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Radiology

COPD: Do Imaging Measurements of Emphysema and Airway Disease Explain Symptoms and Exercise Capacity?[1]

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Purpose: To determine the role of imaging measurements of emphysema and airway disease in determining chronic obstructive pulmonary disease (COPD) symptoms and exercise limitation in patients with COPD, particularly in patients with mild-to-moderate disease.

Materials and Methods: Participants (n = 116) with Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade U (unclassified) or grade I–IV COPD provided informed consent to an ethics board–approved HIPAA-compliant protocol and underwent spirometry and plethysmography, completed the St George's Respiratory Questionnaire (SGRQ), completed a 6-minute walk test for the 6-minute walk distance (6MWD), and underwent hyperpolarized helium 3 (^{3}He) magnetic resonance (MR) imaging and computed tomography (CT). Emphysema was estimated by using the MR imaging apparent diffusion coefficient (ADC) and the relative area of the CT attenuation histogram with attenuation of −950 HU or less (RA_{950}). Airway disease was measured by using the CT airway wall thickness of airways with an internal perimeter of 10 mm and total airway count. Ventilation defect percentage at ^{3}He MR imaging was used to measure ventilation. Multivariable regression models for the 6MWD and SGRQ symptom subscore were used to evaluate the relationships between physiologic and imaging measurements.

Results: Multivariate modeling for the 6MWD in 80 patients with GOLD grade U–II COPD showed that ADC (β = 0.34, P = .04), diffusing capacity of the lung for carbon monoxide (β = 0.60, P = .0008), and residual volume/total lung capacity (β = −0.26, P = .02) were significant variables, while forced expiratory volume in 1 second (FEV_1) and airway disease measurements were not. In 36 patients with GOLD grade III or IV disease, FEV_1 (β = 0.48, P = .01) was the only significant contributor in a multivariate model for 6MWD. MR imaging emphysema measurements also made the greatest relative contribution to symptoms in patients with milder (GOLD grade U–II) COPD (ADC: β = 0.60, P = .005; RA_{950}: β = −0.52, P = .02; FEV_1: β = −0.45, P = .0002) and in grade III or IV disease (ADC: β = 0.95, P = .01; RA_{950}: β = −0.62, P = .07; airway count: β = −0.49, P = .01).

Conclusion: In patients with mild-to-moderate COPD, MR imaging emphysema measurements played a dominant role in the expression of exercise limitation, while both CT and MR imaging measurements of emphysema explained symptoms.

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Decades of research aimed at a better understanding of the pathophysiology of chronic obstructive pulmonary disease (COPD) and toward new drug discovery have not resulted in therapies that alter disease progression (1). Improved outcomes and quality of life for patients with COPD have been elusive as well because treatments are currently developed on the basis of spirometry measurements (2), which cannot help distinguish between underlying COPD phenotypes and are relatively insensitive to mild or early disease (3–5). Moreover, symptoms and exercise capacity are also heterogeneous in patients with mild or early COPD, in whom forced expiratory volume in 1 second (FEV_1) is only modestly abnormal. More sensitive and specific phenotype measurements may provide a better patient-oriented understanding of COPD outcomes, especially in mild or early disease.

COPD phenotypes of airway disease and emphysema can be directly measured by using thoracic computed tomography (CT) and hyperpolarized inhaled gas magnetic resonance (MR) imaging (6,7). The large-scale COPDGene (8) and ECLIPSE (9) studies explored CT airway disease and emphysema measurements of COPD and their progression. COPDGene provided evidence of the genetic determinants and heritability of emphysema (10,11), and its results demonstrated that specific phenotypes may help predict COPD exacerbations (12). The ECLIPSE study showed the high variability of emphysema expression in COPD and that emphysema worsening is variable and related to smoking status and sex (13). Notwithstanding these findings, CT measurements of COPD have some fundamental limitations. For example, emphysema tends to be underestimated when lesions are smaller than 0.5 cm (14), and this is relevant in patients with mild disease. Airway disease estimates are limited by the fundamental spatial resolution limits of CT (15), which result in an inherent bias because only survivor airways can be measured (16). Nevertheless, CT measurements of emphysema and airway disease are correlated with symptoms and exercise limitation in COPD (17–20). Adding to this body of evidence was a recent study (21) in ex-smokers with normal FEV_1 and CT findings but modestly abnormal diffusing capacity of the lung for carbon monoxide (D_{LCO}) and abnormally elevated hyperpolarized helium 3 (^3He) MR imaging apparent diffusion coefficients (ADCs). Importantly, abnormal D_{LCO} and ^3He ADCs reflected mild emphysema in these ex-smokers, and ^3He ADC was related to both symptoms and exercise limitation. These data suggest that MR imaging measurements of emphysema may uniquely explain clinically relevant symptoms and exercise limitation in otherwise healthy (on the basis of spirometric and CT findings) ex-smokers. All these previous reports suggested that imaging measurements of emphysema and airway disease can be exploited to provide a better understanding of the phenotypes responsible for symptoms and exercise limitation in COPD. In many patients with COPD, it is difficult to understand variable exercise abilities and symptoms on the basis of spirometric measurements of airflow limitation, which may only be modestly abnormal.

Therefore, in this study, we evaluated patients across Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD severity grades by using well-established clinical and physiologic and emerging imaging measurements. Given their high sensitivity, we

Advances in Knowledge

- Apparent diffusion coefficients (ADCs) derived by using hyperpolarized helium 3 MR imaging ($P = .04$), diffusion capacity of the lung for carbon monoxide ($P = .0008$) and residual volume/total lung capacity ($P = .02$) significantly added to the multivariate regression equation for 6-minute walk distance (6MWD), but forced expiratory volume in 1 second (FEV_1), CT measurements of emphysema and airway disease, and MR imaging ventilation measurements did not.
- A multivariate model for St George's Respiratory Questionnaire symptom score showed that the ADC ($P = .005$) had the greatest relative contribution, followed by the relative area of the CT attenuation histogram with attenuation of −950 HU or less ($P = .02$) and FEV_1 ($P = .0002$), but CT airway disease and MR imaging ventilation measurements were not significant contributors.

Implication for Patient Care

- Imaging measurements of emphysema help identify and determine disease phenotype in patients with mild chronic obstructive pulmonary disease (COPD) in whom FEV_1 is modestly abnormal and contribute to the understanding of the sources or triggers for clinically important outcomes such as the 6MWD and COPD symptoms (eg, cough, sputum production, wheeze, and breathlessness).

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Abbreviations:
ADC = apparent diffusion coefficient
COPD = chronic obstructive pulmonary disease
D_{LCO} = diffusing capacity of the lung for carbon monoxide
FEV_1 = forced expiratory volume in 1 second
GOLD = Global Initiative for Chronic Obstructive Lung Disease
HU_{15} = 15th percentile of the CT attenuation histogram
Pi10 = airway wall thickness of airways with an internal perimeter of 10 mm
RA_{950} = relative area of the CT attenuation histogram with attenuation of −950 HU or less
RV = residual volume
SGRQ = St George's Respiratory Questionnaire
6MWD = 6-minute walk distance
TLC = total lung capacity
VDP = ventilation defect percentage

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; manuscript final version approval, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, M.K., H.O.C., G.P.; clinical studies, M.K., H.O.C., D.G.M., G.P.; statistical analysis, M.K., D.P., D.D.S., H.O.C., G.P.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

hypothesized that imaging measurements of airway disease and emphysema would help explain symptoms in all patients with COPD as well as in the subgroup of patients with mild-to-moderate COPD. This is important because phenotypes that are related to patient-oriented outcomes can be used to characterize patients and perhaps guide treatment. Therefore, in patients with COPD, and particularly in patients with mild-to-moderate disease, we aimed to determine the role of imaging measurements of emphysema and airway disease in determining COPD symptoms and exercise limitation.

Materials and Methods

Study Participants

Volunteers provided written informed consent to a protocol approved by a local research ethics board and Health Canada that was compliant with the Personal Information Protection and Electronic Documents Act and the Health Insurance Portability and Accountability Act. Participants were recruited from a local tertiary care center and by advertisement and were between 50 and 85 years of age, with a previous diagnosis of COPD and a smoking history of 10 or more pack-years. Details regarding subject recruitment for the study are provided elsewhere (22). Briefly, a total of 231 subjects were enrolled in the study; 16 were excluded owing to MR imaging incompatibilities, six refused patient consent, and four were unable to perform the ^{3}He gas inhalation and breath hold. COPD severity was defined by using GOLD criteria (23). Volunteers with GOLD-Unclassified (GOLD-U) disease were identified on the basis of FEV_1/forced vital capacity $\geq$ 70% and FEV_1 < 80% predicted, as previously described (24). Fifteen patients with GOLD I disease have been described elsewhere (21); that previous study focused on ex-smokers without airflow limitation and motivated the current evaluation, the aim of which was to evaluate patients with GOLD I–IV COPD. In total, 116 participants were evaluated (n = 10 GOLD-U, n = 22 GOLD-I, n = 48 GOLD-II, and n = 36 GOLD-III/IV); 80 participants had mild-to-moderate COPD (all: age = 70 years ± 9, range: 51–87 years; men: 72 years ± 9, range: 51–87 years; women: 68 years ± 8, range: 52–80 years), and 36 patients had severe COPD (all: age = 70 years ± 9, range: 48–86 years; men: 70 years ± 10, range: 48–86 years; women: 69 years ± 7, range: 61–82 years).

Pulmonary Function Testing, 6-Minute Walk Test, and St George's Respiratory Questionnaire

All participants performed spirometry (MedGraphics, St Paul, Minn) according to American Thoracic Society (ATS) guidelines (25). Whole-body plethysmography (MedGraphics) was used to measure lung volumes, and the attached gas analyzer was used to measure DLCO. The St George's Respiratory Questionnaire (SGRQ) was used with permission (26). The 6-minute walk test was also performed according to ATS guidelines (27) to measure the 6-minute walk distance (6MWD).

Image Acquisition

MR imaging was performed by using a 3.0-T Discovery 750MR (GE Healthcare, Milwaukee, Wis) system. Conventional hydrogen 1 MR imaging was performed as previously described (28) at an inspiratory breath hold after inhalation of 1.0 L N_2 from functional residual capacity (FRC) from a 1.0-L Tedlar bag (Jensen Inert Products, Coral Springs, Fla). Hyperpolarized ^{3}He static ventilation and diffusion-weighted imaging were also performed as previously described (28). CT volumes were acquired (at FRC plus 1 L N2 gas) by using a 64-section Lightspeed VCT system (GE Healthcare) within 10 minutes of MR imaging and approximately 1 hour after salbutamol administration, as previously described (21). To reduce potential differences in lung volumes, subjects were transported in a wheelchair to CT, and images were acquired at inspiration breath-hold after inhalation of 1 L N_2 gas from FRC. No expiration scans were acquired. Using our manufacturer settings and the ImPACT CT patient dosimetry calculator (based on the Health Protection Agency [UK] NRPB-SR250), the volumetric CT dose index was 4.4 mGy and the total effective dose was 1.8 mSv. On the basis of these values and the size-dependent conversion factors of 1.00–2.00, the size-specific dose estimates, which were calculated by using the approach described by Christner and colleagues (29), ranged from 9 to 5 mGy.

Image Analysis

All measurements were performed by an expert in quantitative MR imaging and CT image analysis (M.K). Hyperpolarized ^{3}He MR imaging ventilation was measured by using a semiautomated approach (30) to generate ventilation defect percentage (VDP)—the ventilation defect volume normalized to the thoracic cavity volume. Hyperpolarized ^{3}He ADC measurements were generated as previously described (31). Thoracic CT images were evaluated by using Pulmonary Workstation 2.0 (VIDA Diagnostics, Coralville, Iowa). The relative area of the CT attenuation histogram with attenuation of −950 HU or less (RA_{950}), the 15th percentile of the CT attenuation histogram (HU_{15}) and the slope of the low-attenuation cluster frequency distribution were generated. CT airway count, lumen area, airway wall area percentage of the third- to fifth-generation airways, and airway wall thickness of airways with an internal perimeter of 10 mm (Pi10) (15) were also generated.

Statistical Methods

Statistical analyses were performed by using SPSS Statistics V22 (IBM, Armonk, NY). An unpaired two-tailed t test was used to compare the severe and mild-to-moderate COPD subgroups with respect to subject demographic and functional measurements. A Fisher exact test was used to compare the severe and mild-to-moderate COPD subgroups for sex. Multiple comparisons were adjusted by using the Holm-Bonferroni correction (32); 15 P values were included in the multiple comparisons correction procedure for Table 1 , and 13 P values were included in the multiple comparisons correction procedure for Table 2. Although the SGRQ

Table 1

Study Participant Characteristics

Parameter	Patients with Mild-to-Moderate COPD ($n = 80$)	Patients with Severe COPD ($n = 36$)	All Patients ($n = 116$)	*P* Value*
Age (y)				
All patients	70 ± 9 (51–87)	70 ± 9 (48–86)	70 ± 9 (48–87)	.99
Male patients	72 ± 9 (51–87)	70 ± 10 (48–86)	71 ± 9 (48–97)	.99
Female patients	68 ± 8 (52–80)	69 ± 7 (61–82)	68 ± 8 (52–82)	.99
No. of male patients	49	23	72	.99
No. of pack-years	48 ± 28	57 ± 33	52 ± 30	.99
Body mass index (kg/m^2)	27 ± 4	27 ± 26	27 ± 5	.99
FEV_1	73 ± 17	36 ± 7	61 ± 2	<.0001
FEV_1/FVC	59 ± 12	38 ± 8	52 ± 15	<.0001
TLC	112 ± 17	125 ± 17	116 ± 18	.001
RV/TLC (%)	47 ± 10	61 ± 9	51 ± 12	<.0001
D_{LCO}	61 ± 19	43 ± 18	56 ± 21	<.0001
SGRQ symptom subscore	44 ± 22	64 ± 19	51 ± 22	.0001
6MWD (m)	400 ± 77	320 ± 32	378 ± 89	.0003

Note.—Unless otherwise noted, data are means ± standard deviations, with ranges in parentheses. Pulmonary function values are expressed as percentage predicted values. FVC = forced vital capacity, RV = residual volume, TLC = total lung capacity.

* Significant differences ($P < .05$) were determined by using *t* tests for continuous variables and the Fisher exact test for categoric variables. *P* values are Holm-Bonferroni adjusted for the comparison of mild-to-moderate and severe COPD subgroups.

Table 2

Imaging Measurements

Parameter	Patients with Mild-to-Moderate COPD ($n = 80$)	Patients with Severe COPD ($n = 36$)	All Patients ($n = 116$)	*P* Value*
CT measurements				
RA_{950} (%)	7 ± 8	17 ± 12	11 ± 10	<.0001
HU_{15} (HU)	−920 ± 30	−948 ± 21	−934 ± 24	<.0001
LAC *(D)*	−1.8 ± 0.3	−2 ± 0	−1.8 ± 0.2	.48
Pi10 (mm)	4.3 ± 0.2	4.3 ± 0.2	4.3 ± 0.2	.99
Third-generation WA (%)	57 ± 6	55 ± 12	56 ± 6	.99
Fourth-generation WA (%)	63 ± 3	61 ± 11	63 ± 3	.84
Fifth-generation WA (%)	65 ± 2	63 ± 12	65 ± 2	.99
Third-generation LA (mm^2)	39 ± 13	36 ± 11	40 ± 14	.99
Fourth-generation LA (mm^2)	18 ± 5	17 ± 5	18 ± 5	.82
Fifth-generation LA (mm^2)	13 ± 5	14 ± 3	14 ± 5	.84
Airway count *(n)*	78 ± 27	58 ± 21	72 ± 28	.0004
MR imaging measurements				
VDP (%)	13 ± 8	26 ± 8	18 ± 10	<.0001
ADC (cm^2/sec)	0.37 ± 0.10	0.48 ± 0.09	0.42 ± 0.1	<.0001

Note.—Data are means ± standard deviations. LA = lumen area, LAC = low-attenuation cluster analysis power law exponent, WA = airway wall area.

* Significant differences ($P < .05$) were determined by using *t* tests for continuous variables and Fisher exact test for categoric variables. *P* values are Holm-Bonferroni adjusted for the comparison of mild-to-moderate and severe COPD subgroups.

reports a total score as well as three subscores, we evaluated multivariable models for the SGRQ symptom subscore to focus on COPD symptoms. Importantly, SGRQ component scores have been validated in COPD (26). Univariate Pearson correlations were performed for the 6MWD and SGRQ with physiologic and imaging measurements; results are provided Table E2 (online). To provide a better understanding of the underlying imaging phenotype measurements that have the greatest relative contribution to COPD symptoms and exercise capacity, multivariable regression models for the 6MWD and SGRQ symptom subscore were generated by using the stepwise method and SAS 9.2 software (SAS Institute, Cary, NC). Age, sex, body mass index, and smoking status were included in the models because they were previously shown to be significantly associated with SGRQ and 6MWD (17–20). The stepwise selection

method used a combination of forward and backward selection. At each step, variables were added to the model if the F statistic $P < .15$ or were removed from the model if the F statistic $P > .15$. These steps continued until the addition of another variable to the model did not yield $P < .15$. For each independent variable included in the final multivariable models, the unstandardized and standardized regression coefficients (β values) were reported. The unstandardized β coefficients show how a single-unit change in the independent variable influences a change in the dependent variable. We calculated the unit change that was required for a four-unit change in the SGRQ (33) and a 25-m change in the 6MWD (34), the previously published minimal clinically important difference values. The standardized β coefficients are estimates expressed in units of standard deviation, whereby the independent variable with the greatest β coefficient had the greatest relative effect on the dependent variable in terms of standard deviation change. Multicollinearity among variables in the multivariable regression models was evaluated by using the variance inflation factor and was deemed acceptable when less than 10 (35).

Results

Demographics and Pulmonary Function Measurements

Demographic, pulmonary function, SGRQ, and 6MWD measurements are shown in Table 1; a per-subject listing is provided in Table E1 (online). The mild-to-moderate (n = 80) and severe COPD (n = 36) subgroups were different with respect to FEV_1 ($P < .0001$), RV/TLC ($P < .0001$), DLCO ($P < .0001$), SGRQ symptom score ($P < .0001$), and 6MWD ($P = .0002$), but there were no significant differences for age, sex, pack-years, or body mass index.

Imaging Measurements

Imaging measurements for the mild-to-moderate and severe COPD subgroups are provided in Table 2. The COPD subgroups were significantly different for emphysema measurements (RA_{950}: $P < .0001$; HU_{15}: $P < .0001$; ADC: $P < .0001$), as well as for hyperpolarized ^{3}He MR imaging VDP ($P < .0001$), but not CT airway measurements. The Figure shows center-section coronal hyperpolarized ^{3}He static ventilation images with corresponding hyperpolarized ^{3}He ADC maps and CT low-attenuation cluster images for four representative GOLD I and GOLD II participants and a single GOLD III ex-smoker. As shown in the Figure, although the representative GOLD I-II subjects reported similar FEV_1, a patient with COPD with more severe symptoms and greater activity limitation had brighter hyperpolarized ^{3}He ADC maps indicative of more severe emphysematous destruction and larger/more numerous clusters of CT low-attenuation regions also reflective of more advanced bullous emphysema. These findings are similar to the more advanced COPD in the images in the patient with GOLD III disease also shown in the Figure.

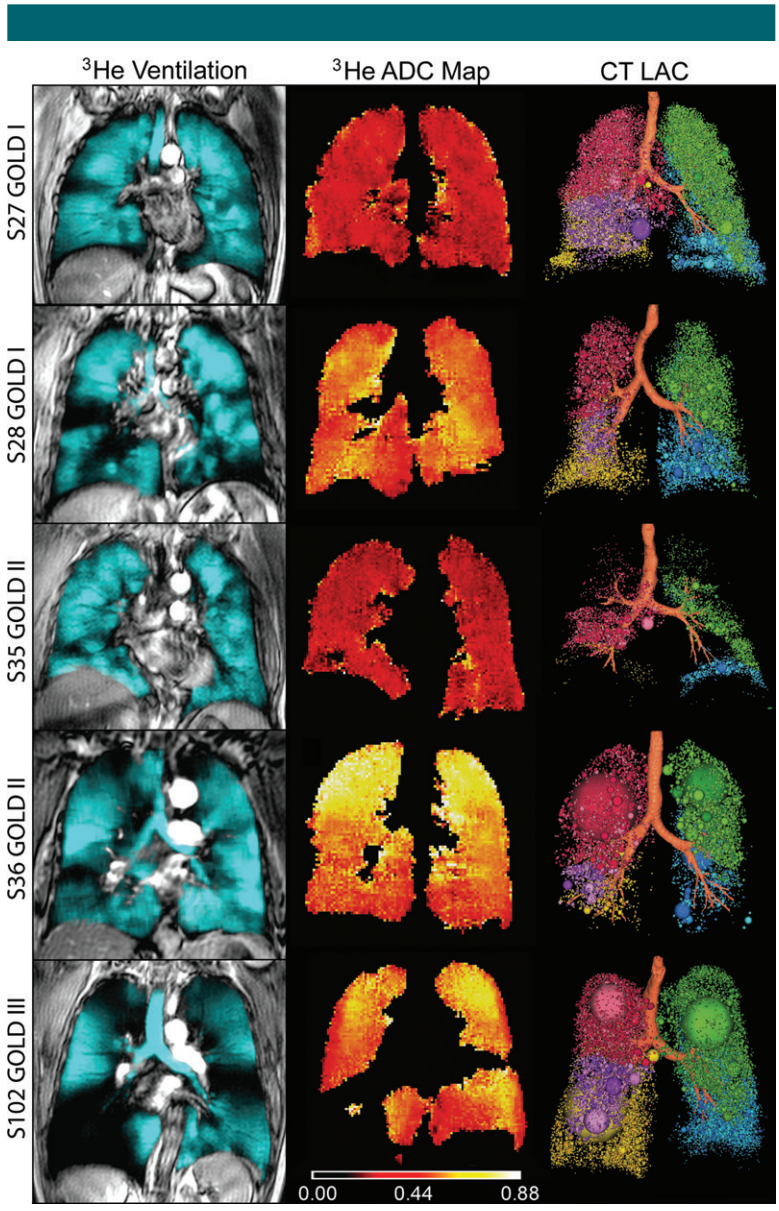
Relationships for Imaging Phenotypes with Symptoms and Exercise

The univariate Pearson correlations for the 6MWD and SGRQ symptom subscore with physiologic and imaging measurements in all patients with COPD are provided in Table E2 and Figure E1 (online); however, multivariate tests that take into account the complex interrelationships among variables were also investigated. Table 3 shows multivariate regression models for 6MWD and SGRQ symptom score; variance inflation factors were acceptable for all variables. For the model that explained the 6MWD in the GOLD U–II subgroup, hyperpolarized ^{3}He ADC significantly added to the regression equation (β = 0.34, P = .04), as did DLCO (β = 0.60, P = .0008) and RV/TLC (β = −0.26, P = .02), but not FEV_1. For the GOLD III-IV subgroup, only FEV_1 added significantly to the regression equation (β = 0.48, P = .01). For all patients with COPD, hyperpolarized ^{3}He ADC (β = 0.22, P = .09) and FEV_1 (β = 0.26, P = .07) added to the regression equation for 6MWD, although DLCO (β = 0.40, P = .006) was the only significant contributor. On the basis of the unstandardized β coefficients, to change the 6MWD more than the minimal clinically important difference (25 m), a relatively large change of approximately 0.10 cm^2/sec for ADC was required for patients with mild-to-moderate COPD.

For the model that explained the SGRQ symptom score in the mild-to-moderate COPD subgroup, hyperpolarized ^{3}He ADC significantly added to the regression equation (β = 0.60, P = .005), as did RA_{950} (β = −0.52, P = .02) and FEV_1 (β = −0.45, P = .0002), with the greatest relative contribution stemming from hyperpolarized ^{3}He ADC. On the basis of the unstandardized β coefficient, to obtain a four-unit (the minimal clinically important difference) change in SGRQ, a relatively small change in ADC of approximately 0.03 cm^2/sec was required in the GOLD U–II subgroup. For the GOLD III-IV subgroup, ADC also provided the greatest relative contribution (β = 0.95, P = .01) to the regression equation for SGRQ symptoms, followed by CT RA_{950} (β = −0.62, P = .07) and CT airway count (β = −0.49, P = .01). Finally, ADC also provided the greatest contribution to the regression equation for the SGRQ symptom score in all patients with COPD (β = 0.52, P = .003), and this was also reported to a lesser extent for FEV_1 (β = −0.46, $P < .0001$), RA_{950} (β = −0.41, P = .03), and Pi10 (β = 0.15, P = .09).

Discussion

We evaluated emerging imaging and well-established physiologic measurements in patients with COPD across a wide spectrum of severity and observed that *(a)* MR imaging emphysema measurements contributed significantly in a multivariable model of the 6MWD for patients with mild-to-moderate COPD, while FEV_1 and CT emphysema measurements did not; and *(b)* in patients with mild-to-moderate or severe COPD, MR imaging emphysema measurements also provided a greater relative contribution than FEV_1, CT emphysema, and other physiologic measurements in a multivariable model for SGRQ symptoms.



Images in representative patients with mild-to-moderate or severe COPD. Left-to-right: hyperpolarized ^{3}He MR imaging ventilation images, ^{3}He MR imaging ADC maps, and CT images showing low-attenuating clusters *(LAC)* for subject 27 *(S27)*, a 74-year-old man (FEV_1 = 86% predicted value, 6MWD = 486 m, SGRQ symptom subscore = 6, VDP = 6%, ADC = 0.37 cm^2/sec, Pi10 = 4.1 mm, RA_{950} = 6%); subject 28 *(S28)*, a 73-year-old man (FEV_1 = 85% predicted value, 6MWD = 360 m, SGRQ symptom subscore = 43, VDP = 9%, ADC = 0.45 cm^2/sec , Pi10 = 4.1 mm, RA_{950} = 4%); subject 35 *(S35)*, a 76-year-old man (FEV_1 = 77% predicted value, 6MWD = 357 m, SGRQ symptom subscore = 37, VDP = 7%, ADC = 0.30 cm^2/sec, Pi10 = 4.4 mm, RA_{950} = 2%); subject 36 *(S36)*, a 77-year-old woman (FEV_1 = 77% predicted value, 6MWD = 240 m, SGRQ symptom subscore = 69, VDP = 13%, ADC = 0.56 cm^2/sec, Pi10 = 4.2 mm, RA_{950} = 13%); and subject 102 *(S102)*, a 74-year-old man (FEV_1 = 34% predicted value, 6MWD = 282 m, SGRQ symptom subscore = 55, VDP = 34%, ADC = 0.50 cm^2/sec, Pi10 = 4.2 mm, RA_{950} = 18%).

In patients with mild-to-moderate COPD and in whom FEV_1 and airway disease measurements were not significant contributors, the MR imaging measurement of emphysema, RV/TLC and DLCO had the greatest relative impact on 6MWD; this is a novel finding. Although previous investigations in patients with moderate-to-severe COPD have revealed a strong relationship between CT emphysema measurements and exercise capacity (17–20), in the patients with COPD examined here, CT emphysema measurements did not significantly contribute to the model for exercise limitation. There is evidence that hyperpolarized ^{3}He MR imaging ADC and DLCO may be more sensitive to early or mild emphysema (21), and this may explain why emphysema measurements made by using MR imaging but not CT played a dominant role in explaining exercise limitation in mild-to-moderate COPD. To provide context, we recognize the important role that dyspnea and exercise intolerance play in milder COPD, as perviously described (3–5,36). Therefore, in this relatively small group of participants, exercise limitation in the patients with mild COPD may be related to relatively modest parenchymal abnormalities that can be sensitively detected by using inhaled gas MR imaging. Certainly, routine clinical assessment using DLCO is also helpful, but the finding of modestly abnormal DLCO itself is not diagnostic for emphysema in patients with COPD, in whom a wide variety of other cardiopulmonary diseases is possible.

We also found, somewhat surprisingly, that emphysema measurements had a greater influence on symptoms than airway disease measurements in severe COPD and in the subgroup of patients with mild-to-moderate COPD. In this regard, it is somewhat intuitive to relate specific COPD symptoms like cough and breathlessness to airway abnormalities, especially because previous work showed that in moderate-to-severe COPD, airway disease measurements provide the greatest contribution to symptoms (18,20). However, patients with COPD with mainly emphysema also report greater rates of dynamic

Table 3

Multivariate Regression Models for 6MWD and SGRQ Symptom Subscore

Parameter	Patients with Mild-to-Moderate COPD				Severe COPD				All COPD			
	Unstandardized β	Standardized β	Partial R^2	*P* Value	Unstandardized β	Standardized β	Partial R^2	*P* Value	Unstandardized β	Standardized β	Partial R^2	*P* Value
Model 1: 6MWD												
FEV_1	…	…	…	…	6.07	0.48	0.27	.01	1.09	0.26	0.04	.07
D_{LCO}	2.56	0.60	0.17	.0008	…	…	…	…	1.78	0.40	0.08	.006
RV/TLC	−1.12	−0.26	0.09	.02	…	…	…	…	−0.79	−0.22	0.04	.08
ADC	256.33	0.34	0.07	.04	…	…	…	…	1.81.76	0.22	0.03	.09
VDP	…	…	…	…	…	…	…	…	…	…	…	…
Count	…	…	…	…	…	…	…	…	…	…	…	…
Pi10	…	…	…	…	…	…	…	…	…	…	…	…
RA_{950}	…	…	…	…	…	…	…	…	…	…	…	…
Model 2: SGRQ symptom subscore												
FEV_1	−0.60	−0.45	0.19	.0002	…	…	…	…	−0.47	−0.46	0.18	<.0001
D_{LCO}	…	…	…	…	…	…	…	…	…	…	…	…
RV/TLC	…	…	…	…	…	…	…	…	…	…	…	…
ADC	127.31	0.60	0.11	.005	185.33	0.95	0.24	.01	104.69	0.52	0.09	.003
VDP	…	…	…	…	…	…	…	…	…	…	…	…
Count	…	…	…	…	−0.40	−0.49	0.23	.01	…	…	…	…
Pi10	…	…	…	…	…	…	…	…	14.24	0.15	0.03	.09
RA_{950}	−1.41	−0.52	0.08	.02	−0.96	−0.62	0.13	.07	−0.87	−0.41	0.05	.03

Note.—Models were adjusted for age, sex (female sex = 1.0), body mass index, smoking status (current smoker = 1.00), TLC, and inspiratory capacity. All variables in the model were significant at the $P = .15$ level.

hyperinflation during exercise, leading to lower peak oxygen consumption and greater dyspnea (37). Therefore, it is also possible that the presence and extent or severity of emphysema may be directly related to "shortness of breath" and "wheezing"—two domains included in the symptom component of the SGRQ questionnaire. Another possible explanation for why CT and MR imaging airway disease measures were not significant contributors in the multivariate models may be related to the inherent limitations of these measurements. CT airway disease measurements based on airway morphometry are limited by the spatial resolution of CT to the larger, more central airways greater than 2 mm in diameter. Moreover, MR imaging ventilation measurements may represent the contributions of both emphysema and airway disease, as previously described in moderate-to-severe COPD (38). Nevertheless, here we demonstrated that CT- and MR imaging–derived emphysema measurements were related to COPD symptoms and may better explain how patients with COPD feel at rest and when walking.

A limitation of our study was that the sample size of 116 patients, which was much smaller than in the COPDGene (18), ECLIPSE (20), and Genetic COPD Study (GenKOLS) (17) studies. Importantly, another limitation was that this study was performed at a single center. Multicenter studies like the PHIL trial, which is the only multicenter study incorporating both CT and hyperpolarized ^{3}He MR imaging in patients with COPD to date (39), are required for external validity of the findings. In addition, a control group of older never-smokers was not included in the main study, and so comparisons with healthy volunteers could not be made. We were also limited by not acquiring CT images at end-expiration in addition to end-inspiration. CT relative area of −856 HU or less is well known to be associated with air trapping and therefore would have been an important measure to include in our analysis. Furthermore, the evaluation of exercise limitation and symptoms in this study was limited because symptoms were not evaluated by

using cardiopulmonary exercise testing (CPET). In recognition of the high variability of the 6-minute walk test in patients with COPD, future studies will incorporate CPET to investigate if imaging-based emphysema measurements are directly related to dynamic hyperinflation and dyspnea during exercise, as previously described by using CPET (37). Another limitation of the study related to the 6-minute walk test was that the subjects were not screened for pulmonary hypertension or left-heart disease, nor did we exclude subjects with comorbidities, including sleep apnea, atherosclerosis, diabetes, and renal dysfunction, that may influence exercise tolerance as measured by the 6MWD. There are other direct limitations of MR imaging that must be acknowledged. Previous studies have reported that MR imaging ventilation measurements were sensitive to abnormalities in early disease (40), but we still do not know the exact etiology of ventilation defects in patients with COPD. Ventilation heterogeneity may be related to airway disease, and a previous study in asthma (41) showed the direct spatial relationship of ventilation defects and airway wall thickening. However, in patients with COPD, hyperpolarized ^{3}He ventilation defects likely reflect both emphysema and airway abnormalities (38)—a mixed-disease phenotype. The hyperpolarized ^{3}He ADCs are critically dependent on the ^{3}He gas reaching the distal airways, and therefore, a limitation of this approach is that measurements can be obtained only in regions of the lung where the gas is present. This may introduce a bias in patients with more severe emphysema or bullous disease. We must also note that ^{3}He gas is in limited supply globally. The lung MR imaging community is moving away from hyperpolarized ^{3}He to the more widely available and less costly hyperpolarized xenon 129 gas for lung imaging (42–44).

Nevertheless, in this relatively small group of mainly patients with mild-to-moderate COPD, there was good evidence to support the use of emerging MR imaging and CT pulmonary imaging phenotypes to explain the root causes of COPD symptoms. We think that the contributions of mild or early emphysema in COPD to symptoms and exercise capacity are often underestimated; to identify the pathophysiologic features that are directly responsible for the heterogeneous manifestations of COPD, highly sensitive measurements of lung structure and function will be required. Our findings suggest that pulmonary imaging measurements have the potential to provide important information about mild COPD, and this supports a role for MR imaging and CT as platforms for COPD research and clinical care. We must note that other approaches for identifying COPD-related disease changes can be used, including CT perfusion imaging (45,46) and dual-energy CT (47), and studies investigating the relationships between these sensitive measurements with symptoms and exercise capacity limitation in early or mild COPD are also warranted.

There are numerous, interrelated factors that contribute to symptoms and exercise limitation in COPD that are often difficult to understand and appreciate, especially in patients with "mild" disease in whom FEV_1 may not be very enlightening. In summary, in patients with mild-to-moderate COPD in whom FEV_1 was modestly abnormal, MR imaging measurements of emphysema played a dominant role in the expression of exercise limitation, while both CT and MR imaging measurements of emphysema explained COPD symptoms. Direct and sensitive measurements of airway disease and emphysema may help identify and phenotype disease in patients with COPD with early or mild disease that cannot be characterized otherwise and may contribute to the understanding of the sources or triggers for clinically important outcomes, including exercise capacity and COPD symptoms.

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