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Chronic Obstructive Pulmonary Disease: Longitudinal Hyperpolarized 3He MR Imaging

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Purpose:
To quantitatively evaluate a small pilot group of ex-smokers with chronic obstructive pulmonary disease (COPD) and healthy volunteers during approximately 2 years by using hyperpolarized helium 3 (3He) magnetic resonance (MR) imaging.

Materials and Methods:
All subjects provided written informed consent to the study protocol, which was approved by the local research ethics board and Health Canada and was compliant with the Personal Information Protection and Electronic Documents Act and HIPAA. Hyperpolarized 3He MR imaging, hydrogen 1 MR imaging, spirometry, and plethysmography were performed in 15 ex-smokers with COPD and five healthy volunteers (with the same mean age and age range) at baseline and 26 months ± 2 (standard deviation) later. Apparent diffusion coefficients (ADCs) derived from 3He MR imaging were calculated from diffusion-weighted 3He MR images, and 3He ventilation defect volume (VDV) and ventilation defect percentage (VDP) were generated after manual segmentation of 3He MR spin-density images.

Results:
For subjects with COPD, significant increases in 3He MR imaging–derived VDV (P = .03), VDP (P = .006), and ADC (P = .02) were detected, whereas there was no significant change in forced expiratory volume in 1 second (FEV1) (P = .97). For healthy never-smokers, there was no significant change in imaging or pulmonary function measurements at follow-up. There was a significant correlation between changes in FEV1 and changes in VDV (r = −0.70, P = .02) and VDP (r = −0.70, P = .03).

Conclusion:
For this small pilot group of ex-smokers with COPD, 3He MR imaging–derived VDV, VDP, and ADC measurements worsened significantly, but there was no significant change in FEV1, suggesting increased sensitivity of hyperpolarized 3He MR imaging for depicting COPD changes during short time periods.

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Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality and affects at least 600 million people worldwide (1). It is the world’s fourth leading cause of death and the most common chronic, terminal respiratory disease (2). Because of the heterogeneous nature of COPD, studies of its natural history and progression are complex, typically requiring large-study sample sizes and long durations to obtain relevant longitudinal end points. Accordingly, much of our current understanding of the natural history of COPD arises from the landmark study of Fletcher and Peto (3) and is based on cross-sectional spirometric measurements of forced expiratory volume in 1 second (FEV1). The current functional definition of COPD (4) is also based on FEV1, and change in FEV1 over the course of time is still the most widely accepted measure of COPD progression. However, a number of limitations of spirometry for the diagnosis, classification, and longitudinal monitoring of COPD are motivating the development of new COPD measurements (5), including those derived from noninvasive imaging (6,7). For example, thin-section multidetector computed tomography (CT) (8–11) has been used to identify phenotypes of both emphysema and airway disease (12–14) and depicts significant COPD changes during relatively short periods of time (15).

Hyperpolarized helium 3 (3He) magnetic resonance (MR) imaging has recently emerged as another research method for the evaluation of COPD (16–20). In particular, previous work showed that the apparent diffusion coefficient (ADC) derived from 3He MR imaging (16,21–23) was a sensitive measurement of emphysematous destruction (19,23,24) and airspace size (16,17,25,26) and correlated with pulmonary function (FEV1 and diffusion capacity of lung for carbon monoxide) (27), as well as histologic measurements of lung surface area (28). Importantly, 3He MR imaging–derived ADC is also age dependent (29) and reflects differences in patient anatomic position (30), disease severity (31), and smoking history (32). Quantitative focal 3He MR imaging–derived ventilation defects have also been shown in COPD (24,32–34), and these reflect differences in subject age (35) and disease status (20). To better understand the potential for hyperpolarized 3He MR imaging to provide quantitative longitudinal COPD end points, we designed a pilot longitudinal 3He MR imaging study of COPD. The purpose of this study was to quantitatively evaluate a small pilot group of ex-smokers with COPD and healthy volunteers over the course of approximately 2 years by using hyperpolarized 3He MR imaging.

Materials and Methods

Subjects
Twenty subjects were enrolled from the general population of the local tertiary health care center, as previously described (20). All subjects provided written informed consent to the study protocol, which was approved by the local research ethics board and Health Canada, and the study was compliant with the Personal Information Protection and Electronic Documents Act and the Health Insurance Portability and Accountability Act. Subjects with COPD were enrolled who were ex-smokers between the ages of 30–70 years and who had a clinical diagnosis of COPD. Those enrolled subjects with COPD were categorized according to the Global Initiative for Chronic Obstructive Lung Disease criteria (4) and had a smoking history of at least 10 pack-years and had fewer than three COPD exacerbations within the past 12 months. Exacerbations during the follow-up period were defined as hospitalization for COPD or as the patient’s first-time need for antibiotic or prednisone therapy, and these were reported from hospital records (36) and subject charts and were additionally verified with a telephone interview with the subject after follow-up imaging was completed. Subjects with COPD were excluded during a screening visit

Advances in Knowledge
- In a small group of ex-smokers with chronic obstructive pulmonary disease (COPD), hyperpolarized 3He MR imaging measurements showed significant progression after 26 months, whereas forced expiratory volume in 1 second (FEV1) did not significantly change.
- There was a significant inverse correlation between changes in 3He MR imaging–derived ventilation defect volume measurements and FEV1.
- Hyperpolarized 3He MR imaging is a sensitive tool for the quantitative longitudinal evaluation of COPD.

Implication for Patient Care
- In a small group of ex-smokers with COPD, hyperpolarized 3He MR imaging depicted significant changes in apparent diffusion coefficient and ventilation measurements, whereas there was no significant change in FEV1; this finding suggests that regional 3He MR imaging measurements provide adequate sensitivity for detecting COPD changes during relatively short time periods, before significant changes in FEV1 can be detected.
if FEV₁ was greater than 3% after administration of salbutamol. Healthy volunteers were enrolled (same age range as the subjects with COPD) who had a smoking history of less than 1 pack-year with no smoking in the previous 25 years and no history of previous chronic or current respiratory disease. All tests and imaging were performed at baseline and at 20 months ± 2 (standard deviation).

**Pulmonary Function Tests**

Spirometry was performed by using a spirometer (ndd EasyOne; Medizinotechnik, Zurich, Switzerland) to report FEV₁ and forced vital capacity with a minimum of three acceptable spirometry maneuvers; the best FEV₁ and forced vital capacity were selected for analysis according to American Thoracic Society guidelines (37). Whole-body plethysmography was performed by using a stand-alone body plethysmograph (Elite Series; MedGraphics, St Paul, Minn) for the measurement of total lung capacity, inspiratory capacity, residual volume, and functional residual capacity.

**MR Imaging**

Subjects were screened for MR imaging and coil compatibility (inner diameter of elliptical coil = 50 cm) prior to imaging, and digital pulse oximetry was used to monitor arterial blood oxygenation levels during breath-hold MR imaging. A turnkey, spin-exchange polarizer system (HeliSpin; GE Healthcare, Milwaukee, Wis) with broadband imaging capability, as previously described (23). All ³He MR imaging was performed with a whole-body gradient set with a maximum gradient amplitude of 1.94 G/cm and a single-channel, rigid elliptical transmit-receive chest coil (RAPID Biomedical, Würzburg, Germany). The basis frequency of the coil was 97.3 MHz, and excitation power was 3.2 kW by using a radiofrequency power amplifier (AMT 3T90; GE Healthcare, Milwaukee, Wis).

Coronal two-dimensional multiple-section hydrogen ¹ (¹H) images were acquired prior to ³He MR imaging, with subjects imaged during 1.5 breath hold of the ³He-N₂ mixture from a starting point of functional residual capacity by using a whole-body radiofrequency coil and a proton fast spoiled-gradient-echo sequence (16-second total data acquisition; repetition time msec/echo time msec, 4.7/1.2; flip angle, 30°; field of view, 40 × 40 cm; matrix, 256 × 256; 14 sections; 15-mm section thickness; 0-cm intersection gap). For diffusion-weighted imaging, coronal multisection images were obtained by using a fast gradient-echo method with centric k-space sampling. Two interleaved images (14-second total data acquisition; 7.6/3.7; flip angle, 8°; field of view, 40 × 40 cm; matrix, 128 × 128; seven sections; 30-mm section thickness), with and without additional diffusion sensitization (maximum gradient amplitude = 1.94 G/cm, rise and fall time = 0.5 msec, gradient duration = 0.46 msec, diffusion time = 1.46 msec, b value = 1.6 sec/cm²), were acquired. For ventilation, or spin-density, imaging, coronal multisection images were obtained by using the same ³He coil (14-second total data acquisition; 4.3/1.4; flip angle, 7°; bandwidth, 31.25 kHz; field of view, 40 × 40 cm; matrix, 128 × 128; 14 sections; 15-mm section thickness; 0-cm intersection gap) and multisection two-dimensional simultaneous acquisition of a ventilation image (no T₁-weighted sensitization) and a T₁-weighted image. Only images without T₁-weighting were used for ventilation analysis in this study. All imaging was completed within approximately 7–10 minutes of subjects first lying in the imager.

**Image Analysis**

The signal-to-noise ratio for all images acquired was determined by calculating the mean pixel value within a 10 × 10-voxel region of interest for four representative regions of interest within the lung parenchyma and dividing by the standard deviation of the mean pixel values for noise inside a region of interest of the same size at the corners of the image where there was no lung structure. Signal-to-noise ratio was determined for each subject and then was averaged to obtain a single signal-to-noise ratio for each subject and time point. Images were analyzed in a controlled image visualization environment with room lighting levels equivalently established for all image analysis sessions. ADC maps were processed by using in-house software programmed in the interactive data language Virtual Machine platform (Research Systems, Denver, Colo) as previously described (33) with a b value of 1.6 sec/cm². Spin-density images were examined for analysis of ventilation defects in all coronal sections by two expert observers (M.K. and L.M.) blinded to subject identity, disease status, and time point, as well as the other observer’s measurements. As previously described (39), a ventilation defect was identified by each observer independently as any lung region of diminished signal intensity but not those areas of signal loss associated with the pulmonary vascular structures, heart, hilum, and mediastinum. Images were reviewed such that ³He and ¹H images were visible on a digital workstation monitor system (consisting of identical 19-inch flat panel monitors). Manual segmentation of ventilation defects was performed by using custom-designed image visualization software that also provided a method for two-dimensional rigid single-point image registration (¹H and ³He sections) based on the carina, which facilitated the manual segmentation of ventilation defects in all sections. Ventilation defect volume (VDP) and thoracic cavity volume were recorded following manual segmentation of ³He and ¹H images, respectively, and were used to calculate ventilation defect percentage (VDP) (16,25,26,40). VDV was derived from the manually analyzed signal-to-noise ratio map.
segmented ventilation defect area for each section, and this was multiplied by the section thickness; VDV for all sections was summed to obtain whole-lung VDV. For the center section, which was the middle section acquired that clearly showed the carina and two main bronchi, VDV was also manually segmented and reported. In addition, whole-lung and center-section measurements were recorded for thoracic cavity volume for calculation of whole-lung and center-section VDV, as well as for ADC.

Statistical Methods

For 3He MR imaging ventilation measurements, observer reproducibility was evaluated for two observers by using the interclass correlation coefficient, coefficient of variation, and linear regression (r2) by using software (Prism, version 16.00; SPSS, Chicago, Ill.). Comparison of baseline and follow-up means was performed by using a Wilcoxon matched-pairs two-tailed t test (SPSS, version 16.00). The relationship between changes in 3He MR imaging measurements and changes in pulmonary function measurements at follow-up was determined by using linear regression and Spearman correlation coefficients by using software (Prism, version 4.00; GraphPad Software, San Diego, Calif). The relationship between the changes in 3He MR imaging–derived VDV and smoking history was determined by using linear regression and Spearman correlation coefficients (Prism, version 4.00). The Holm-Bonferroni correction [41] was used for multiple paired t tests and all correlations. The Holm-Bonferroni–adjusted P values were determined by ordering P values from smallest to largest, with the smallest P value multiplied by k, where k is the number of hypotheses to be tested. If the resulting modified P value was less than α (type I error rate), the hypothesis was rejected. The next smallest P value was then multiplied by k – 1, and the new modified P value was compared with α. This process was repeated until the modified P value could not be rejected. In all statistical analyses, results were considered significant when the probability of making a type I error was less than 5% (P < .05). A retrospective sample size (n) calculation was performed to detect a significant change (δ) in FEV1 with α equal to .05 and power β equal to .80 and where SD is standard deviation; accordingly, Zα was 1.645 and Zβ was 0.2, and n was calculated according to the following equation (42):

\[ n = \frac{2(Z_\alpha + Z_\beta)^2 \text{SD}^2}{\delta^2} \]

Results

Demographic characteristics are provided in Table 1. All subjects with COPD were nonsmokers at baseline with a mean smoking history of 47 pack-years ± 22 (range, 11–85 pack-years) and mean years of not smoking at baseline of 11 years ± 10 (range, 10 weeks to 34 years). Three subjects experienced a single COPD exacerbation during the follow-up period.

Table 2 shows mean and median whole-lung and center-section hyperpolarized 3He MR imaging measurements for healthy never-smokers and subjects with COPD. The absolute change and annualized rates of change of FEV1 and hyperpolarized 3He MR imaging measurements for subjects with COPD are provided in Table 3. For ADC, annualized rate of change for ex-smokers with COPD was 0.01 cm2/sec and that for never-smokers was 0.002 cm2/sec. There was no significant association between the changes in image signal-to-noise ratio and the changes in ADC (r = −0.51, P = .12) and VDV (r = −0.17, P = .55). Interobserver reproducibility of 3He MR imaging–derived VDV was previously evaluated for three observers, and this was the same as intraobserver variability (coefficient of variation = 10%, unpublished results). For two observers, interobserver reproducibility was assessed for whole-lung VDV (intraclass correlation coefficient = .93, coefficient of variation = 38%, and r2 = .84 [P < .0001]) and whole-lung VDP (intraclass correlation coefficient = .91, coefficient of variation = 43%, and r2 = .81 [P < .0001]).
Figure E1 (online) shows the relationship between ventilation defect measurements (whole-lung VDV \( r^2 = 0.84, P < .0001 \)) and whole-lung VDP \( r^2 = 0.81, P < .0001 \)) for observer 1 and 2. The change at follow-up for observer 1 and 2 were significantly correlated for whole-lung VDP \( r^2 = 0.51, P = .0004 \) and whole-lung VDP \( r^2 = 0.39, P = .007 \). The change in whole-lung VDV and whole-lung VDP for each observer and the mean for both observers is provided in Table E1 (online), and throughout the main body of the article, a single observer’s results are described. Table E2 (online) shows a subject listing of baseline and follow-up pulmonary function and \(^3\)He MR imaging measurements.

Wilcoxon matched-pairs two-tailed \( t \) tests indicated that all \(^3\)He MR imaging measurements were significantly different at follow-up for subjects with COPD. There was no significant change observed in FEV\(_1\) (percentage predicted) for subjects with COPD at follow-up. For healthy never-smokers, there was no detectable change in any pulmonary function or imaging measurement. The changes detected in the ex-smokers with COPD were significantly different than the changes measured in the healthy volunteers for whole-lung VDV \( P = .04 \) and whole-lung VDP \( P = .01 \) but were not significantly different for whole-lung ADC \( P = .96 \) or FEV\(_1\) \( P = .21 \).

Table 2

| Parameter                | Healthy Never-Smokers (n = 5) | Ex-Smokers with COPD (n = 15) |
|--------------------------|-------------------------------|-------------------------------|
|                          | Baseline | Follow-up | Baseline | Follow-up |
| Whole-lung ADC (cm\(^2\)/sec) | 0.27 (0.25) [0.02] | 0.29 (0.29) [0.03] | 0.43 (0.45) [0.08] | 0.46 (0.46) [0.07] |
| Center-section ADC (cm\(^2\)/sec) | 0.28 (0.27) [0.02] | 0.28 (0.30) [0.03] | 0.44 (0.45) [0.09] | 0.47 (0.46) [0.08] |
| Whole-lung VDV (L)       | 0.023 (0.006) [0.04] | 0.020 (0.017) [0.02] | 0.52 (0.24) [0.54] | 0.92 (0.77) [0.93] |
| Center-section VDV (L)   | 0.003 (0.000) [0.005] | 0.002 (0.001) [0.002] | 0.056 (0.023) [0.053] | 0.11 (0.11) [0.11] |
| Whole-lung VDP (%)       | 0.5 (0.2) [0.9] | 0.5 (0.5) [0.4] | 9 (6) [9] | 16 (15) [14] |
| Center-section VDP (%)   | 0.6 (0.2) [0.9] | 0.4 (0.2) [0.4] | 9 (11) [13] | 16 (16) [22] |

Note.—Data are means, with medians in parentheses and standard deviations in brackets.

Table 3

| Parameter                        | Healthy Never-Smokers | Ex-Smokers with COPD | P-Value* |
|----------------------------------|-----------------------|----------------------|---------|
| FEV\(_1\) (percentage predicted) | -1                    | -0.4                 | .97 (.97) |
| Whole-lung ADC (cm\(^2\)/sec)   | 0.02                  | 0.01                 | .01 (.02) |
| Center-section ADC (cm\(^2\)/sec) | 0.03                  | 0.01                 | .004 (.02) |
| Whole-lung VDV (L)               | 0.4                   | 0.20                 | .007 (.03) |
| Center-section VDV (L)           | 0.05                  | 0.03                 | .003 (.02) |
| Whole-lung VDP (%)               | 7                     | 4                    | .0009 (.008) |
| Center-section VDP (%)           | 7                     | 3                    | .01 (.03) |

* Data are \( P \) values determined with Wilcoxon matched-pairs two-tailed \( t \) tests, with Holm-Bonferroni-adjusted \( P \) values in parentheses.

Discussion

Several observations were made in this small longitudinal pilot study. First, we observed that mean \(^3\)He MR imaging–derived VDV and FEV\(_1\) There was no significant correlation between pack-years smoking and the change in FEV\(_1\) \( r = 0.05, P = .83 \), and the relationship between pack-years smoking and whole-lung VDP was moderate, but once corrected for multiple tests, this relationship was on the threshold of significance (whole-lung VDV \( r = 0.52; P = .02 \), uncorrected; \( P = .06 \), Holm-Bonferroni corrected).

There was no detectable change in any pulmonary function or imaging measurement. The changes detected in the ex-smokers with COPD were significantly different than the changes measured in the healthy volunteers for whole-lung VDV \( P = .04 \) and whole-lung VDP \( P = .01 \) but were not significantly different for whole-lung ADC \( P = .96 \) or FEV\(_1\) \( P = .21 \).

Figure 1 shows ventilation images, ADC maps, and ADC histograms for two representative healthy never-smokers at baseline and follow-up. Figure 2 shows ventilation images, ADC maps, and ADC histograms for two representative healthy never-smokers at baseline and follow-up.
**Figure 1:** Representative hyperpolarized $^3$He MR data at baseline (top) and follow-up (bottom) in healthy never-smokers. Left: A, Ventilation image, B, ADC map, and, C, ADC histogram in 58-year-old man (subject 1001). Right: A, Ventilation image, B, ADC map, and, C, ADC histogram in 73-year-old man (subject 1007).

**Figure 2:** Representative hyperpolarized $^3$He MR data show VDV and ADC changes during follow-up in COPD. Left: A, Ventilation image, B, ADC map, and, C, and ADC histogram in 75-year-old man with stage III COPD (subject 3004). Right: A, Ventilation image, B, ADC map, and, C, ADC histogram in 61-year-old man with stage II COPD (subject 2009). Top = baseline, bottom = follow-up.
Table 4

| Parameter                  | FEV₁ (L)       | FEV₁ (Percentage Predicted) |
|----------------------------|----------------|----------------------------|
| Whole-lung ADC (cm²/sec)   | −0.02 (.93) [.93] | 0.17 (.56) [>.99]           |
| Center-section ADC (cm²/sec)| −0.06 (.84) [>.99] | 0.15 (.60) [.60]           |
| Whole-lung VDV (L)         | −0.56 (.03) [.09] | −0.53 (.04) [.12]          |
| Center-section VDV (L)     | −0.70 (.003) [.02] | −0.67 (.007) [.04]         |
| Whole-lung VDP (%)         | −0.69 (.02) [.09] | −0.55 (.03) [.12]          |
| Center-section VDP (%)     | −0.70 (.005) [.03] | −0.70 (.005) [.03]         |

Note.—Data are Spearman correlation coefficients, with \(P\) values in parentheses and Holm-Bonferroni–adjusted \(P\) values in brackets.

Figure 3

These preliminary longitudinal findings suggest that regional disease markers derived at noninvasive imaging can be used in a small number of subjects with COPD during short time periods to quantitatively detect significant changes.

Fletcher and Peto (3), as well as the more recent findings of a tiotropium intervention trial (43), were not surprised to find that in ex-smokers with COPD, FEV₁ did not significantly change. Indeed, this study was not powered to detect such changes in FEV₁ during an approximately 2-year time frame; a retrospective power analysis showed that a sample size of approximately 1000 patients with COPD and 1000 healthy volunteers would be required to detect significant change in FEV₁ in this study. Unlike the Fletcher curve prediction that longitudinal changes in hyperpolarized \(^{3}\)He MR imaging measurements in ex-smokers with COPD would be similar to those observed in healthy never-smokers, we observed an annualized rate of change in \(^{3}\)He MR imaging–derived ADC of 0.01 cm²/sec—an order of magnitude greater than the rate previously reported (0.001 cm²/sec) for healthy nonsmokers in a cross-sectional multicenter study at 1.5 T (29) and for the healthy never-smokers reported in this study (0.002 cm²/sec). In addition, we observed no significant change in \(^{3}\)He MR imaging–derived ADC, ventilation defect measurements, or pulmonary function measurements for healthy never-smokers at follow-up.

Unlike the Fletcher curve prediction that longitudinal changes in FEV₁ in ex-smokers with COPD would be similar to those observed in healthy never-smokers, we observed an annualized rate of change in \(^{3}\)He MR imaging–derived ADC of 0.01 cm²/sec—an order of magnitude greater than the rate previously reported (0.001 cm²/sec) for healthy nonsmokers in a cross-sectional multicenter study at 1.5 T (29) and for the healthy never-smokers reported in this study (0.002 cm²/sec). In addition, we observed no significant change in \(^{3}\)He MR imaging–derived ADC, ventilation defect measurements, or pulmonary function measurements for healthy never-smokers at follow-up.
and finite numbers of subjects because of the relative complexity of these studies and the prediction for increased costs and decreased availability of 3He gas for clinical research (44). Nevertheless, the preliminary findings of this pilot hyperpolarized 3He MR imaging longitudinal study provide clear guidance for future COPD imaging studies on established and emerging imaging tools such as optical coherence tomography (45), oxygen-enhanced and proton MR imaging methods (46,47), and hyperpolarized xenon 129 MR imaging.

Finally, we showed in an exploratory analysis, the potential relationship between smoking history and changes in 3He MR imaging–derived VDV but not with changes in FEV1. Previous cross-sectional studies suggest ongoing inflammation in ex-smokers with COPD (3,29) and that smoking history correlated with current inflammatory markers such as eosinophils (48) and vascular endothelial growth factor (49), which supports the hypothesis that there is a predictive relationship between pack-years and inflammation after smoking cessation. The results of this exploratory analysis of 3He MR imaging changes and smoking history generate important hypotheses that future studies should explore in more detail.

Although this pilot study showed significant increases in 3He MR imaging–derived measurements in just more than 2 years, we must acknowledge a number of specific limitations of our approach. We recognize that the relatively small group of subjects with COPD and healthy never-smokers who were evaluated and the relatively short period of follow-up compared with other COPD longitudinal studies (5) certainly limited the applicability of our results. The small sample size necessitates cautious interpretation of the results, as well as the future requirement for larger studies to test the hypotheses generated. For example, because of the small number of healthy volunteers and subjects with COPD evaluated, significant differences were not detected for pulmonary function measurements in either group. In addition, although we have previously demonstrated that ventilation defects are highly reproducible (20), the lack of longitudinal information regarding the variability of ventilation defects necessitates that the findings of this study be interpreted with caution.

Although this pilot study showed that ex-smokers with COPD differed from never-smokers, it was not designed to show the relationship between the significant imaging changes and more-established clinical measurements of COPD worsening. To make the important conclusion that 3He MR imaging measurements are specifically related to clinical measurements of COPD worsening, future work in longer or larger studies must show that the detected 3He MR imaging changes occurred in patients who had measureable clinical changes. Nevertheless, the results suggest that 3He MR imaging provides a sensitive method for the detection of structural and functional changes of the lung that accompany COPD longitudinally. In the future, larger studies that directly compare 3He MR imaging and other well-established clinical measurements of COPD progression will be required to better understand the relationship between 3He MR imaging–derived measurements and other changes that occur in COPD over the course of time.

In addition, a comparison of ex-smokers with COPD, healthy smokers, and current smokers with COPD may help to establish and directly compare rates of structural and functional decline of the lung. It will also be critical to track patient exacerbations and changes in treatment during longer time periods to probe potential treatment effects with imaging. We also acknowledge that for this pilot study, we limited the COPD cohort to those with minimal FEV1 reversibility, although clearly many subjects with COPD have varying degrees of FEV1 reversibility, which necessitates further work in such patients.

CT images were not prospectively acquired for this study; and therefore, our results cannot be directly compared with more-established CT measurements such as percentage of low attenuation areas (measurement of the extent of emphysema) or wall area percentage (measurement of airway wall thickness). Clearly, a direct comparison of CT and hyperpolarized 3He MR imaging–derived measurements in the same subjects will allow for a better understanding of differences in measurement sensitivity these imaging modalities provide.

A previous study (32) has shown significant correlation between ADC and the measurement of diffusing capacity.
of lung for carbon monoxide. A direct comparison in this study would have provided another quantitative measure of global emphysematous changes in these subjects. While Woods and colleagues (28) have previously shown the significant correlation between $^3$He MR imaging–derived ADC and histologic measurements of emphysema, we have not yet determined the underlying disease that results in the $^3$He MR imaging–derived ventilation defects we observe, which may be a result of small airway occlusion, mucous plugs, airway wall thickening and inflammation, or bullous disease. Related to this is the fact that there is important information in regions of intermediate signal intensity and in both hyper- and hypointense regions that has not yet been quantitatively or spatially exploited. The development and validation of $^3$He MR image analysis techniques that quantify heterogeneous signal intensity information are required in the future to fully characterize the important ventilation information contained on the image. Whether regions of diminished ventilation and emphysema develop independently and the extent to which one leads to the other cannot be ascertained by results of this preliminary longitudinal study and has yet to be determined in other longitudinal imaging studies. Importantly, however, our group previously described the high reproducibility of $^3$He MR imaging–derived ventilation defects in COPD (20), suggesting that the significant changes measured in this study may be because of changes in lung morphology or function and not because of the variability of the imaging or measurement technique or because of short-term changes in small airway diameter or patency.

In summary, in this small pilot study of ex-smokers with COPD, by using $^3$He MR imaging we detected significant lung changes that occurred during a relatively short time period, perhaps before FEV$_1$ changes could be detected or perhaps because such longitudinal changes occurred within the FEV$_1$’s silent zones, where disease might have accumulated without detection.

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