A Novel Method of Estimating Small Airway Disease Using Inspiratory-to-Expiratory Computed Tomography

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Keywords

Computed tomography · Small airway disease · Disease probability measure · Chronic obstructive pulmonary disease

Abstract

Background: Disease accumulates in the small airways without being detected by conventional measurements. **Objectives:** To quantify small airway disease using a novel computed tomography (CT) inspiratory-to-expiratory approach called the disease probability measure (DPM) and to investigate the association with pulmonary function measurements. **Methods:** Participants from the population-based CanCOLD study were evaluated using full-inspiration/full-expiration CT and pulmonary function measurements. Full-inspiration and full-expiration CT images were registered, and each voxel was classified as emphysema, gas trapping

(GasTrap) related to functional small airway disease, or normal using two classification approaches: parametric response map (PRM) and DPM (VIDA Diagnostics, Inc., Coralville, IA, USA). **Results:** The participants included never-smokers ($n = 135$), at risk ($n = 97$), Global Initiative for Chronic Obstructive Lung Disease I (GOLD I) ($n = 140$), and GOLD II chronic obstructive pulmonary disease ($n = 96$). PRM_{GasTrap} and DPM_{GasTrap} measurements were significantly elevated in GOLD II compared to never-smokers ($p < 0.01$) and at risk ($p < 0.01$), and for GOLD I compared to at risk ($p < 0.05$). Gas trapping measurements were significantly elevated in GOLD II compared to GOLD I ($p < 0.0001$) using the DPM classification only. Overall, DPM classified significantly more voxels as gas trapping than PRM ($p < 0.0001$); a spatial comparison revealed that the expiratory CT Hounsfield units (HU) for voxels classified as DPM_{GasTrap} but PRM_{Normal} (PRM_{Normal} - DPM_{GasTrap} = -785 ± 72 HU) were significantly reduced compared to voxels classified normal by both approaches

($\text{PRM}_{\text{Normal}} - \text{DPM}_{\text{Normal}} = -722 \pm 89 \text{ HU}$; $p < 0.0001$). DPM and $\text{PRM}_{\text{GasTrap}}$ measurements showed similar, significant associations with forced expiratory volume in 1 s (FEV_1) ($p < 0.01$), $\text{FEV}_1/\text{forced vital capacity}$ ($p < 0.0001$), residual volume/total lung capacity ($p < 0.0001$), bronchodilator response ($p < 0.0001$), and dyspnea ($p < 0.05$). **Conclusion:** CT inspiratory-to-expiratory gas trapping measurements are significantly associated with pulmonary function and symptoms. There are quantitative and spatial differences between PRM and DPM classification that need pathological investigation.

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Introduction

The concept that the major site of increased resistance to airflow in normal lungs is the small conducting airways was first proposed by Rohrer in 1915 [1]. This opinion remained well established until the appearance of Weibel's famous monograph in 1963 depicting a model of the tracheobronchial system [2]. Weibel's data showed that the total cross-sectional area of airway lumina increased exponentially at each generation of airway branching, and Green's [3] calculations later indicated that the rapid expansion in the total cross-sectional area of the smaller airway lumina results in a sharp reduction in the resistance to flow. This was later confirmed by Macklem and Mead [4] using a novel technique that allowed the total airways resistance to be partitioned into two components located central and peripheral to a catheter tip wedged into airways 2 mm in diameter. Based on this finding and using the same technique, Hogg et al. [5] demonstrated that the small airways offer little resistance in the normal human lungs, but become the major site of increased resistance to flow in chronic obstructive pulmonary disease (COPD). Taken together, Mead postulated that the smaller conducting airways < 2 mm in diameter represent a "quiet zone" within the normal human lung where disease can accumulate over many years without being noticed [6]. Collectively, these developments led to the decades-long search for noninvasive methods to assess the small airways.

The introduction and rapid development of computed tomography (CT), coupled with the development of quantitative imaging methods, have led to their increased use in the diagnosis and management of many chronic lung diseases [7]. However, even with the advances in CT technology, the spatial resolution is still not great enough to visualize the small airways directly. Recently, a novel analysis method called the parametric response map

(PRM) was introduced to indirectly assess the functional effects of small airway disease [8]. By registering CT images acquired at full inspiration to images acquired at full expiration and applying established Hounsfield unit (HU) thresholds, regions of the lung that trap gas that are not related to emphysema, and hence may be attributed to small airway disease, can be quantified. Although measurements of gas trapping related to "functional" small airway disease generated using this technique have been shown to be reproducible over short periods of time [9], to be correlated with pulmonary function [8], to show spatial agreement with other imaging modalities [10], and to be associated with longitudinal changes in forced expiratory volume in 1 s (FEV_1) [11], these measurements have yet to be pathologically validated. Furthermore, measurements generated using a single HU threshold have obvious limitations, and therefore there is motivation to investigate other CT inspiratory-to-expiratory classification approaches.

The purpose of this report was to investigate a novel approach for quantifying CT inspiratory-to-expiratory gas trapping related to functional small airway disease called the disease probability measure (DPM) (VIDA Diagnostics, Inc., Coralville, IA, USA). Furthermore, we aimed to determine the association between CT inspiratory-to-expiratory gas trapping related to small airway disease measurements with pulmonary function and symptoms.

Subjects and Methods

Participants

Participants between 45 and 90 years from the multisite, population-based CanCOLD study were evaluated [12, 13]; the sites include Vancouver, Calgary, Ottawa, Quebec City, Montreal, Toronto, Halifax, Kingston, and Saskatoon. Ethics approval was obtained from the institutional review board at each CanCOLD study site. COPD status and severity grade were defined using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria whereby participants with a $\text{FEV}_1/\text{forced vital capacity}$ (FVC) ratio < 0.7 were considered to be part of the COPD group [14]. Current or ex-smokers with normal lung function ($\text{FEV}_1/\text{FVC} > 0.7$) were defined as "at risk", and never-smokers had normal lung function with no smoking history [14]. From this entire cohort, a subset of 504 CanCOLD participants (never-smokers, at risk, GOLD I, and GOLD II) were randomly selected for DPM analysis. The 504 participants were enrolled between February 2010 and December 2013. Of the 504 participants selected for analysis, 36 were excluded due to missing plethysmography lung volumes, and therefore a total of 468 participants were investigated. Given the paucity of GOLD III/IV participants in studies that recruit from the population compared to convenience samples, no GOLD III/IV participants were included in this analysis.

Fig. 1. CT inspiratory-to-expiratory DPM classification methodology. CT inspiratory and expiratory images were first registered using a nonlinear, deformable registration algorithm. Next, the DPM method took into account the HU value within each voxel at inspi-

ration and expiration and, using probability density functions, computed the probability (between 0 and 100%) that each voxel contains gas trapping and emphysema. CT, computed tomography; DPM, disease probability measure; HU, Hounsfield unit.

Pulmonary Function Tests

Spirometry and plethysmography were performed according to the American Thoracic Society guidelines [15–17]. For spirometry, FEV₁, FVC, and FEV₁/FVC were reported. Bronchodilator response was defined as the percent change in FEV₁ (L) after bronchodilator inhalation: [(FEV₁ post-BD – FEV₁ pre-BD)/FEV₁ pre-BD] × 100. Whole-body plethysmography was also performed for measurement of functional residual capacity, residual volume (RV), total lung capacity (TLC), and diffusing capacity of the lung for carbon monoxide.

Symptom Scores

Dyspnea was evaluated using the modified Medical Research Council scale [18]. Participants were also asked whether COPD symptoms of chronic cough, chronic phlegm, and wheeze were present or absent (binary variable). As previously described [19, 20], chronic cough and chronic phlegm were defined as cough or phlegm on most days for at least 3 months in two consecutive years; wheeze was defined as whistling or wheezing in the chest at any time in the last 12 months.

CT Image Acquisition

CT images were acquired at multiple sites using various CT system makes and models with the participant supine at suspended full inspiration and full expiration from the apex to the base of the lung [13]. The CT parameters for image acquisition in the par-

ticipants investigated were as follows: 100 kVp, 50 mAs, 0.5 s gantry rotation, pitch of 1.375, 1.00–1.25 mm slice thickness, and an intermediate reconstruction kernel (GE: Standard; Siemens: b35; Philips: B) was used for quantitative analysis.

CT Image Analysis

All CT analyses were performed by VIDA Diagnostics, Inc. The full-inspiration and full-expiration CT images were registered using a nonlinear registration algorithm, as previously described [21]. The registration was validated using manually selected landmarks in participants with and without COPD; the target registration error was approximately 1–2 voxels (data not shown). Classification of the registered inspiratory-to-expiratory CT lung voxels was performed using both the established PRM [8] and the DPM approach. PRM classification of emphysema and gas trapping were generated using the –950-HU and –856-HU thresholds on registered full-inspiration and full-expiration CT images, respectively [8]. The following measurements were generated: PRM_{Normal}: percentage of lung voxels without gas trapping and emphysema; PRM_{GasTrap}: percentage of lung voxels with gas trapping but no emphysema; and PRM_{Emph}: percentage of lung voxels with both gas trapping and emphysema. The DPM classification developed by VIDA Diagnostics, Inc. is described in Figure 1 for a GOLD II COPD participant (56-year-old male, FEV₁ = 77%_{pred}, FEV₁/FVC = 56). In contrast to the PRM method which applied the same single threshold across the whole lung for each partici-

Table 1. Subject demographics and pulmonary function measurements for all participants

Parameter	Never-smoker (n = 135)	At risk (n = 97)	GOLD I (n = 140)	GOLD II (n = 96)
<i>Subject demographics</i>				
Age, years	65 (10)	66 (9)	68 (10) ^a	67 (11)
Female sex	68 (50%)	49 (51%)	50 (36%) ^{a,b}	44 (46%)
Caucasian race	68 (93%)	49 (98%)	50 (97%)	44 (99%) ^a
Current smoker	0 (0%)	12 (12%) ^a	23 (16%) ^a	23 (24%) ^{a,b}
Pack-years	0 (0)	24 (33) ^a	19 (23) ^a	28 (27) ^{a,c}
Body mass index	27 (5)	28 (5)	28 (5)	28 (5)
<i>Pulmonary function</i>				
FEV ₁ , % _{pred}	107 (78)	100 (12) ^a	95 (11) ^{a,b}	71 (8) ^{a,b,c}
FEV ₁ /FVC, %	78 (5)	77 (5)	64 (5) ^{a,b}	59 (7) ^{a,b,c}
FRC, L	3.23 (0.89)	3.15 (0.69)	3.64 (0.89) ^{a,b}	3.63 (1.06) ^{a,b}
RV, L	2.20 (0.54)	2.26 (0.56)	2.66 (0.66) ^{a,b}	2.84 (0.83) ^{a,b}
TLC, L	6.10 (1.33)	5.98 (1.16)	6.72 (1.36) ^{a,b}	6.18 (1.49) ^c
RV/TLC, %	37 (8)	38 (7)	40 (8) ^a	46 (9) ^{a,b,c}
DL _{CO} , % _{pred}	118 (23)	113 (24)	110 (24) ^a	97 (23) ^{a,b,c}

Figures in parentheses are standard deviations or percentages. DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; RV, residual volume; TLC, total lung capacity; %_{pred}, percent predicted. Significance of difference ($p < 0.05$): ^a significantly different from never-smoker; ^b significantly different from at risk; ^c significantly different from GOLD I.

pant, the DPM method takes into account the HU value within each registered voxel at inspiration and expiration. First, an exponential decay function determined the continuous probability of gas trapping using the difference between CT inspiration and expiration intensity; the exponential decay function was optimized using an external cohort [22]. For example, a difference between CT inspiration and expiration of 0 HU, indicating no lung emptying on expiration, corresponded to a gas trapping probability of 100%, while a difference between CT inspiration and expiration of ≥ 0 HU corresponded to a lower probability of gas trapping (exponentially approaching 0%). The continuous probability that the voxel contained emphysema was also determined using an optimized exponential function computed from the average normalized CT inspiration and expiration intensity values. The normalized HU values for both inspiration and expiration were defined as 1 for ≥ 0 HU and 0 for $\leq -1,000$ HU, and intensity values between these boundaries were assigned linearly. For example, a CT inspiration and expiration voxel with $-1,000$ HU (pure air) had 100% probability of emphysema. After the continuous probability of gas trapping and emphysema had been determined, voxels with $<50\%$ probability of gas trapping and $<50\%$ probability of emphysema were classified as normal (DPM_{Normal}), voxels with $>50\%$ probability of gas trapping and $>50\%$ probability of emphysema were classified as emphysema (DPM_{Emph}), and voxels with $>50\%$ probability of gas trapping and $<50\%$ probability of emphysema were classified as gas trapping (DPM_{GasTrap}).

Statistical Analysis

A one-way analysis of variance was used for comparisons between never-smokers, at risk, GOLD I, and GOLD II participants

for demographics and pulmonary function, and a two-way analysis of variance was used for comparison of PRM and DPM measurements between never-smokers, at risk, GOLD I, and GOLD II participants; multiple-comparisons test correction was performed using a Tukey test (GraphPad Prism 6, La Jolla, CA, USA). To compare the spatial overlap between PRM and DPM measurements, we calculated the Dice similarity coefficient (DSC) [23]; all voxels with measurements $<0.5\%$ were excluded from the analysis. A multivariable linear regression analysis (SAS 9.4 software, Cary, NC, USA) was used to determine the association between pulmonary function and clinical measurements (symptom score response variables were treated as ordinal) with PRM_{GasTrap} and DPM_{GasTrap} adjusted for age, sex, race, body mass index, and scanner model.

Results

Participant Demographics and Pulmonary Function Measurements

Table 1 shows the demographics and pulmonary function measurements for all participants. The GOLD I participants were slightly but significantly older than the never-smokers (never-smokers 65 ± 10 years, GOLD I participants 68 ± 10 years, $p > 0.05$) and had significantly fewer female participants than the never-smokers (never-smokers 50%, GOLD I 36%) and at risk (51%) groups.

Fig. 2. Expiratory CT and registered inspiratory CT images with corresponding PRM and DPM map for a never-smoker, at risk, GOLD I, and GOLD II subject. Never-smoker: 47-year-old male, $FEV_1 = 107\%_{pred}$, $FEV_1/FVC = 85\%$, $PRM_{Normal} = 100\%$, $PRM_{Emph} = 0\%$, $PRM_{GasTrap} = 0\%$, $DPM_{Normal} = 99\%$, $DPM_{Emph} = 0\%$, $DPM_{GasTrap} = 1\%$. At risk: 82-year-old female ex-smoker, pack-years = 21, $FEV_1 = 99\%_{pred}$, $FEV_1/FVC = 73\%$, $PRM_{Normal} = 97\%$, $PRM_{Emph} = 0\%$, $PRM_{GasTrap} = 3\%$, $DPM_{Normal} = 89\%$, $DPM_{Emph} = 0\%$, $DPM_{GasTrap} = 11\%$. GOLD I: 59-year-old female ex-smoker, pack-years = 59, $FEV_1 = 87\%_{pred}$, $FEV_1/FVC = 69\%$,

$PRM_{Normal} = 92\%$, $PRM_{Emph} = 2\%$, $PRM_{GasTrap} = 6\%$, $DPM_{Normal} = 71\%$, $DPM_{Emph} = 2\%$, $DPM_{GasTrap} = 27\%$. GOLD II: 56-year-old male current smoker, pack-years = 86, $FEV_1 = 77\%_{pred}$, $FEV_1/FVC = 56\%$, $PRM_{Normal} = 92\%$, $PRM_{Emph} = 1\%$, $PRM_{GasTrap} = 7\%$, $DPM_{Normal} = 62\%$, $DPM_{Emph} = 1\%$, $DPM_{GasTrap} = 37\%$. CT, computed tomography; DPM, disease probability measure; FEV_1 , forced expiratory volume in 1 s; fSAD, functional small airway disease; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PRM, parametric response map.

There were no differences between the groups for body mass index. Pulmonary function measurements and smoking history worsened significantly according to GOLD grade.

PRM and DPM Measurements

Figure 2 shows a representative image of the expiratory CT, the registered inspiration CT, and the corresponding PRM- and DPM-derived map for a never-smoker, at risk, GOLD I, and GOLD II COPD participant. While the number of voxels classified as $PRM_{GasTrap}$

Fig. 3. Comparison of PRM_{GasTrap} and DPM_{GasTrap} (a) and PRM_{Emph} and DPM_{Emph} (b) measurements for never-smokers, at risk, GOLD I, and GOLD II COPD. COPD, chronic obstructive pulmonary disease; DPM, disease probability measure; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PRM, parametric response map.

and DPM_{GasTrap} (shown in yellow) increased with increasing GOLD grade, reflective of more severe gas trapping related to functional small airway disease, there were visually a greater number of voxels classified as DPM_{GasTrap} than PRM_{GasTrap} in each group. There were relatively few voxels classified as PRM_{Emph} and DPM_{Emph} (shown in red); however, these voxels also increased with increasing GOLD grade, indicating more emphysematous tissue destruction.

A quantitative comparison between the PRM and DPM measurements for never-smokers, at risk, GOLD I, and GOLD II is shown in Figure 3. Overall, DPM_{GasTrap} measurements were significantly elevated compared to PRM_{GasTrap} measurements ($p < 0.0001$). For both PRM_{GasTrap} and DPM_{GasTrap}, measurements were signifi-

cantly elevated in GOLD II compared to never-smokers ($p = 0.007$ and $p < 0.0001$, respectively) and at risk ($p = 0.006$ and $p < 0.0001$, respectively) participants, and for GOLD I compared to at risk ($p = 0.04$ and $p = 0.002$, respectively); DPM_{GasTrap} measurements were significantly elevated in GOLD II compared to GOLD I ($p < 0.0001$), but not PRM_{GasTrap} measurements.

There were no overall differences between PRM_{Emph} and DPM_{Emph} measurements ($p = 0.77$). For both PRM_{Emph} and DPM_{Emph}, measurements were significantly elevated in GOLD II compared to never-smokers ($p = 0.003$ and $p = 0.003$, respectively), at risk ($p = 0.007$ and $p = 0.008$, respectively), and GOLD I ($p = 0.04$ and $p = 0.03$, respectively), although there were no other differences between the groups.

Fig. 4. Box and whisker plots of DSCs for PRM and DPM voxel classification. **a** Box and whisker plot (whiskers represent the 5th to 95th percentiles) shows DSCs for PRM_{Normal} and DPM_{Normal} measurements (DSC = 0.65 ± 0.29), PRM_{Emph} and DPM_{Emph} (DSC = 0.50 ± 0.12), and PRM_{GasTrap} and DPM_{GasTrap} measurements (DSC = 0.36 ± 0.18). **b** The expiratory CT HU value for voxels classified as PRM_{Normal} and DPM_{Normal} (-722 ± 89 HU) was significantly greater than voxels classified as PRM_{GasTrap} and DPM_{GasTrap} (-884 ± 21 HU, $p < 0.0001$) and PRM_{Normal} but DPM_{GasTrap} (-785 ± 72 HU, $p < 0.0001$). The expiratory CT HU value for voxels classified as PRM_{Normal} but DPM_{GasTrap} was significantly greater than voxels classified as PRM_{GasTrap} and DPM_{GasTrap} ($p < 0.0001$). * $p < 0.05$. CT, computed tomography; DPM, disease probability measure; DSC, Dice similarity coefficient; HU, Hounsfield unit(s); PRM, parametric response map.

PRM and DPM Measurements: Spatial Comparison

Figure 4 shows the spatial comparison between the PRM and the DPM classification. The greatest spatial agreement for the PRM and DPM approach, as indicated by the DSC, was for voxels classified as normal (DSC = 0.65 ± 0.29), followed by emphysema (DSC = 0.50 ± 0.12), and the lowest spatial agreement was for gas trapping (DSC = 0.36 ± 0.18) (Fig. 4a).

To determine whether voxels classified as PRM_{Normal} but DPM_{GasTrap} showed evidence of greater expiratory CT gas trapping, the expiratory CT HU values were investigated. As shown in Figure 4b, the mean expiration CT HU measurement for voxels classified as PRM_{Normal} but DPM_{GasTrap} (PRM_{Normal}-DPM_{GasTrap} = -785 ± 72 HU) was significantly greater compared to voxels classified as gas trapping by both approaches (PRM_{GasTrap}-DPM_{GasTrap} = -884 ± 21 HU, $p < 0.0001$), but significantly reduced compared to voxels classified as normal by both approaches (PRM_{Normal}-DPM_{Normal} = -722 ± 89 HU; $p < 0.0001$).

PRM and DPM Measurements: Associations with Pulmonary Function Measurements and Symptoms

Table 2 shows separate multivariable linear regression models for pulmonary function measurements and symptoms with PRM_{GasTrap} and DPM_{GasTrap} measurements. After adjusting for confounding variables, both PRM_{GasTrap} and DPM_{GasTrap} were significantly associated

with FEV₁ ($p < 0.001$), FEV₁/FVC ($p < 0.0001$), RV/TLC ($p < 0.0001$), bronchodilator response ($p < 0.0001$), and dyspnea ($p < 0.05$).

Discussion

The search for reliable and meaningful biomarkers of early COPD-related changes has been ongoing for several decades. The use of these biomarkers is thought to be vital if therapeutic interventions at an early and potentially modifiable time point are to be developed. Our data from a population-based study of mild-to-moderate COPD participants indicate that (1) both PRM and DPM measurements of gas trapping related to functional small airway disease distinguished participants with mild and moderate COPD from those at risk, (2) DPM classified significantly more voxels as gas trapping than PRM and spatial analysis of the HU values indicated that DPM_{GasTrap} but PRM_{Normal} voxels had significantly lower HU values than voxels classified as normal by both approaches, and (3) both PRM and DPM showed similar, significant associations with pulmonary function measurements and dyspnea.

Both the PRM_{GasTrap} and DPM_{GasTrap} measurements were significantly elevated in GOLD I and GOLD II participants compared to those who had never smoked or were at risk of COPD but had normal lung function. How-

Table 2. Multivariable regression models for pulmonary function and symptoms with PRM_{GasTrap} and DPM_{GasTrap} measurements

	PRM _{GasTrap}		DPM _{GasTrap}	
	model R^2 , stand. β	p value	model R^2 , stand. β	p value
<i>Pulmonary function measurements</i>				
FEV ₁ , % _{pred}	0.13, -0.15	0.002	0.13, -0.15	0.001
FEV ₁ /FVC, %	0.24, -0.33	<0.0001	0.19, -0.21	<0.0001
RV/TLC, %	0.30, 0.17	<0.0001	0.31, 0.20	<0.0001
BDR, L	0.09, 0.26	<0.0001	0.06, 0.19	<0.0001
<i>Symptoms</i>				
Dyspnea	0.18, 0.13	0.02	0.18, 0.14	0.03
Chronic cough	0.03, 0.05	0.51	0.03, 0.11	0.14
Wheeze	0.09, 0.09	0.13	0.08, 0.06	0.32
Chronic phlegm	0.04, -0.03	0.73	0.04, -0.07	0.38

Adjusted for age, sex, race, pack-years, body mass index, and scanner model. BDR, bronchodilator response; DPM, disease probability measure; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PRM, parametric response map; RV, residual volume; stand., standardized; TLC, total lung capacity; %_{pred}, percent predicted.

ever, only DPM_{GasTrap} distinguished between GOLD I and GOLD II COPD, and overall, the DPM approach classified significantly more voxels as gas trapping related to small airway disease than PRM. While this suggests that DPM_{GasTrap} measurements may be more sensitive than PRM, without pathological validation it is unclear whether DPM improved specificity as well as sensitivity. We do note that emphysema measurements were consistent between PRM and DPM. Both PRM and DPM emphysema measurements were low in all participant groups and were only significantly elevated in GOLD II participants.

To provide a deeper understanding of the differences in the voxels that PRM and DPM classified as gas trapping related to small airway disease, we evaluated the spatial relationship of the two techniques using DSCs. These data showed that the gas trapping measurements had the lowest spatial agreement in comparison to voxels classified as normal and emphysema. Investigation of this discordance revealed that voxels classified as normal using PRM but gas trapping using DPM classification had significantly more expiratory gas trapping than voxels which both approaches classified as normal, thus indicating that DPM may identify regions that trap gas but do not reach the -856-HU CT threshold, which may explain the apparent greater sensitivity. Longitudinal and/or pathological studies are required to confirm that the DPM ap-

proach identifies gas trapping regions *before* they reach the -856-HU threshold and are detected by the PRM approach.

Finally, we demonstrated that both PRM and DPM showed similar, significant associations with pulmonary function measurements and dyspnea. This finding that both PRM and DPM are associated with established physiological tests of small airways obstruction and COPD symptoms bodes well for CT inspiratory-to-expiratory small airway disease measurements, and indicates that future investigation of both methods is warranted.

There are some limitations of this study that deserve mention. An important consideration and source of variability [24] for CT inspiratory-to-expiratory measurements are insufficient inhalation and/or exhalation to the target lung volume during image acquisition as well as technical factors such as the mismatch of reconstruction kernels and slice thickness between inspiration and expiration CT images [24]. Unlike other multicenter COPD cohort studies such as COPDGene [22] and SPIROMICS [25], the CanCOLD study acquired plethysmography measurements, and therefore we were able to directly compare plethysmography-derived lung volumes to CT-derived lung volumes for quality control. Our data show that even without a standardized breath-hold protocol to carefully control for lung volume, there was good agreement between CT and pulmonary function testing-derived lung volumes, indicating that routine clinical instructions during image acquisition allow for adequate inspiratory and expiratory images to be acquired (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000478865). While we acknowledge that efforts should be made to acquire CT images at the target lung volumes, such as implementing a standardized protocol for coaching prior to and during image acquisition [26], this finding bodes well for this advanced analysis technique in future clinical research studies conducted at multiple sites, with different CT systems and technologists. It is also important to note that we reported significant associations for PRM and DPM measurements with pulmonary function measurements and dyspnea regardless of whether we investigated all participants, only those with CT images acquired using the same convolution kernel/slice thickness between full-inspiration and full-expiration images, or only those with CT-measured lung volumes that were in agreement with the plethysmography-measured lung volumes (see online suppl. material).

We would also like to acknowledge that while the gas trapping measurements generated by the two classifica-

tion approaches were not in good agreement, it was beyond the scope of this study to determine which approach more closely represents ground truth. However, obtaining inspiration and expiration CT before surgical resection and performing morphometric analysis on the excised lung tissue samples may provide a way to validate these measurements. Furthermore, following these participants longitudinally will aid in determining whether these measurements provide prognostic information and reflect longitudinal changes in clinical outcomes. It is important to note, however, that both the PRM and DPM methods are equally accessible and can be obtained commercially (Imbio, Minneapolis, MN, USA; VIDA Diagnostics, Inc.).

In conclusion, CT registration-based measurements may provide a method to untangle the underlying small airway disease and emphysema disease contributions. The results of our study indicate that the functional effects of small airway obstruction quantified using inspiratory-to-expiratory CT PRM and DPM measurements are associated with pulmonary function measurements and COPD symptoms. Future research involving longitudinal evaluations will help determine the potential of these measurements as intermediate endpoints in clinical trials.

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