJ, Dahmen AM, Stavngaard T, et al. Hyperpolarised ^3He MRI versus HRCT in COPD and normal volunteers: PHIL trial. *Eur Respir J* 2009;34(6):1311–1321.
 42. Fain SB, Altes TA, Panth SR, et al. Detection of age-dependent changes in healthy adult lungs with diffusion-weighted ^3He MRI. *Acad Radiol* 2005;12:1385–1393.
 43. Waters B, Owers-Bradley J, Silverman M. Acinar structure in symptom-free adults by Helium-3 magnetic resonance. *Am J Respir Crit Care Med* 2006;173:847–851.
 44. Webb WR. High-resolution computed tomography of obstructive lung disease. *Radiol Clin North Am* 1994;32(4):745–757.
 45. Chen XJ, Hedlund LW, Möller HE, Chawla MS, Maronpot RR, Johnson GA. Detection of emphysema in rat lungs by using magnetic resonance measurements of ^3He diffusion. *Proc Natl Acad Sci U S A* 2000;97(21):11478–11481.
 46. Mata JF, Altes TA, Cai J, et al. Evaluation of emphysema severity and progression in a rabbit model: comparison of hyperpolarized ^3He and ^{129}Xe diffusion MRI with lung morphometry. *J Appl Physiol* 2007;102(3):1273–1280.
 47. Peces-Barba G, Ruiz-Cabello J, Cremillieux Y, et al. Helium-3 MRI diffusion coefficient: correlation to morphometry in a model of mild emphysema. *Eur Respir J* 2003;22(1):14–19.
 48. Saam BT, Yablonskiy DA, Kodibagkar VD, et al. MR imaging of diffusion of (^3He) gas in healthy and diseased lungs. *Magn Reson Med* 2000;44(2):174–179.
 49. Woods JC, Choong CK, Yablonskiy DA, et al. Hyperpolarized ^3He diffusion MRI and histology in pulmonary emphysema. *Magn Reson Med* 2006;56(6):1293–1300.
 50. Gierada DS, Woods JC, Bierhals AJ, et al. Effects of diffusion time on short-range hyperpolarized (^3He) diffusivity measurements in emphysema. *J Magn Reson Imaging* 2009;30(4):801–808.
 51. Remy-Jardin M, Edme JL, Boulenguez C, Remy J, Mastora I, Sobaszek A. Longitudinal follow-up study of smoker's lung with thin-section CT in correlation with pulmonary function tests. *Radiology* 2002;222(1):261–270.