Pulmonary ventilation visualized using hyperpolarized helium-3 and xenon-129 magnetic resonance imaging: differences in COPD and relationship to emphysema

Miranda Kirby,1,2 Sarah Svenningsen,1,2 Nikhil Kanhere,1,3 Amir Owragi,1,3 Andrew Wheatley,1 Harvey O. Coxson,4 Giles E. Santyr,1,2 Nigel A. M. Paterson,1,5 David G. McCormack,1,5 and Grace Parraga1,2,3

1Imaging Research Laboratories, Robarts Research Institute, London, Ontario, Canada; 2Department of Medical Biophysics, The University of Western Ontario, London, Ontario, Canada; 3Graduate Program in Biomedical Engineering, The University of Western Ontario, London, Ontario, Canada; 4Department of Radiology & James Hogg Research Centre, Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, Canada; and 5Division of Respirology, Department of Medicine, The University of Western Ontario, London, Ontario, Canada

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Kirby M, Svenningsen S, Kanhere N, Owragi A, Wheatley A, Coxson HO, Santyr GE, Paterson NA, McCormack DG, Parraga G. Pulmonary ventilation visualized using hyperpolarized helium-3 and xenon-129 magnetic resonance imaging: differences in COPD and relationship to emphysema. J Appl Physiol 114: 707–715, 2013. First published December 13, 2012; doi:10.1152/japplphysiol.01206.2012.—In subjects with chronic obstructive pulmonary disease (COPD), hyperpolarized xenon-129 (129Xe) magnetic resonance imaging (MRI) reveals significantly greater ventilation defects than hyperpolarized helium-3 (3He) MRI. The physiological and/or morphological determinants of ventilation defects and the differences observed between hyperpolarized 3He and 129Xe MRI are not yet understood. Here we aimed to determine the structural basis for the differences in ventilation observed between 3He and 129Xe MRI in subjects with COPD using apparent diffusion coefficients (ADC) and computed tomography (CT). Ten COPD ex-smokers provided written, informed consent and underwent MRI, CT, spirometry, and plethysmography. 3He and 129Xe MRI ventilation volume was generated using semiautomated segmentation, and ADC maps were registered to generate ADC values for lung regions of interest ventilated by both gases (ADC3He) and by 3He gas only (ADCH3). CT wall area percentage and the lowest 15th percentile point of the CT lung density histogram (HU15%) were also evaluated. For lung regions accessed by 3He gas only, mean 3He ADC3He was significantly greater than for regions accessed by both gases (ADCH3 = 0.503 ± 0.119 cm2/s, ADCH3 = 0.470 ± 0.125 cm2/s, P < 0.0001). The difference between 3He and 129Xe ventilation volume was significant correlated with CT HU15% (r = –0.65, P = 0.04) and 3He ADCH3 (r = 0.70, P = 0.02), but not CT wall area percentage (r = –0.34, P = 0.33). In conclusion, in this small study in COPD subjects, we observed significantly decreased 129Xe MRI ventilation compared with 3He MRI, and these regions of decreased 129Xe ventilation were spatially and significantly correlated with regions of increased pulmonary emphysema, but not airway wall thickness.

chronic obstructive pulmonary disease; emphysema; hyperpolarized helium-3 magnetic resonance imaging; hyperpolarized xenon-129 magnetic resonance imaging

IN CHRONIC OBSTRUCTIVE PULMONARY disease (COPD), irreversible airflow limitation is a consequence of increased time constants for lung emptying related to airway narrowing/occlusion, as well as loss of elastic recoil due to emphysematous tissue destruction (36).1 Magnetic resonance imaging (MRI) using hyperpolarized helium-3 (3He) provides high spatial and temporal resolution images of pulmonary ventilation and ventilation abnormalities (7, 18, 26), and, with the recent advances in polarization physics (13, 14, 34, 37), hyperpolarized xenon-129 (129Xe) MRI now also provides high-resolution images of pulmonary ventilation and transmembrane diffusion (1, 5, 9–12, 19, 27–29, 34, 35, 42). The lung microstructure can also be probed using diffusion-weighted MRI, which takes advantage of the rapid 3He and 129Xe atom Brownian motion to generate apparent diffusion coefficients (ADC) (19, 29, 38, 39, 42, 50, 51), now a well-established surrogate measurement of alveolar dimensions (48). In a small group of COPD subjects, it was also recently demonstrated that there were significantly greater ventilation abnormalities measured using 129Xe compared with 3He gas, and this was not observed in healthy age-matched subjects (21). Moreover, in this previous work, some COPD subjects had greater 3He-129Xe ventilation differences than others, suggesting that patient-specific, disease-related mechanisms might be responsible for this difference.

We still do not have a clear understanding of the etiology of noble gas MRI ventilation defects, nor their relationship to patient symptoms, exercise capacity, or other outcomes; it is also unclear what the structural determinants or mechanisms are behind the differences between 3He and 129Xe ventilation in COPD. A large number of studies have investigated the convective and diffusive gas transport within the lung using multiple-breath washout studies (3, 6, 83, 39, 41), and it is clear from this previous work that there are many factors affecting ventilation distribution within the lung, including the inhaled gas physical properties. For example, gas density and viscosity affect flow resistance, and this itself is dependent on airway lumen dimensions (46). In the small airways (<2 mm in diameter) where flow is fully laminar, viscosity provides the main influence on flow resistance. However, in the large airways where turbulent flow dominates, resistance is mainly affected by gas density. The major site of airflow limitation in COPD occurs within the small conducting airways (16), and, therefore, it is predicted that the gas viscosity would be the most important gas physical property affecting flow resistance. However, both the greater density and viscosity of 129Xe gas

1 This article is the topic of an Invited Editorial by J. C. Woods (47a).
Address for reprint requests and other correspondence: G. Parraga, Imaging Research Laboratories, Robarts Research Institute, 100 Perth Dr., London, Ontario, Canada N6A 5K8 (e-mail: gparraga@robarts.ca).

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(pure $^{129}$Xe gas has $\sim$40 times greater density and 1.5 times greater viscosity than pure $^3$He gas) (15, 31) may result in greater resistance to flow, regardless of the location of airway abnormalities and, therefore, may contribute to greater $^{129}$Xe ventilation abnormalities compared with $^3$He MRI in COPD. Another potential mechanism responsible for $^3$He/$^{129}$Xe ventilation differences in COPD is the presence of emphysema and the effects of collateral ventilation (45). In emphysema, lung tissue compliance is increased, and resistance to flow through obstructed airways is higher than through collateral pathways (17, 44).

To provide a better understanding of the clinical or physiological meaning of MRI-derived ventilation abnormalities, we investigated the relationship between emphysema and airway wall morphology with differences observed between hyperpolarized $^3$He and $^{129}$Xe MRI gas distribution. As a first step, here we evaluated a small group of COPD subjects (21) and hypothesized that emphysematous lung regions would more readily fill with $^3$He compared with $^{129}$Xe gas under the same physiological conditions. In other words, lung regions that could not be accessed by $^{129}$Xe gas would be more emphysematous, leading to decreased $^{129}$Xe MRI ventilation. To test this hypothesis, we evaluated regional $^3$He MRI ADC using image registration/segmentation methods (20) and X-ray computed tomography (CT) measurements of airway wall thickness and emphysema to probe the structure-function relationships in lung regions accessed by both gases and those that were accessed only by $^3$He gas.

### MATERIALS AND METHODS

**Subjects.** We enrolled 10 COPD subjects in a hyperpolarized $^3$He and $^{129}$Xe MRI study (21), and they provided written, informed consent to a protocol approved by the local research ethics board and Health Canada, which was compliant with the Personal Information Protection and Electronic Documents Act (Canada) and the Health Insurance Portability and Accountability Act (US). COPD subjects were ex-smokers 50–85 yr of age and were categorized according to the global initiative for chronic obstructive lung disease (GOLD) criteria (36), with a smoking history of at least 10 pack-yr.

**Pulmonary function tests.** Spirometry was performed using an EasyOne spirometer (ndd Medizintechnik AG, Zurich, Switzerland), according to the American Thoracic Society guidelines (24). Static lung volumes and the diffusing capacity for carbon monoxide were measured using a whole body plethysmograph (MedGraphics, St. Paul, MN). All spirometry and plethysmography measurements were performed $\sim$1 h following administration of 400 $\mu$g salbutamol inhaled via a spacer device.

**Image acquisition.** MRI was performed on a whole body 3.0-T Discovery 750MR (General Electric Health Care, Milwaukee, WI) MRI system (23). Subjects were instructed to inhale a gas mixture from a 1.0-liter Tedlar bag (Jensen Inert Products) from functional residual capacity, and image acquisition was performed during a 8- to 15-breath hold. To minimize the potential for differences in the levels of inspiration between $^3$He and $^{129}$Xe MRI, extensive coaching was performed before the imaging sessions to ensure subjects could inspire the entire bag and throughout the duration of all imaging sessions. To ensure that each inhalation was performed from functional residual capacity, the subjects were instructed to perform two tidal breaths before inhalation from the bag. The order of $^3$He and $^{129}$Xe MRI acquisition was also randomized for each subject.

$^3$He gas was polarized to 30–40% (HeliSpin), and doses (5 ml/kg body wt) were administered in 1.0-liter Tedlar bags diluted with medical grade nitrogen (N$_2$) (Spectra Gases, Alpha, NJ). $^3$He MRI diffusion-weighted images were acquired using a fast gradient-recalled-echo (FGRE) sequence immediately following inhalation of the $^3$He/N$_2$ gas mixture during breath-hold conditions (33). Two interleaved images were acquired (14-s total data acquisition, repetition time/echo time/flip angle = 7.6 ms/3.7 ms/8°, field of view = 40 $\times$ 40 cm, matrix 128 $\times$ 128, 7 slices, 30-mm slice thickness, 0 gap), with and without additional diffusion sensitization with $b = 1.6$ s/cm$^2$ (gradient amplitude $G$ = 1.94 G/cm, rise and fall time = 0.5 ms, gradient duration = 0.46 ms, diffusion time = 1.46 ms). $^{129}$Xe gas was polarized to 10–60% (XeBox-E10, Xemed) and doses (50:50 $^{129}$Xe/$^3$He) were administered in 1.0-liter Tedlar bags. $^{129}$Xe MRI diffusion-weighted images were acquired using a fast gradient-recalled-echo sequence immediately following inhalation of the $^{129}$Xe/$^3$He gas mixture (21). $^{129}$Xe gas was diluted with $^3$He instead of N$_2$ to try to reduce the differences in the physical properties of the inhaled $^3$He and $^{129}$Xe gas mixtures and better mimic the mixture of gaseous oxygen in air. Two interleaved images (16-s total data acquisition, echo time/repetition time/flip angle = 10 ms/13.5 ms/1°, field of view = 40 $\times$ 40 cm, matrix 128 $\times$ 80, 7 slices, 30-mm slice thickness, 0 gap), with and without additional diffusion sensitization with $b = 12$ s/cm$^2$ ($G = 2.90$ G/cm, rise and fall time = 0.5 ms, gradient duration = 2.0 ms, diffusion time = 5 ms) were acquired (21). A low-dose CT was performed on a 64-slice Lightspeed VCT scanner (GEHC, Milwaukee, WI), as previously described (21).

**Image analysis.** Hyperpolarized $^3$He and $^{129}$Xe MRI ADC maps were generated from diffusion-weighted and nondiffusion-weighted images, as previously described using MATLAB R2007b (The Mathworks, Natick, MA) (20). To ensure ADC was generated for voxels corresponding to ventilated lung regions, the nondiffusion-weighted images were segmented to obtain a binary mask for each slice. The resulting binary masks were applied to the corresponding nondiffusion-weighted images, and the ADC maps were generated on a voxel-by-voxel basis. An overview of the image analysis methodology adapted from (20) is provided in Fig. 1. $^3$He and $^{129}$Xe ADC maps were registered using landmark-based image registration. The trachea and visible major airways were removed semiautomatically, permitting ADC calculation within the lung parenchyma. A single ADC value was calculated for each subject by averaging the mean ADC for each slice to obtain a whole lung slice average ADC. Following registration of the $^3$He and $^{129}$Xe ADC maps, the lung regions of interest (ROI) within the ADC maps accessed by both gases were identified as the intersection (regions of overlap) of the $^3$He and $^{129}$Xe ADC maps; mean ADC within those ROI was generated for each slice and then averaged to obtain a mean $^3$He ADC value accessed by both gases (ADC$_{3He}$). Lung ROI accessed by both $^3$He and $^{129}$Xe were used as a binary mask on the $^3$He ADC maps to calculate mean ADC in $^3$He-only ROI (ADC$_{3He}$). It is important to note that no lung regions were accessed only by $^{129}$Xe gas. $^3$He and $^{129}$Xe ventilation volume (VV) (47) was generated by summing the voxels in the segmented nondiffusion-weighted image following the removal of the trachea and visible major airways.

CT airway and emphysema analysis was performed using VIDA’s Pulmonary Workstation 2.0 (VIDA Diagnostics, Coralville, IA). Wall area percentage (WA%) and lumen area (LA) were measured for the third- to seventh-generation airways (30). The extent of emphysema was estimated using lowest 15th percentile point of the CT lung density histogram (HU$_{15%}$) (8).

### Density and viscosity estimates

The density and viscosity of the inspired $^{23}$Xe gas diluted with $^3$He and the inspired $^3$He gas diluted with N$_2$, as well as the density and viscosity of the pulmonary gases, were estimated. The density of gases ($\rho$) may be estimated using Eq. 1:

$$\rho = \frac{MP}{RT}$$

where $M$ is the molar mass, $P$ is the pressure, $R$ is the universal gas constant, and $T$ is the absolute temperature. The density of a mixture of gases $A$ and $B$ ($\rho_{mixture}$) may be estimated using Eq. 2:

$$\rho_{mixture} = \frac{\rho_A v_A + \rho_B v_B}{v_A + v_B}$$
The viscosity of a mixture of gases $A$ and $B$ may be estimated using the Chapman-Enskog viscosity equation, as previously described (15) and shown below in Eq. 3:

$$\mu = \frac{(M)^{\frac{1}{2}}}{\sigma_A D}.$$

where $M$ is the molecular weight, $\Omega_D$ is the collision integral for diffusion between molecules (31), and $\sigma_C$ is the collision diameter. The viscosity of a mixture of gases $A$ and $B$ ($\mu_{AB}$) may be estimated using Eq. 4:

$$\mu_{AB} = \frac{X_A \mu_A M_A^{\frac{1}{2}} + X_B \mu_B M_B^{\frac{1}{2}}}{X_A M_A^{\frac{1}{2}} + X_B M_B^{\frac{1}{2}}}.$$

where $X_A$ and $X_B$ are the mole fractions of gases $A$ and $B$, respectively, $M_A$ and $M_B$ are the molecular weights of gases $A$ and $B$, respectively, and $\mu_A$ and $\mu_B$ are the respective viscosities of gases $A$ and $B$. This equation was selected because it can represent, with reasonable accuracy, the viscosity of a gas mixture at low or moderate pressures. For the viscosity calculations of the $^3$He-N$_2$ mixture, we used the average volume of $^3$He gas given to each subject (390 ml) to determine the mole fraction, which was $\sim$40/60, and for the $^{129}$Xe-$^4$He mixture it was 50/50. We also calculated the characteristic diffusion length ($L_1$) of the gases and gas mixtures using Eq. 5:

$$L_1 = \sqrt{2D_0\Delta}.$$

where $D_0$ is the diffusion coefficient, and $\Delta$ is the diffusion time.

Density and viscosity calculations for the $^3$He-N$_2$ and $^{129}$Xe-$^4$He gas mixtures administered at 310K and 1 atm are provided in Table 1. The estimated density of $^3$He-N$_2$ mixture and $^{129}$Xe-$^4$He mixture was 0.61 and 2.65 kg/m$^3$, respectively, and the estimated viscosity of $^3$He-N$_2$ mixture and $^{129}$Xe-$^4$He mixture was 1.99 and 2.55 $\times$ 10$^{-4}$ Pa, respectively. The estimated characteristic diffusion length for the $^3$He-N$_2$ mixture and $^{129}$Xe-$^4$He mixture was 460 and 490 $\mu$m, respectively. The calculations for the estimated diffusion coefficient of $^{129}$Xe diluted with $^4$He and air and the diffusion coefficient of $^3$He diluted with N$_2$ and air (21). $^*$Diffusion time was 1.46 ms. $^{\dagger}$Diffusion time was 5 ms.

Table 1. Density and viscosity estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$^3$He</th>
<th>$^4$He</th>
<th>$^{129}$Xe</th>
<th>N$_2$</th>
<th>Air</th>
<th>$^{129}$Xe-$^4$He</th>
<th>$^3$He-N$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M$, g/mol</td>
<td>3</td>
<td>4</td>
<td>129</td>
<td>28</td>
<td>28.85</td>
<td>3.050</td>
<td>3.175</td>
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<td>$\sigma$, A</td>
<td>2.551</td>
<td>2.551</td>
<td>4.047</td>
<td>3.798</td>
<td>3.711</td>
<td>0.843</td>
<td>0.728</td>
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<td>$\Omega_D$, cm$^2$/s</td>
<td>0.623</td>
<td>0.623</td>
<td>1.257</td>
<td>0.869</td>
<td>0.888</td>
<td>0.216</td>
<td>0.211*</td>
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<tr>
<td>$D_0$, cm$^2$/s</td>
<td>2.04</td>
<td>1.77</td>
<td>0.061</td>
<td>0.216</td>
<td>0.218</td>
<td>0.211*</td>
<td>0.826*</td>
</tr>
<tr>
<td>$L_1$, $\mu$m</td>
<td>770$^\dagger$</td>
<td>720$^\dagger$</td>
<td>250$^\dagger$</td>
<td>460$^\dagger$</td>
<td>470$^\dagger$</td>
<td>460$^\dagger$</td>
<td>490$^\dagger$</td>
</tr>
<tr>
<td>$\mu \times 10^{-6}$, Pa</td>
<td>2.033</td>
<td>2.321</td>
<td>2.593</td>
<td>1.984</td>
<td>2.064</td>
<td>2.552</td>
<td>1.993</td>
</tr>
<tr>
<td>$\rho$, kg/m$^3$</td>
<td>0.118</td>
<td>0.157</td>
<td>0.071</td>
<td>1.101</td>
<td>1.140</td>
<td>2.651</td>
<td>0.6095</td>
</tr>
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</table>

$^\dagger$Collision integral for diffusion between molecules; $D_0$, diffusion coefficient; $L_1$, characteristic diffusion length; $\mu$, viscosity; $\rho$, density. $^*$The diffusion coefficient of $^{129}$Xe diluted with $^4$He and air and the diffusion coefficient of $^3$He diluted with N$_2$ and air (21). $^\dagger$Diffusion time = 1.46 ms. $^{\dagger}$Diffusion time = 5 ms.
Table 2. Subject listing of pulmonary function measurements

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age, yr</th>
<th>Sex</th>
<th>BMI, kg/m²</th>
<th>FEV₁, %pred</th>
<th>FVC, %pred</th>
<th>FEV₁/FVC</th>
<th>TLC, %pred</th>
<th>RV, %pred</th>
<th>RV/TLC</th>
<th>IC, %pred</th>
<th>FRC, %pred</th>
<th>DLCO, %pred</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>77</td>
<td>F</td>
<td>19.8</td>
<td>50</td>
<td>76</td>
<td>0.50</td>
<td>114</td>
<td>156</td>
<td>0.63</td>
<td>86</td>
<td>135</td>
<td>22</td>
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<td>2</td>
<td>78</td>
<td>M</td>
<td>26.5</td>
<td>59</td>
<td>82</td>
<td>0.52</td>
<td>102</td>
<td>145</td>
<td>0.45</td>
<td>82</td>
<td>112</td>
<td>—</td>
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<td>50</td>
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<td>M</td>
<td>30.6</td>
<td>77</td>
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<td>0.54</td>
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<td>M</td>
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<td>6</td>
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<td>23.7</td>
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<td>86</td>
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<td>115</td>
<td>121</td>
<td>0.45</td>
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<td>110</td>
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<td>8</td>
<td>76</td>
<td>M</td>
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<td>10</td>
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<td>M</td>
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<td>86</td>
<td>0.27</td>
<td>109</td>
<td>121</td>
<td>42</td>
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</table>

All ± SD 74 ± 4 25.4 ± 5.0 57 ± 24 91 ± 19 0.46 ± 0.14 115 ± 8 159 ± 46 0.53 ± 0.14 85 ± 31 141 ± 35 41 ± 17

F, female; M, male; BMI, body mass index; FEV₁, forced expiratory volume in 1 s; %pred, percent predicted; FVC, forced vital capacity; TLC, total lung capacity; RV, reserve volume; IC, inspiratory capacity; FRC, functional residual capacity; DLCO, carbon monoxide diffusion capacity of the lung; SD, standard deviation. *n = 7.

diluted with N₂ and air were reported elsewhere (21) and are shown in Table 1.

Statistical methods. A two-way mixed-effects repeated-measures ANOVA was used to determine the interaction between ³He and ¹²⁹Xe VV, as well as the interaction between ³He ADC₃HX and ADC₁₀⁻ₓ using IBM SPSS Statistics 20.0 (SPSS, Chicago, IL). Linear regression (r²) and Pearson correlation coefficients (r) were used to determine the relationships for the difference between ³He and ¹²⁹Xe VV with CT HU15%, spirometry, and ADCHO using GraphPad Prism version 4.00 (GraphPad Software, San Diego, CA). In all statistical analyses, results were considered significant when the probability of making a Type I error was <5% (P < 0.05).

RESULTS

Table 2 shows subject demographics and pulmonary function measurements for all 10 COPD ex-smokers (GOLD Class I, n = 1; GOLD Class II, n = 6; GOLD Class III, n = 2; GOLD Class IV, n = 1).

Table 3 shows a subject listing of mean ³He and ¹²⁹Xe whole lung slice average ADC and VV, as well as regional ADC measurements. As previously described in the same group of subjects using static ventilation images (21), ³He VV derived from nondiffusion-weighted images was significantly greater than ¹²⁹Xe VV (³He VV = 5.17 liters, ¹²⁹Xe VV = 4.34 liters, P < 0.0001). There was a significant interaction for VV between inhaled gas (³He and ¹²⁹Xe) and subject (P = 0.04), and this finding may indicate that some COPD subjects had greater ³He and ¹²⁹Xe ventilation differences than others. Importantly, the difference between ³He and ¹²⁹Xe signal-to-noise ratio (SNR) was not significantly correlated with the difference between ³He and ¹²⁹Xe VV (r = −0.25, P = 0.48).

Figure 2 shows ³He and ¹²⁹Xe ADC maps for all slices for two representative subjects. Visually obvious differences in ventilation between ³He and ¹²⁹Xe MRI were apparent in the subject with higher mean ADC for all slices, but to a much lesser extent in the subject with moderate ADC values.

Figure 3 shows the ³He and ¹²⁹Xe ADC maps, as well as the ADC₃HX for a subject with moderately severe COPD. As shown in Table 3, regional analysis showed that mean ADC₃HX (= 0.503 ± 0.119 cm²/s) was significantly greater than mean ADC₁₀⁻ₓ (= 0.470 ± 0.125 cm²/s, P < 0.0001). Moreover, to ensure that ¹²⁹Xe ventilation abnormalities in regions of emphysema were not due to signal attenuation within those regions in the diffusion-weighted images, we compared ventilation measured from the nondiffusion-weighted images (nondiffusion-weighted ¹²⁹Xe VV = 4.27 ± 0.76 liters) and the ADC maps and determined there was no significant ventilation difference (ADC map ¹²⁹Xe VV = 4.31 ± 0.69 liters, P = 0.80). To determine whether airways leading to regions ac-

Table 3. ³He and ¹²⁹Xe MRI WL and regional ADC for all subjects

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>WL ³He MRI</th>
<th>WL ¹²⁹Xe MRI</th>
<th>Regional ³He ADC, cm²/s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VV, liter</td>
<td>ADC, cm²/s</td>
<td>VV, liter</td>
</tr>
<tr>
<td>1</td>
<td>4.25</td>
<td>0.608</td>
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<td>4.99</td>
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<td>5.16</td>
<td>0.332</td>
<td>4.90</td>
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<td>5</td>
<td>6.06</td>
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<td>8</td>
<td>6.24</td>
<td>0.479</td>
<td>4.50</td>
</tr>
<tr>
<td>9</td>
<td>3.10</td>
<td>0.290</td>
<td>2.85</td>
</tr>
<tr>
<td>10</td>
<td>4.83</td>
<td>0.527</td>
<td>3.77</td>
</tr>
</tbody>
</table>

All ± SD 5.17 ± 0.97* 0.478 ± 0.124 4.34 ± 0.71* 0.078 ± 0.015 0.470 ± 0.125* 0.503 ± 0.119*

WL, whole lung; MRI, magnetic resonance imaging; VV, ventilation volume; ADC, apparent diffusion coefficient; ADC₃HX, lung regions of interest with signal at both ³He and ¹²⁹Xe time points; ADC₁₀⁻ₓ, lung regions of interest with signal during the ³He breath hold only. *P value <0.0001 for comparison between WL ³He and ¹²⁹Xe MRI VV. †P value <0.0001 for comparison between regional ³He ADC₃HX and ³He ADC₁₀⁻ₓ.
cessed only by $^3$He gas might be abnormally thickened or obstructed, we compared the lung side with the greatest difference between $^3$He and $^{129}$Xe ventilation with the lung side with the lower $^3$He-$^{129}$Xe difference and observed no significant difference in WA% ($/H_9004/WA%/H_11005/1\%$, $/P/H_11005/0.64$) or LA ($/LA/H_9004/6.7\, \text{mm}^2$, $/P/H_11005/0.33$).

In Fig. 4, the differences between $^3$He and $^{129}$Xe VV are shown, and these were significantly correlated with CT HU$_{15\%}$ ($/r/H_11005/H_11002/0.65$, $/P/H_11005/0.04$) and mean $^3$He ADC$_{100}$ ($/r/H_11005/H_11002/0.70$, $/P/H_11005/0.02$). However, there was no significant correlation for the difference between $^3$He and $^{129}$Xe VV with CT WA% ($/r/H_11005/H_11002/-0.34$, $/P/H_11005/0.33$) for all airway generations or for each of the third- to seventh-generation airways individually. There was also a significant correlation for the difference between $^3$He and $^{129}$Xe VV with forced expiratory volume in 1 s/forced vital capacity ($/r/H_11005/H_11002/-0.79$, $/P/H_11005/0.007$), but not with forced expiratory volume in 1 s ($/r/H_11005/H_11002/-0.48$, $/P/H_11005/0.16$) or diffusing capacity for carbon monoxide ($/r/H_11005/H_11002/-0.37$, $/P/H_11005/0.41$).

### DISCUSSION

Hyperpolarized noble gas MRI has been developed over the last two decades because it has the potential for clinical translation, providing quantitative microstructural and dynamic pulmonary functional information and measurements. However, while $^3$He MRI allows the acquisition of very high-quality images, the global availability and costs are motivating a transition to hyperpolarized $^{129}$Xe MRI. Recently, a pilot study performed with both $^3$He and $^{129}$Xe MRI showed there were visually obvious and quantitatively greater gas distribution abnormalities for $^{129}$Xe MRI in COPD subjects, but not healthy elderly never-smokers (21). The reasons for the difference were not clear, and so in the current evaluation we investigated emphysema as a contributor to the observed differences in $^3$He and $^{129}$Xe ventilation. Accordingly, here we report: 1) significantly greater $^3$He ADC in regions only accessed by $^3$He gas (ADC$_{100}$) compared with regions accessed

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**Fig. 2.** $^3$He and $^{129}$Xe ADC maps for two representative subjects with slices in the anterior-to-posterior direction. The CT density mask shown in green is in the bottom panel for each slice to highlight the areas with attenuation less than −950 HU. A: subject is 78-yr-old man with Stage II COPD: FEV$_1$ = 59% predicted, FVC = 82% predicted, FEV$_1$/FVC = 52%, relative area with attenuation values below −950 HU (RA$_{950}$) = 36.70, lowest 15th percentile (HU$_{15\%}$) = −975. B: subject is a 73-yr-old man with Stage IV COPD: FEV$_1$ = 26% predicted, FVC = 66% predicted, FEV$_1$/FVC = 29%, RA$_{950}$ = 5.00, HU$_{15\%}$ = −930.
Fig. 3. Regional $^3$He and $^{129}$Xe ADC. Shown are $^3$He and $^{129}$Xe ADC maps, with the ADC map for the ROI ventilated only by $^3$He registered to the binary ADC map for those regions accessed by both $^3$He and $^{129}$Xe gas (shown in gray), for the three centermost slices, for a 79-yr-old man with Stage II COPD (FEV$_1$ = 52% predicted, FVC = 104% predicted, FEV$_1$/FVC = 36%, RA$_{55}$ = 31.7, HU$_{15}$ = −972).
by both gases ($^{3}$He ADC$_{1}$), and 2) a significant relationship between the difference in $^{3}$He and $^{129}$Xe VV and the extent of emphysema assessed by CT but not with CT airway WA% measurements.

We observed that mean $^{3}$He ADC in pulmonary ROI accessed only by $^{3}$He gas were elevated relative to the mean $^{3}$He ADC in the remaining lung. This finding suggests that more emphysematous or damaged lung was more readily filled with $^{3}$He compared with $^{129}$Xe gas for the duration of the breath-hold imaging performed in this study. We acknowledge, however, that SNR was lower for $^{129}$Xe than with $^{3}$He MRI (21), and, therefore, there is the potential for regions of the lung with reduced signal intensity to appear as ventilation defects in low SNR $^{129}$Xe images. However, for this investigation, we observed that the difference between $^{3}$He and $^{129}$Xe SNR was not significantly correlated with the difference between $^{3}$He and $^{129}$Xe VV. Moreover, to ensure that $^{129}$Xe ventilation abnormalities in regions of emphysema were not due to signal attenuation within those regions in the diffusion-weighted images, we compared ventilation measured from the nondiffusion-weighted images and the ADC maps and determined there was no significant ventilation difference. We think, therefore, that it is unlikely that this finding is due to SNR alone, and another possible explanation for this observation is that the highly diffusive and less dense and viscous $^{3}$He gas may readily access the slower filling emphysematous lung during the inhalation period and the breath-hold interval. Alternatively, the $^{3}$He gas may fill emphysematous lung regions via collateral channels. Collateral channels have been identified in emphysema (45), and, although resistance to flow through collateral channels is high in the normal lung, in emphysema resistance to flow through collateral channels is lower than through obstructed airways (17). Collateral ventilation has been demonstrated with $^{3}$He MRI (2, 4) and more recently, indirect, nonairway-dependent or collateral ventilation was directly visualized using $^{3}$He MRI in COPD (23) within a single breath hold. For $^{129}$Xe gas, however, it is likely that there are longer time constants for gas filling in emphysematous regions; $^{129}$Xe gas may fill emphysematous regions more slowly by diffusion than $^{3}$He and, therefore, have a much shorter diffusion distance due to the short breath-hold duration, which may contribute to lower $^{129}$Xe signal intensity in regions of significant emphysema. Accordingly, we calculated the characteristic diffusion length for the $^{129}$Xe/$^{3}$He and $^{4}$He/$^{3}$He gas mixtures and showed that the characteristic diffusion length for the $^{129}$Xe atoms is smaller than that for the $^{3}$He atoms. Regardless of the exact mechanisms that are in play, the finding of significant emphysema in lung regions probed only with $^{3}$He gas suggests that these lung regions cannot be penetrated by $^{129}$Xe gas in the same time frame.

Importantly, our laboratory previously showed that the mixture of $^{129}$Xe/$^{4}$He gas administered in this study better approximates the self-diffusion coefficient of oxygen mixed with air in the lung (21), suggesting that $^{129}$Xe MRI ventilation may be a better estimate of ground truth pulmonary ventilation. The $^{3}$He/$^{4}$He gas mixture has a lower density and viscosity than air, and studies have previously demonstrated that inspiring oxygen mixed with helium reduces airway resistance by decreasing turbulent flow (32). This interesting finding suggests that inhaled $^{3}$He gas and its mixtures may be less sensitive to peripheral airway obstruction. Clearly, there are advantages to utilizing inhaled gases such as $^{129}$Xe and mixtures thereof that may have increased sensitivity to airway obstruction and emphysema for targeted treatments and interventions. On the other hand, the increased density/viscosity and lower diffusion coefficient of $^{129}$Xe may limit signal from those regions of the lung most affected by emphysema or receiving collateral flow. Clearly, both gases provide application-specific advantages.

Importantly, we did not detect a significant correlation for the difference in $^{3}$He and $^{129}$Xe ventilation and WA%. However, we cannot ascertain whether this might be the case regionally, wherein specific airways leading to regions accessed only by $^{3}$He gas might be abnormally thickened or obstructed. In other words, it is possible that the whole lung estimates of WA% might not be representative of regional differences. We investigated this possibility by regionally comparing the lung side with the greatest difference between $^{3}$He and $^{129}$Xe ventilation with the lung side with the lower $^{3}$He-$^{129}$Xe difference and observed no significant difference in WA% or LA. However, we must also acknowledge that, for some subjects, the lung region that showed a $^{3}$He-$^{129}$Xe ventilation difference was very small, and this may have also contributed to the lack of significant relationship observed with WA%.

A large number of studies have investigated convective and diffusive gas transport within the lung using multiple-breath washout studies (3, 6, 40, 41) and modeling (43), and it is evident from these previous studies that the inhaled gas physical properties are important factors affecting ventilation distribution within the lung. Clearly there is significant work to be done to better understand how the different properties of $^{3}$He and $^{129}$Xe gas affect ventilation distribution and, most importantly, what information these differences in ventilation distribution provide us regarding the sensitivity of the different...
gases and their mixtures for detecting airway and ventilation abnormalities. Directely visualizing the distribution of the gases using mixtures of $^3$He and $^{129}$Xe with well-controlled viscosities and densities during a breath hold in the same subjects using time-resolved imaging sequences, as was recently performed with $^3$He MRI (23), could certainly be utilized to test some of our important hypotheses regarding delayed/collateral ventilation within emphysematous lung regions in COPD subjects. Moreover, while several modeling studies have aimed to evaluate gas transport in the lung using $^3$He and $^{129}$Xe (22, 25), more studies of this nature are required to fully understand the role of the gas properties on regional ventilation distribution with noble gas MRI, as well as to determine the gas mixture that best approximates the distribution of typical room air within the lung.

We recognize that this work was limited by the small number of subjects evaluated, meaning that extrapolation of these results to a general COPD population cannot be confirmed until studies with larger sample sizes are performed. This study was also limited by the different diffusion times and $b$-values that were utilized for $^3$He and $^{129}$Xe image acquisition, and, therefore, we may be probing different lung structures. Previous studies have demonstrated that greater diffusion time results in greater diffusion distances, and there is, therefore, the potential to probe a fundamentally different spatial scale (49). However, significant and strong correlations have been previously observed between $^3$He and $^{129}$Xe ADC (21), suggesting that both methods are probing similar spatial dimensions. In addition, the acquisition of clinical measurements, such as dyspnea scores and measurements of exercise tolerance, for direct comparison to $^3$He and $^{129}$Xe MRI measurements may have aided in determining the clinical meaning of these differences. Future studies should aim to evaluate the differences between $^3$He and $^{129}$Xe MRI in terms of their relationships with clinical measurements, as well as the relative sensitivities for detecting improvements following treatment or interventions.

In summary, we used regional hyperpolarized $^3$He and $^{129}$Xe ADC image registration/segmentation methods to quantify ADC in the lung regions accessed by both gases and the lung regions accessed by $^3$He gas only. We reported a significantly greater mean ADC in the lung regions accessed by $^3$He gas only than in the remaining lung tissue, and a significant relationship between the difference in $^3$He and $^{129}$Xe VV and emphysema. In COPD, the lower resistance to flow within emphysematous lung regions is a potential determinant of the differences observed in $^3$He and $^{129}$Xe ventilation defects.

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DISCLOSURES

H. O. Coxson has a consultancy with Spiration and GSK. He also has one service contract related to the quantitative analysis of lung CT scans for spiration and two service contracts related to the quantitative analysis of lung CT scans for GSK. He has also received payment for lectures from AstraZeneca, and travel/accommodations for meetings from Spiration, AstraZeneca, and GSK. The authors paid $100,000 annually for the use of an onsite hyperpolarized $^3$He gas polarizer [Helispin, General Electric Health Care (GEHC), Durham, NC]. We also paid $60,000 for 4-wk use of a $^{129}$Xe gas polarizer model NeBox-E10 (Xenned LLC) during the period of September–October 2011.

AUTHOR CONTRIBUTIONS


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