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Pulmonary Imaging Biomarkers of Gas Trapping and Emphysema in COPD: $^3$He MR Imaging and CT Parametric Response Maps

**Purpose:** To directly compare magnetic resonance (MR) imaging and computed tomography (CT) parametric response map (PRM) measurements of gas trapping and emphysema in ex-smokers both with and without chronic obstructive pulmonary disease (COPD).

**Materials and Methods:**
Participants provided written informed consent to a protocol that was approved by a local research ethics board and Health Canada and was compliant with the HIPAA (Institutional Review Board Reg. #00000940). The prospectively planned study was performed from March 2014 to December 2014 and included 58 ex-smokers (mean age, 73 years ± 9) with (n = 32; mean age, 74 years ± 7) and without (n = 26; mean age, 70 years ± 11) COPD. MR imaging (at functional residual capacity plus 1 L), CT (at full inspiration and expiration), and spirometry or plethysmography were performed during a 2-hour visit to generate ventilation defect percent (VDP), apparent diffusion coefficient (ADC), and PRM gas trapping and emphysema measurements. The relationships between pulmonary function and imaging measurements were determined with analysis of variance (ANOVA), Holm-Bonferroni corrected Pearson correlations, multivariate regression modeling, and the spatial overlap coefficient (SOC).

**Results:** VDP, ADC, and PRM gas trapping and emphysema (ANOVA, $P < .001$) measurements were significantly different in healthy ex-smokers than they were in ex-smokers with COPD. In all ex-smokers, VDP was correlated with PRM gas trapping ($r = 0.58, P < .001$) and with PRM emphysema ($r = 0.68, P < .001$). VDP was also significantly correlated with PRM in ex-smokers with COPD (gas trapping: $r = 0.47$ and $P = .03$; emphysema: $r = 0.62$ and $P < .001$) but not in healthy ex-smokers. In a multivariate model that predicted PRM gas trapping, the forced expiratory volume in 1 second normalized to the forced vital capacity (standardized coefficients [β]: $P = .001$) and airway wall area percent ($P = .02$) were significant predictors. PRM emphysema was predicted by the diffusing capacity for carbon monoxide ($P = .003$; emphysema: $P = .001$) and airway wall area percent ($P = .02$). Helium 3 ADC values were significantly elevated in PRM gas-trapping regions ($P < .001$). The spatial relationship for ventilation defects was significantly greater with PRM gas trapping than with PRM emphysema in patients with mild (for gas trapping, SOC = 36% ± 28; for emphysema, SOC = 1% ± 2; $P = .001$) and moderate (for gas trapping, SOC = 34% ± 28; for emphysema, SOC = 7% ± 15; $P = .006$) COPD. For severe COPD, the spatial relationship for ventilation defects with PRM emphysema (SOC = 64% ± 30) was significantly greater than that for PRM gas trapping (SOC = 38% ± 18; $P = .01$).

**Conclusion:** In all ex-smokers, ADC values were significantly elevated in regions of PRM gas trapping, and VDP was quantitatively and spatially related to both PRM gas trapping and PRM emphysema. In patients with mild to moderate COPD, VDP was related to PRM gas trapping, whereas in patients with severe COPD, VDP correlated with both PRM gas trapping and PRM emphysema.

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An earlier incorrect version of this article appeared online. This article was corrected on January 12, 2016.
Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation.

**Advances in Knowledge**

- In 58 ex-smokers with \((n = 32)\) and without \((n = 26)\) chronic obstructive pulmonary disease (COPD), \(^3\)He MR imaging ventilation defect percent (VDP) was significantly correlated with inspiratory and expiratory CT parametric response map (PRM) measurements of gas trapping \((r = 0.58, P < .001)\) and emphysema \((r = 0.68, P < .001)\).

- In a significant multivariate model, \(^3\)He apparent diffusion coefficient (ADC) values were also significantly correlated with PRM gas trapping \((r = 0.55, P < .001)\) and PRM emphysema \((r = 0.62, P < .001)\).

- In all ex-smokers, spatial CT and MR imaging relationships showed that \(^3\)He MR imaging ADC values were significantly elevated in regions of PRM gas trapping \((P < .001)\).

- In patients with mild (for gas trapping, the forced inspiratory volume in 1 second normalized to the forced vital capacity (standardized coefficient \(\beta_i = −0.69, P = .001)\) and airway wall area percent \(\beta_s = −0.22, P = .02)\) were significant predictors, whereas PRM emphysema was predicted by MR imaging VDP \(\beta_e = 0.41, P = .001)\) and diffusing capacity for carbon monoxide \(\beta = −0.29, P = .03)\).

- In all ex-smokers, spatial overlap coefficient [SOC] = 36% ± 28; for emphysema, SOC = 1% ± 2; \(P = .001)\) and moderate (for gas trapping, SOC = 34% ± 28; for emphysema, SOC = 7% ± 15; \(P = .006)\) COPD \((n = 25)\), \(^3\)He MR imaging ventilation defects were quantitatively and spatially related to PRM gas trapping, whereas in patients with severe COPD \((n = 7)\), MR imaging ventilation defects were quantitatively and spatially related to both PRM gas trapping and emphysema (for gas trapping, SOC = 36% ± 18; for emphysema, SOC = 64% ± 30; \(P = .01)\).

**Implications for Patient Care**

- In ex-smokers with mild \((P = .001)\) and moderate \((P = .006)\) COPD, regions of PRM gas trapping were spatially and quantitatively related to MR imaging ventilation abnormalities, whereas in patients with severe COPD, ventilation abnormalities were related to both PRM gas trapping \((P = .009)\) and PRM emphysema \((P = .01)\).

- While \(^3\)He MR imaging is unlikely to be translated clinically, this information may be used to help better understand PRM gas trapping measurements, which may be more widely adopted for clinical phenotyping in patients with COPD.

Single photon emission computed tomography and positron emission tomography have also been used to depict pulmonary function abnormalities in patients with COPD \((14,15)\). In addition, hyperpolarized \(^3\)He MR imaging apparent diffusion coefficients (ADCs) reflect the size of the lung acinar units. Such values are abnormally elevated in smokers with and without COPD \((20,21)\). \(^3\)He MR imaging ventilation defects may reflect both airways disease and emphysema in patients with advanced COPD, but in mild COPD and asthma, ventilation defects reflect airflow disease \((22,23)\). Despite the potential of \(^3\)He MR imaging, limited use to differentiate among current and former smokers with and without COPD, but the clinical relevance and cause of PRM measurements of airways disease is uncertain \((13)\).

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Content codes: CH CT MR

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**Abbreviations:**

- ADC = apparent diffusion coefficient
- COPD = chronic obstructive pulmonary disease
- \(D_{\text{CO}}\) = diffusing capacity for carbon monoxide
- \(FEV_1\) = forced expiratory volume in 1 second
- \(FEV_1/FVC\) = \(FEV_1\) normalized to the forced vital capacity
- GOLD = Global initiative for Chronic Obstructive Lung Disease
- PRM = parametric response map
- SOC = spatial overlap coefficient
- VDP = ventilation defect percent

**Author contributions:**

Guarantor of integrity of entire study, G.P.; study concepts/ study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, D.P.I.C., N.Z., F.G., D.P., M.K., G.P.; clinical studies, D.P.I.C., D.G.M., G.P.; experimental studies, D.P.I.C., N.Z., F.G., D.G.M.; statistical analysis, D.P.I.C., F.G., D.P., M.K., G.P.; and manuscript editing, D.P.I.C., N.Z., D.P., M.K., G.P.

Conflicts of interest are listed at the end of this article.
and unpredictable global quantities and high cost have hampered clinical translation. We wanted to determine the quantitative and spatial relationships of PRM gas trapping and PRM emphysema measurements with MR imaging measurements of parenchymal tissue integrity (ie, ADC) and ventilation because these are clinically important imaging findings and phenotypes of COPD. Thus, our objective was to directly compare MR imaging and CT PRM measurements of gas trapping and emphysema in ex-smokers with and without COPD.

Materials and Methods

Study Volunteers

Participants provided written informed consent to a protocol that was approved by a local research ethics board and Health Canada and that was compliant with the Health Insurance Portability and Accountability Act (Institutional Review Board Reg. #00000940). The study was prospectively planned and performed from March 2014 to December 2014.

MR Imaging

Acquisition of conventional proton (hydrogen 1 \(^{1}\)H), \(^{3}\)He static ventilation, and \(^{3}\)He diffusion-weighted MR images was performed with a whole-body 3-T Discovery MR750 system (GE Healthcare, Milwaukee, Wis), as was previously described (24). Polarization (Polarclean; HeliSpin, Durham, NC) was achieved to 40%, and the magnetized gas was diluted with medical-grade nitrogen 2 (N\(_2\)) gas to a level of 5 mL per kilogram of body weight. Coronal images (multisection, with no gaps) were acquired with breath holding from functional residual capacity after subjects inhaled a 1-L gas mixture (helium 4 and N\(_2\) for \(^{1}\)H MR imaging and \(^{3}\)He and N\(_2\) for \(^{3}\)He MR imaging). Hydrogen 1 MR imaging was performed with a whole-body radiofrequency coil and a fast spoiled gradient-recalled-echo sequence with a partial echo and the following parameters: total acquisition time, 12 sec; repetition time msec/echo time msec, 4.3/1.0; flip angle, 30°; field of view, 40 × 40 cm; matrix, 128 × 80 (zero padded to 128 × 128); partial-echo percent, 62.5%; bandwidth, 62.50 kHz; one excitation; 14 sections; section thickness, 15 mm; zero gap. \(^{3}\)He static ventilation MR images were acquired by using a fast spoiled gradient-recalled-echo method with a partial echo and the following parameters: total acquisition time, 10 sec; 3.8/1.0; flip angle, 7°; field of view, 40 × 40 cm; matrix, 128 × 80 (zero-padded to 128 × 128); partial-echo percent, 62.5%; bandwidth, 62.50 kHz; one excitation; 14 sections; section thickness, 15 mm; zero gap. \(^{3}\)He diffusion-weighted MR images were also acquired by using fast spoiled gradient-recalled-echo sequence with centric k-space sampling and the following parameters: total acquisition time, 14 sec; 6.8/4.5; flip angle, 8°; field of view, 40 × 40 cm; matrix, 128 × 128; bandwidth, 62.50 kHz; one excitation; seven sections; section thickness, 30 mm; zero gap. Two interleaved images were also acquired, both with and without additional diffusion sensitization and the following parameters: 1.94 G/cm; \(b = 1.6 \text{ sec/cm}^2\); rise and fall time, 0.5 msec; gradient duration, 0.46 msec; diffusion time, 1.46 msec.

CT Imaging

As was previously described, CT images were acquired with subjects in the supine position approximately 10 minutes before MR imaging and 1 hour after administration of salbutamol. A 64-section Lightspeed VCT imager (GE Healthcare, Milwaukee, Wis) was used to acquire breath-hold images at full inspiration and full expiration by using a spiral acquisition approach and the following parameters: detector configuration, 64 × 0.625 mm; peak voltage, 120 kVp; effective current, 100 mA; rotation time, 500 msec; pitch, 1.0; section thickness, 1.25 mm; number of sections, 200–250, depending on patient size; matrix, 512 × 512 (25). CT data were reconstructed by using a standard convolution kernel to 1.25 mm. The IMPACT CT patient dosimetry calculator (http://www.impactsan.org/ctdosimetry.htm), which is based on the United Kingdom Health Protection Agency NRPB-SR250, and our manufacturer settings were used to calculate total effective dose (1.8 mSv for inspiration and 1.4 mSv for expiration). For inspiration CT, size-specific dose estimate was calculated to be 5–9 mGy on the basis of volumetric CT dose index of 4.4 mGy, total effective dose of 1.8 mSv, and size-dependent conversion factor of 1.00–2.00, an approach used by Christener et al (26,27). For expiration CT, the size-specific dose estimate was 3–7 mGy on the basis of volumetric CT dose index of 3.3 mGy, total effective dose of 1.4 mSv, and size-dependent conversion factor of 1.00–2.00.

MR Image Analysis

As was previously described, \(^{3}\)He MR imaging semiautomated segmentation was performed by a single observer (D.P., with 3 years of experience) to generate ventilation defect percent (VDP), with the ventilation defect volume normalized to \(^{1}\)H MR imaging thoracic cavity volume (28). A detailed description of this process is provided in Appendix E1 (online).

CT Image Analysis

CT images were analyzed with Pulmonary Workstation 2.0 (VIDA Diagnostics, Coralville, IA) by a single observer (D.P.I.C., with 2 years of experience) to measure wall area percent and segment the lung regions. These analyses are fully automated, as was previously described and validated (29,30). The relative area of the CT attenuation histogram of less than −950 HU and −856 HU at inspiratory and expiratory CT, respectively, were determined by using MATLAB (Mathworks, Natick, Mass).

Briefly, pulmonary PRM results can be generated by coregistering inspiratory and expiratory CT images and classifying voxel values on the basis of their specific thresholds into healthy, gas-trapping, or emphysema tissue components. The specific details of this process are given in Appendix E1 (online).

Statistics

Analysis of variance was performed with post hoc analysis and Tukey correction to determine differences in
Table 1

**Subject Demographics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy Ex-Smokers (n = 25)</th>
<th>All Ex-smokers with COPD (n = 32)</th>
<th>GOLD I Ex-smokers (n = 12)</th>
<th>GOLD II Ex-smokers (n = 13)</th>
<th>GOLD III/IV Ex-smokers (n = 7)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>70 ± 11</td>
<td>74 ± 7</td>
<td>75 ± 8</td>
<td>74 ± 8</td>
<td>73 ± 6</td>
<td>.104</td>
</tr>
<tr>
<td>No. of male subjects</td>
<td>15</td>
<td>25</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>...</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30 ± 4</td>
<td>26 ± 3</td>
<td>26 ± 3</td>
<td>27 ± 3</td>
<td>26 ± 4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking history (pack-years)</td>
<td>28 ± 16</td>
<td>43 ± 26</td>
<td>31 ± 17</td>
<td>50 ± 28</td>
<td>51 ± 30</td>
<td>.012</td>
</tr>
<tr>
<td>FEV₁*</td>
<td>103 ± 19</td>
<td>73 ± 27</td>
<td>101 ± 14</td>
<td>64 ± 10</td>
<td>39 ± 7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>80 ± 7</td>
<td>55 ± 11</td>
<td>63 ± 4</td>
<td>55 ± 8</td>
<td>40 ± 5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total lung capacity*</td>
<td>96 ± 13</td>
<td>110 ± 16</td>
<td>103 ± 34†</td>
<td>106 ± 17</td>
<td>115 ± 20</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Inspiratory capacity*</td>
<td>103 ± 23</td>
<td>91 ± 27</td>
<td>100 ± 23</td>
<td>94 ± 32</td>
<td>70 ± 10</td>
<td>.078</td>
</tr>
<tr>
<td>Residual volume*</td>
<td>100 ± 21</td>
<td>140 ± 39</td>
<td>123 ± 16</td>
<td>134 ± 33</td>
<td>180 ± 53</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DLco*</td>
<td>89 ± 18†</td>
<td>68 ± 23</td>
<td>73 ± 29†</td>
<td>66 ± 24</td>
<td>51 ± 15</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note.—Unless otherwise indicated, data are mean plus or minus standard deviation. \( P \) values were determined by analysis of variance with Tukey correction.

* Percent of predicted value.
† \( n = 31 \).
‡ \( n = 11 \).
§ \( n = 25 \).

Results

**Participant Characteristics**

Table 1 shows demographic characteristics and pulmonary function measurements for 58 participants (mean age, 73 years ± 9), including 26 ex-smokers with normal spirometry results (mean age, 70 years ± 11) and 32 ex-smokers with COPD (mean age, 74 years ± 7). Patient subgroups were significantly different with respect to body mass index (P < .001), smoking history (pack-years, P = .01), forced expiratory volume in 1 second (FEV₁, P < .001), FEV₁ normalized to the forced vital capacity (FEV₁/FVC, P < .001), and diffusing capacity for carbon monoxide (DLco, P < .001), but not age (P = .1).

**Qualitative Ventilation and PRM Results**

Figure 1 shows MR and CT images in a representative ex-smoker with no airflow limitation and three ex-smokers with COPD. In the two ex-smokers with more advanced COPD (an 84-year-old man with Global Initiative for Chronic Obstructive Lung Disease [GOLD] grade II; FEV₁, 52% of predicted value; FEV₁/FVC, 44%; and a 67-year-old woman with GOLD III disease; FEV₁, 33% of predicted value; FEV₁/FVC, 39%), more pronounced ³He ventilation defects; a greater number of PRM voxels, a finding reflective of emphysema; and elevated ADC values were present. Alternatively, in two ex-smokers with mild or no disease (a 53-year-old man with FEV₁, 83% of predicted value and FEV₁/FVC, 77% and a 69-year-old man with GOLD I disease; FEV₁, 89% of predicted value; FEV₁/FVC, 69%), more homogeneous ventilation and a greater number of PRM voxels were present, findings reflective of normal or healthy tissue.

**Ventilation and PRM Measurements by GOLD Severity**

Table 2 summarizes the measurements for MR imaging ventilation and emphysema and for CT-derived gas trapping, emphysema, and PRM measurements. In ex-smokers with COPD, VDP (P < .001), ADC (P < .001), relative area of the CT attenuation histogram of less than −950 HU (P < .001), PRM gas trapping (P < .001), and emphysema (P < .001) were significantly greater than in ex-smokers with no airflow limitation. There were no significant differences in CT airway measurements of wall area percent (P = .9).

Figure 2 shows that VDP was significantly different between healthy ex-smokers (8% ± 4) and ex-smokers with moderate (GOLD II, 20% ± 11, P < .001) to severe (GOLD III/IV, 37% ± 9, P < .001) COPD, but not in ex-smokers with mild COPD (GOLD I, 11% ± 6, P = .5). VDP was also significantly different between those with GOLD I and GOLD II disease (P = .04), those with GOLD II and GOLD II/IV disease (P < .001), and those with GOLD I and GOLD III/IV disease (P < .001). PRM measurements were significantly different for healthy ex-smokers and patients with COPD.
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Relationships for MR Imaging and PRM Measurements

Tables 3 and 4 show the Holm-Bonferroni-corrected Pearson correlations and multivariate regression model results for CT-derived PRM gas trapping and

(gas trapping, 13% ± 10; emphysema, 0.5% ± 0.5) and those with moderate (GOLD II: gas trapping, 27 ± 14%, $P = .003$; emphysema, 8 ± 11%, $P = .003$) to severe (GOLD III/IV: gas trapping, 41 ± 8%, $P < .001$; emphysema, 13 ± 12%, $P < .001$) COPD. PRM gas trapping was significantly different between ex-smokers and those with mild COPD (GOLD I, 31% ± 11, $P < .001$). PRM emphysema was significantly different between those with GOLD I and GOLD III/IV disease ($P = .03$). ADC values were significantly different between healthy ex-smokers (0.29 cm²/s ± 0.08) and those with GOLD II (0.36 cm²/s ± 0.06, $P = .02$) and GOLD III/IV (0.41 ± 0.05 cm²/s, $P < .001$) disease, but not those with GOLD I disease (0.34 cm²/s ± 0.03, $P = .2$).

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Relationships for MR Imaging and PRM Measurements

Tables 3 and 4 show the Holm-Bonferroni-corrected Pearson correlations and multivariate regression model results for CT-derived PRM gas trapping and
emphysema measurements. In ex-smokers with COPD only, PRM gas trapping
was significantly related to FEV1/FVC (\( r = -0.58, P = .003 \)), ADC (\( r = 0.53, P = .01 \)), and VDP (\( r = 0.47, P = .03 \)). PRM emphysema was significantly correlated with FEV1 (\( r = -0.43, P = .03 \)), HEV/FVC (\( r = -0.52, P = .008 \)), DLco (\( r = -0.69, P < .001 \)), and VDP (\( r = 0.62, P < .001 \)) in ex-smokers with COPD. Figure 3 shows linear regressions for PRM gas trapping and emphysema and shows that VDP was significantly correlated with PRM gas trapping (\( r = 0.58, P < .001 \)) and PRM emphysema (\( r = 0.68, P < .001 \)) in all subjects and in ex-smokers with COPD (gas trapping: \( r = 0.47, P = .03 \); emphysema: \( r = 0.62, P < .001 \)), but not in healthy ex-smokers. ADC was also significantly correlated with PRM gas trapping (\( r = 0.53, P < .001 \)) and PRM emphysema (\( r = 0.62, P < .001 \)) in all subjects and in ex-smokers with COPD (gas trapping: \( r = 0.53, P = .01 \); emphysema: \( r = 0.69, P < .001 \)), but not in healthy ex-smokers. Figure 3 also shows Bland-Altman plots for PRM gas trapping and emphysema. In relation to VDP, there was a negative bias for PRM gas trapping (\( -9\% \pm 12 \); 95% confidence interval: \(-32\%,15\%)\) and a positive bias for PRM emphysema (\( 11\% \pm 9 \); 95% confidence interval: \(-6\%,28\%)\). Table 4 shows that, in the multivariate regression model that explains PRM gas trapping, FEV1/FVC (standardized coefficient \( \beta_1 = 0.69, P = .001 \)) and wall area percent (\( \beta_2 = 0.22, P = .02 \)) make significant contributions, whereas, for the PRM emphysema model, DLco (\( \beta_3 = -0.29, P = .03 \)) and VDP (\( \beta_4 = 0.41, P = .001 \)) were significant.

**Spatial and Regional Relationships**

Given the significant quantitative relationships between MR imaging and PRM COPD measurements, we evaluated the spatial correlations of ventilation defects with PRM measurements. Qualitative examples are shown in Figure 4 for an ex-smoker with mild COPD and another with GOLD III COPD. The spatial relationship between ventilation defects and PRM gas trapping is more obvious in the ex-smoker with mild disease, whereas colocalization of PRM emphysema and ventilation defects is present in the ex-smoker with severe airflow limitation.

To explore these relationships in more detail, we quantitatively evaluated the spatial overlap of PRM gas trapping and emphysema voxels with ADC and ventilation defects (Table 5, Fig 5). As shown in Figure 5, 3He ADC was significantly elevated in areas of PRM gas trapping compared with healthy tissue (\( P = .004 \) in a healthy ex-smoker, \( P = .01 \) in patients with GOLD I and GOLD II disease, \( P = .03 \) in a patient with GOLD III/IV disease). Helium 3 ADC values were also significantly greater in the regions of PRM emphysema compared with regions of PRM gas trapping in patient with GOLD I disease (\( P = .03 \)), but not in healthy ex-smokers or those with GOLD II, III, or IV disease. Table 5 shows that, in mild and moderate COPD, the MR imaging spatial overlap coefficient (SOC) for 3He ventilation defects with PRM gas trapping tissue (MR imaging SOC = \( 36\% \pm 28 \) and MR imaging SOC = \( 34\% \pm 28 \)) in those with mild and moderate disease, respectively) was significantly greater than for PRM emphysema.

### Table 2

<table>
<thead>
<tr>
<th>Imaging Measurements</th>
<th>Healthy Ex-Smokers (( n = 26 ))</th>
<th>Ex-smokers with COPD All (( n = 32 ))</th>
<th>GOLD I (( n = 12 ))</th>
<th>GOLD II (( n = 13 ))</th>
<th>GOLD III/IV (( n = 7 ))</th>
<th>( P^\dagger ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>2 ± 1</td>
<td>10 ± 9</td>
<td>6 ± 4</td>
<td>10 ± 10</td>
<td>15 ± 12</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>RA seq (%)</td>
<td>14 ± 10</td>
<td>37 ± 18</td>
<td>34 ± 13</td>
<td>35 ± 20</td>
<td>53 ± 16</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6G wall area percent (%)</td>
<td>65 ± 2</td>
<td>65 ± 2</td>
<td>65 ± 2</td>
<td>66 ± 2</td>
<td>66 ± 2</td>
<td>.882</td>
</tr>
<tr>
<td>3He MR imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilation (%)</td>
<td>92 ± 4</td>
<td>20 ± 13</td>
<td>88 ± 6</td>
<td>80 ± 11</td>
<td>63 ± 9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VDP (%)</td>
<td>8 ± 4*</td>
<td>12 ± 4</td>
<td>12 ± 6</td>
<td>20 ± 11</td>
<td>37 ± 9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ADC (cm(^2/)sec)</td>
<td>0.29 ± 0.08*</td>
<td>0.36 ± 0.06*</td>
<td>0.34 ± 0.03*</td>
<td>0.36 ± 0.06*</td>
<td>0.41 ± 0.05*</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PRM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy (%)</td>
<td>85 ± 11</td>
<td>60 ± 18</td>
<td>64 ± 13</td>
<td>63 ± 20</td>
<td>46 ± 17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gas trapping (%)</td>
<td>13 ± 10</td>
<td>31 ± 12</td>
<td>31 ± 11</td>
<td>27 ± 14</td>
<td>41 ± 9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Emphysema (%)</td>
<td>0.5 ± 0.5</td>
<td>7 ± 10</td>
<td>3 ± 3</td>
<td>8 ± 11</td>
<td>13 ± 12</td>
<td>.001</td>
</tr>
</tbody>
</table>

* \( n = 24 \), † \( n = 30 \), ‡ \( n = 11 \), § \( n = 12 \).

Note.—Data are mean plus or minus standard deviation. \( P \) values were determined by analysis of variance with Tukey correction. RA seq = relative area of the lung with attenuation values less than \(-950\) HU at inspiration CT, RA seq = relative area of the lung with attenuation values less than \(-856\) HU at expiration CT, 6G = sixth-generation airway.
In patients with severe COPD, the CT SOC for $^3$He ventilation defects with PRM emphysema (CT SOC = 64% ± 30) was significantly greater than that for PRM gas trapping voxels (CT SOC = 36% ± 18; $P = .01$). Therefore, for patients with severe COPD, PRM emphysema was mainly localized within regions of $^3$He ventilation defects. In addition, in patients with severe COPD, MR imaging SOC for $^3$He ventilation defects with PRM gas trapping voxels (SOC = 62% ± 25) was significantly greater than that for PRM emphysema (SOC = 11% ± 20; $P = .009$). Hence, in patients with severe COPD, regions of

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**Figure 2:** $^3$He MR imaging ventilation and PRM measurements by COPD grade. A, Box plot shows $^3$He MR imaging VDP in ex-smokers without COPD (8% ± 4) and with GOLD I (11% ± 6), GOLD II (20% ± 11), and GOLD III/IV (37% ± 9) disease. There was a significant difference in VDP between ex-smokers without COPD and those with GOLD II disease ($P < .001$), ex-smokers without COPD and those with GOLD III/IV disease ($P < .001$), with GOLD I and GOLD II disease ($P = .04$), those with GOLD II and GOLD III/IV disease ($P < .001$), and those with GOLD I and GOLD III/IV disease ($P < .001$). B, Box plot shows PRM-derived gas-trapping voxels in ex-smokers without COPD (13% ± 10) and ex-smokers with GOLD I (31% ± 11), GOLD II (27% ± 14), and GOLD III/IV (41% ± 8) disease. There is a significant difference in PRM gas trapping between ex-smokers without COPD and those with GOLD I disease ($P < .001$), ex-smokers without COPD and those with GOLD II disease ($P = .003$), and ex-smokers without COPD and those with GOLD III/IV disease ($P < .001$). C, Box plot shows $^3$He MR imaging ADC values in ex-smokers without COPD (0.29 cm$^2$/s ± 0.08) and those with GOLD I (0.34 cm$^2$/s ± 0.03), GOLD II (0.36 cm$^2$/s ± 0.06), and GOLD III/IV (0.41 cm$^2$/s ± 0.05) disease. There is a significant difference in ADC values between ex-smokers without COPD and those with GOLD II disease ($P = .02$), ex-smokers without COPD and those with GOLD III/IV disease ($P < .001$), and those with GOLD I and GOLD III/IV disease ($P = .04$). D, Box plot shows PRM-derived emphysema voxels in ex-smokers without COPD (0.5% ± 0.5) and those with GOLD I (3% ± 3), GOLD II (8% ± 11), and GOLD III/IV (13% ± 12) disease. There is a significant difference in PRM emphysema between ex-smokers without COPD and those with GOLD II disease ($P = .009$), ex-smokers without COPD and those with GOLD III/IV disease ($P = .001$), and those with GOLD I and GOLD III/IV disease ($P = .03$). Significant differences between subgroups ($P < .05$) were determined with analysis of variance and post hoc Tukey analysis. Error bars = standard deviation.
3He ventilation defects mostly consisted of PRM gas trapping voxels, although there was a mixture of PRM gas trapping and emphysema.

**Discussion**

We evaluated 58 ex-smokers in the first direct comparison of PRM and MR imaging measurements of COPD. We acquired inspiration and expiration CT images and noble gas MR images within 1 hour and observed the following findings: (a) with increasing severity of airflow limitation, PRM gas trapping, PRM emphysema, ADC, and VDP measurements were significantly greater; (b) 3He ventilation and PRM measurements were correlated in COPD but not in healthy ex-smokers; (c) in a multivariate model that predicted PRM gas trapping, wall area percent and FEV1/FVC were significant, whereas VDP and DLCO were significant for PRM emphysema; and (d) 3He ADC values were significantly elevated in regions of PRM gas trapping, and there were quantitative and spatial correlations for both PRM gas trapping and emphysema with 3He ventilation defects that differed according to COPD severity.

PRMs are used to classify lung tissue on the basis of the presence of pulmonary air, either as a consequence of emphysema and gas trapping from airways disease and/or emphysema (9). We were curious about the potential relationships between PRM and MR imaging phenotypes of COPD, especially because both ventilation defects and PRM gas trapping have been suggested as biomarkers of small airways disease. First, we observed that, with increasing severity of airflow limitation, PRM gas trapping, PRM emphysema, ADC, and VDP measurements were significantly greater. We also noted that 3He VDP and PRM measurements were correlated in ex-smokers with COPD but not in ex-smokers with normal pulmonary function. This finding might be expected because correlations in ex-smokers with mainly normal pulmonary function are statistically difficult to ascertain in small sample sizes, since the range of values for normal lung function is small (31).

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy Ex-Smokers*</th>
<th>PValue</th>
<th>Ex-Smokers with COPD†</th>
<th>PValue</th>
<th>Healthy Ex-Smokers*</th>
<th>PValue</th>
<th>Ex-Smokers with COPD†</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (%)</td>
<td>−0.09</td>
<td>.9</td>
<td>−0.29</td>
<td>.1</td>
<td>−0.11</td>
<td>.9</td>
<td>−0.43</td>
<td>.03</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>−0.33</td>
<td>.6</td>
<td>−0.58</td>
<td>.003</td>
<td>−0.34</td>
<td>.6</td>
<td>−0.52</td>
<td>.008</td>
</tr>
<tr>
<td>DLCO (%)</td>
<td>−0.06</td>
<td>.8</td>
<td>−0.36</td>
<td>.09</td>
<td>−0.21</td>
<td>.9</td>
<td>−0.69</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ADC (cm²/sec)</td>
<td>0.08</td>
<td>.9</td>
<td>0.53</td>
<td>.01</td>
<td>0.30</td>
<td>.8</td>
<td>0.69</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6G (%)</td>
<td>−0.16</td>
<td>.9</td>
<td>−0.44</td>
<td>.07</td>
<td>−0.22</td>
<td>.9</td>
<td>−0.14</td>
<td>.4</td>
</tr>
<tr>
<td>VDP (%)</td>
<td>0.13</td>
<td>.9</td>
<td>0.47</td>
<td>.03</td>
<td>0.10</td>
<td>.7</td>
<td>0.62</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note.—Unless otherwise indicated, data are Pearson correlation coefficients. P values were determined with Holm-Bonferroni correction. Data were adjusted for age, sex, height, weight, and smoking history. P = .15 indicates a significant difference. 6G = sixth-generation airway wall area percent.

* n = 26.
† n = 32.
‡ Percent of predicted value.

### Table 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>PRM Gas Trapping</th>
<th>PRM Emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>βu, βs, Partial R², PValue</td>
<td>βu, βs, Partial R², PValue</td>
</tr>
<tr>
<td>FEV1*</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>−0.65, −0.69</td>
<td>0.53, .001</td>
</tr>
<tr>
<td>DLCO*</td>
<td>...</td>
<td>−0.10, −0.29</td>
</tr>
<tr>
<td>ADC (cm²/sec)</td>
<td>...</td>
<td>0.10, 0.41</td>
</tr>
<tr>
<td>6G (%)</td>
<td>−1.72, −0.22</td>
<td>0.08, .02</td>
</tr>
<tr>
<td>VDP (%)</td>
<td>...</td>
<td>0.29, 0.41</td>
</tr>
</tbody>
</table>

Note.—Unless otherwise indicated, data are Pearson correlation coefficients. P values were determined with Holm-Bonferroni correction. Data were adjusted for age, sex, height, weight, and smoking history. P = .15 indicates a significant difference. n = 58. 6G = sixth-generation airway. βu = unstandardized regression coefficient; βs = standardized regression coefficient.

* Percent of predicted value.
is also worth noting that, in this study, CT emphysema measurements for healthy ex-smokers were in agreement with previously reported values for healthy subjects (7,32). Importantly, CT may not be adequately sensitive to very mild or subclinical parenchymal and obstructive disease; this may also partially explain the negligible VDP and PRM correlations in healthy ex-smokers (33).

In addition to these bilateral relationships, multivariate modeling identified the parameters that significantly added to the model for PRM gas trapping (wall area percent and FEV1/FVC) and PRM emphysema (VDP and DLCO). The PRM gas trapping model is intuitive and was developed on the basis of our previous knowledge of the role of airway wall morphologic characteristics in functional small airways disease (34). This finding is also consistent with the major pulmonary imaging and clinical phenotypes that were recently summarized by the Fleischner Society (35). However, we note that, while the significant contribution of DLCO to PRM emphysema is also consistent with a large body of previous work, the contribution of PRM emphysema to ventilation defects is a novel and somewhat surprising result (36). Strong hints that ventilation defects may stem from emphysematous bullae were previously reported in patients with advanced or severe COPD and numerous exacerbations that required hospitalization (22). Together, this information suggests a role for pulmonary imaging to phenotype COPD beyond FEV1 to help guide therapy and change exacerbations and other outcomes.

These quantitative associations and some obvious qualitative regional relationships led to our exploration of potential spatial correlations. Notably (and unexpectedly), we observed that 3He ADC values were significantly elevated in regions of PRM gas trapping. This surprising result suggested that PRM functional small-airway disease that leads to gas trapping may be seen as enlarged air spaces, which is reflected by elevated ADC values. This is one of the first studies to spatially compare 3He ADC to gas-trapping measurements. This novel finding is in agreement with other studies that demonstrated gravitational and lung volume effects on pulmonary ADC values (39–39). This also suggests that abnormally elevated ADC values may not always reflect emphysematous abnormalities in patients with COPD. There were also spatial correlations in patients with mild and moderate COPD, in whom 3He MR imaging ventilation defects were spatially related to PRM gas trapping. In contrast, in the small group of seven patients with severe COPD, MR imaging ventilation defects were spatially related to both PRM gas trapping and emphysema, which were identified with CT and MR imaging SOC. The rationale for performing SOC analysis in
overlap analysis in both directions because the results showed that, in severe COPD, PRM emphysema voxels were mainly occupied by ventilation defect voxels. In contrast, ventilation defect voxels were mainly occupied by PRM gas-trapping voxels. This means that both PRM emphysema and gas-trapping voxels are spatially coincident with ventilation defects. This exciting result provides, for the first time, a deeper understanding of the source of ventilation defects and gas trapping in COPD.

We think that these findings underscore the importance of phenotyping COPD cases with quantitative imaging. Future work should aim to determine the spatial relationships between continuous pixel-wise data and PRM, as this may provide a better understanding of these relationships.

Numerous studies have used paired inspiratory and expiratory lung CT images to provide COPD phenotypes (42–44). In patients with COPD, gas trapping is influenced by both emphysema and small-airways disease, differentiation of which is attempted with PRM (43,45). In addition, severe small-airways disease sometimes appears at CT as emphysema, making it challenging to delineate between the two phenotypes. Regardless, in this study, we determined the different relationships between MR imaging and CT phenotypes of COPD cases across GOLD grades of severity. We think that these results underscore the need to adopt multimodality approaches to deeply phenotype COPD cases so that the independent contributions of emphysema and airways disease may be ascertained, which may help optimize COPD therapy and improve outcomes.

In summary, in all ex-smokers, ventilation defects and ADC values were correlated with PRM gas trapping and emphysema. In a subset of ex-smokers with mild to moderate COPD, ventilation defects were quantitatively and spatially related to PRM gas trapping, whereas in severe COPD, there were spatial and quantitative relationships for ventilation defects with both PRM gas trapping and emphysema.
Table 5

Quantitative Spatial Relationships for 3He MR imaging Ventilation Defects with CT PRM Voxels

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy Ex-Smokers (n = 26)</th>
<th>All (n = 32)</th>
<th>GOLD I (n = 12)</th>
<th>GOLD II (n = 13)</th>
<th>GOLD III/IV (n = 7)</th>
<th>P* Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy Ex-Smokers (n = 26)</td>
<td>All (n = 32)</td>
<td>GOLD I (n = 12)</td>
<td>GOLD II (n = 13)</td>
<td>GOLD III/IV (n = 7)</td>
<td>P* Value</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spatial Overlap Coefficient Normalized with CT Voxels</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gas trapping to VDP (%)</td>
<td>3 ± 12</td>
<td>15 ± 16</td>
<td>4 ± 4</td>
<td>13 ± 13</td>
<td>36 ± 18</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Emphysema to VDP (%)</td>
<td>0 ± 0</td>
<td>22 ± 32</td>
<td>3 ± 9</td>
<td>16 ± 27</td>
<td>64 ± 30</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Significant difference*</td>
<td>0.2</td>
<td>0.06</td>
<td>0.5</td>
<td>0.5</td>
<td>0.01</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Spatial Overlap Coefficient Normalized with MR Imaging Voxels</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VDP to gas trapping (%)</td>
<td>3 ± 8</td>
<td>41 ± 29</td>
<td>36 ± 28</td>
<td>34 ± 28</td>
<td>62 ± 25</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VDP to emphysema (%)</td>
<td>0 ± 0</td>
<td>6 ± 14</td>
<td>1 ± 2</td>
<td>7 ± 15</td>
<td>11 ± 20</td>
<td>.04</td>
</tr>
<tr>
<td>Significant difference*</td>
<td>0.09</td>
<td>&lt;.001</td>
<td>0.001</td>
<td>0.006</td>
<td>0.009</td>
<td>...</td>
</tr>
</tbody>
</table>

Note.—Unless otherwise indicated, data are mean plus or minus standard deviation. *P values were determined with analysis of variance and Tukey correction; P < .05 indicates a significant difference. *Significant difference was measured with paired t test for spatial overlap coefficients of MR imaging ventilation defects with PRM gas trapping and emphysema.

Acknowledgment: We thank Sandra Blamires, CCRC, for clinical coordination and for performing MR imaging of research volunteers.


References


