Computed tomography–based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression

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Chronic obstructive pulmonary disease (COPD) is increasingly being recognized as a highly heterogeneous disorder, composed of varying pathobiology. Accurate detection of COPD subtypes by image biomarkers is urgently needed to enable individualized treatment, thus improving patient outcome. We adapted the parametric response map (PRM), a voxel-wise image analysis technique, for assessing COPD phenotype. We analyzed whole-lung computed tomography (CT) scans acquired at inspiration and expiration of 194 individuals with COPD from the COPDGene study. PRM identified the extent of functional small airways disease (fSAD) and emphysema as well as provided CT-based evidence that supports the concept that fSAD precedes emphysema with increasing COPD severity. PRM is a versatile imaging biomarker capable of diagnosing disease extent and phenotype while providing detailed spatial information of disease distribution and location. PRM’s ability to differentiate between specific COPD phenotypes will allow for more accurate diagnosis of individual patients, complementing standard clinical techniques.

COPD is an increasingly prevalent disorder characterized by incompletely reversible airflow limitation1,2. Presently, it is the fourth leading cause of death in the United States, with over 11 million people suffering from the disease. The immense scope of this disease has led to major US National Institutes of Health–funded initiatives such as COPDGene3. COPD is a heterogeneous disorder that arises from pathological processes including emphysematous lung tissue destruction, gross airway disease and functional small-airways disease (fSAD) in varying combinations and severity within an individual. It is widely accepted that fSAD and emphysema are two main components of COPD and that a spectrum of COPD phenotypes with varying contributions of these components exists in individual patients; thus, the ability to diagnose the underlying phenotypes could improve prognostication and treatment of individuals afflicted by this disease2,4,6.

CT is a minimally invasive imaging technique capable of providing both high-contrast and high-resolution detail of the lungs and airways. CT has proven instrumental in identifying structural abnormalities associated with COPD. Although most of the clinically useful information today from lung CT comes from qualitative visual inspection, extensive research has been devoted to the application of quantitative techniques to high-resolution CT data sets using a wide variety of quantitative CT-based metrics to define COPD structural abnormality and disease severity. The percentage of emphysema, well accepted for identifying and quantifying the emphysema component of COPD, is determined using an attenuation-based method in which the sum of all image voxels of the smallest measureable unit of volume in an image data set, less than –950 Hounsfield units (HU) is normalized by the total lung volume on the inspiratory CT scan5,6. This metric is easily calculated from data acquired using standard imaging protocols. However, this metric only identifies one component of the heterogeneous COPD process. The second component, fSAD, remains a quantitative CT challenge, owing to the complexity of the histopathological features of COPD-affected lung tissue. Other attenuation-based techniques, such as the sum of all image voxels less than –856 HU normalized by the total lung volume on the expiratory CT scan, have been proposed as a measure of gas trapping but are unable to distinguish the contributions of small airways disease and emphysema from the gas-trapping measurement3. This challenge has prompted research that strives toward a more accurate and complete quantitative tool for the evaluation of COPD7–15.

The motivation for the present study was to develop a robust CT-based imaging biomarker that would allow for visualization and quantification of COPD phenotypes. Previously, we developed the PRM as a voxel-based method for improving the sensitivity of diffusion–magnetic resonance imaging (MRI) data for identifying early therapeutic response in patients with glioma16. This technique has since been validated as an early surrogate imaging biomarker of survival for gliomas, head and neck cancer, breast cancer and metastatic prostate cancer to the bone17–20. In 2009, we also demonstrated...
patients. Here we have considerably modified the PRM analytical approach to leverage the power of its pairwise analysis on inspiratory and expiratory CT lung scans to allow for quantification of fSAD separately from emphysema, which is not possible when the scans are analyzed independently. Our proposed PRM method is therefore a unique quantitative biomarker approach for assessment of COPD severity, phenotype and spatial heterogeneity using CT images. There are three fundamental steps in applying PRM to CT data before clinical diagnosis (Fig. 1). These steps involve image acquisition, image processing (that is, segmentation and co-registration) and classification of voxels with HU values characteristic of lung parenchyma representing normal (green), fSAD (yellow) or emphysema (red). The PRM method proposed in this study is a fundamentally new and different approach from prior work using this technique and a distinctly different approach from other CT-based quantitative measures (see Supplementary Note).

Commonly used CT metrics for diagnosis of lung disease use tissue volumetric summary statistics of lung fields such as the percentage of emphysema and mean lung density from inspiratory and expiratory phases. PRM, however, classifies local variations in lung function on the basis of a voxel-by-voxel comparison of lung attenuation changes from digitally co-registered inspiratory and expiratory CT scans to provide both global and local evaluation of COPD severity and phenotype. Using a well-defined COPD cohort, we show that this methodology allows for detection and quantification of not only emphysema but also tissue that comprises fSAD that can be monitored longitudinally in a single unified approach. PRM, being able to distinguish the relative contributions of fSAD and emphysema in COPD phenotypes, may serve as a complementary readout to current pulmonary function tests (PFTs) and CT-based metrics that will allow for more accurate diagnosis and improve the treatment management of individual patients.

RESULTS

Inspiratory and expiratory CT scans were acquired from 10,000 subjects as part of the COPDGene study. Of these, we used 194 with varying GOLD status, a classification of severity of airflow limitation in COPD based on post-bronchodilator PFTs (Supplementary Table 1) to demonstrate the PRM method for quantifying fSAD and emphysema. The ability of PRM to identify individuals with varying phenotypes of COPD is shown in representative coronal PRM images with corresponding inspiratory and expiratory CT scans from four subjects with varying GOLD status (Fig. 2 and Table 1). Details on the classification scheme are provided in the Supplementary Methods and Supplementary Figure 1. In the extreme cases, forced expiratory volume in 1 s (FEV1) and percentage of emphysema, defined as

Figure 2 COPD phenotypes identified by PRM. The strength of PRM to identify ISAD (PRM\(^ {\text{ISAD}}\)) from emphysema (PRM\(^ {\text{Emph}}\)) is demonstrated in representative coronal PRM images with corresponding inspiratory and expiratory CT scans from four individuals with varying GOLD status. From the three classifications, normal lung tissue is denoted green, fSAD is denoted yellow and emphysema is denoted red. Yellow scale bar indicates 5 cm. A modified figure has also been provided for easier visualization for those with some forms of color blindness (Supplementary Fig. 4).
percentage of lung < −950 HU (percentage emphysema in Table 1), accurately assess the severity of COPD, with subjects A and D having low and high levels, respectively, of emphysema (Fig. 2). Where PRM is most useful is in the identification of the underlying COPD phenotypes and the location of the specific disease classifications. Subjects B and C had near-identical FEV₁ measurements, yet the percentage of emphysema was elevated in subject C compared to subject B. Current techniques for assessing COPD severity were unable to accurately diagnose subject B, leaving the subject’s clinician to presume on the basis of FEV₁ and percentage of emphysema that the COPD in this individual is due primarily to airway obstruction. Our PRM measurements revealed that 26% of the lung tissue in subject B was fSAD (PRM^{fSAD}) tissue localized primarily in the upper lobes of both lungs, with minimal signs of emphysema (PRM^{Emph}). In subject C, we found that emphysema had progressed throughout the upper left lung, identified by the low attenuation on the inspiratory CT scan. PRM easily identified, quantified and spatially displayed fSAD expanding in the right upper lobe, which would have been missed by current clinical diagnostic methods such as percentage of emphysema.

The ability of PRM to identify and track individual voxels from inspiratory and expiratory scans allows for the individual components of COPD to be quantified and monitored (Supplementary Fig. 2). In addition, PRM provided unique information on the contribution of fSAD and emphysema in a variety of clinical tests that have been identified as being prognostic of COPD (Supplementary Table 2). We also found our PRM metrics highly sensitive when modeling airway obstruction while controlling for other CT-based airway measurements (Supplementary Table 3).

We observed a trend that involved the spatial distribution and association of fSAD tissue with emphysema (Fig. 3). We further analyzed PRM signatures for each individual to identify a pattern of disease progression in our cohort of 194 subjects. As part of the PRM approach, each voxel is classified on the basis of its location within a coordinate system. Figure 3a (see Supplementary Results for details) depicts the distribution of voxels with varying values at inspiration and expiration for a subject with normal status as determined by spirometry (FEV₁/forced vital capacity (FVC) = 83%, FEV₁ = 81%). Most of the voxels reside within the normal lung classification of PRM (green field), with voxels generally having more attenuation at expiration than inspiration as indicated by the hyperintensity of the expiration CT scan (Fig. 3a). In contrast, an individual with GOLD 4 status (FEV₁/FVC = 25%, FEV₁ = 18%) had a PRM signature distinct from the normal status. For this individual, voxels reside primarily within the fSAD (yellow field) and emphysema (red field) classifications. We observed similar attenuation on CT scans at inspiration and expiration and extensive emphysema (33% based on COPDGene percentage of emphysema metric) (Fig. 3b), which is characteristic of an individual with dyspnea (Modified Medical Research Council Dyspnea Scale = 3). As observed for these two subjects, voxels tended to concentrate on the Cartesian plot (that is, the PRM signature), with red and blue regions denoting high and low voxel density, respectively, such that an elliptical pattern is generated that has a location, distribution and orientation that is unique for each individual. On the basis of the distribution of voxels (Fig. 3a,b), we calculated for each subject the center of distribution that is the median values of all voxel data for both axes (position of the arrows) and the direction of largest covariance component (that is, the principal eigenvector that designates the longest axes of the ellipse) of each subject’s scatter plot (arrows; direction of arrowheads are arbitrarily chosen) and plotted data from all individuals on the inspiration-expiration diagram (that is, the Cartesian plot), which consists of the three PRM color codes defined in Figure 1. We observed a pattern suggestive of COPD progression that, to our knowledge, has never been demonstrated previously by CT-based measures. In fact, the data from the 194 subjects studied suggests that fSAD precedes emphysema in the progression of COPD. We also identified a unique relationship between fSAD and emphysema when plotting PRM^{fSAD} against PRM^{Emph} for all 194 subjects (Supplementary Fig. 3). We found that many of the

Table 1 Subject measures

| Subject | A | B | C | D |
|---------|---|---|---|---|
| GOLD   | NA| 2 | 2 | 4 |
| FEV₁   | 99| 55| 59| 18|
| Percentage emphysema | 4 | 5 | 19 | 23 |
| PRM^{Normal} | 85 | 66 | 54 | 21 |
| PRM^{Emph} | 1 | 4 | 16 | 28 |
| PRM^{fSAD} | 6 | 26 | 22 | 45 |

NA, not applicable. Percentage emphysema is the relative volume of lung with attenuation < −950 HU on the inspiratory scan.

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Figure 4 PRM as an imaging biomarker of COPD progression. Inspiratory CT scans, PRM and spirometry data are presented from two subjects not part of the COPDGene study. (a) PRM analysis of serial CT data acquired 11 months apart from an individual identified as GOLD 4. Conventional FEV\textsubscript{1} measurements were 18% and 17% 11 months later. (b) The PRM analysis of serial CT data acquired 26 months apart from an individual identified as GOLD 2. FEV\textsubscript{1} percentage were 66% to 75% at follow-up. PRM superscripts indicate the tissue classification (that is, normal, fSAD and emphysema), with Σ denoting all three classifications presented in the map. Yellow scale bars indicate 5 cm.

subjects have less than 10% emphysema, yet some can have fSAD that makes up 10–30% of their lung parenchyma (Supplementary Fig. 3). Notably, there appears to be a plateau in the amount of fSAD that can be present in the lung. More severe lung obstruction, as determined by FEV\textsubscript{1} (GOLD 3 and 4), seems to be attributable to contributions of both fSAD and emphysema, with PRM\textsuperscript{fSAD} plateauing around 40–50% and PRM\textsuperscript{Emph} increasing to >20% of the lung volume (Supplementary Fig. 3). These results suggest that fSAD precedes the onset of emphysema (Fig. 3 and Supplementary Fig. 3). Our findings agree with a recent study that demonstrated by pathology the narrowing and disappearance of small airways before the onset of emphysema in subjects with COPD\textsuperscript{22}. Notably, our data (Fig. 3c and Supplementary Fig. 3) are not longitudinal but rather snap shots of a cohort of individual subjects at various stages of the disease. This finding, obtained from a heterogeneous population, shows a specific trend in the CT data analyzed by our PRM methodology that suggests that airway obstruction associated with fSAD seems to be a precursor to the development of emphysema.

To provide some insight into the feasibility of PRM as an imaging biomarker to monitor individuals longitudinally over time, we obtained additional retrospective imaging data outside of the COPDGene study from subjects who had previously visited the University of Michigan pulmonary clinic and underwent an inspiratory/expiratory CT scanning protocol over a period of time. We present here examples from the unique PRM signature for each individual and the sufficient large population available for such an analysis. When plotting the metrics center of distribution and principle eigenvector for each of the 194 subjects, we observed not a random distribution of values within our inspiration-expiration plot (the Cartesian plot) but a continuous ribbon originating from healthy lung, through fSAD and ending at emphysema (Fig. 3). As each arrow is only a snap shot of disease state, we acquired additional longitudinal data from individuals not accrued as part of the COPDGene study to demonstrate the utility of PRM as an imaging biomarker for monitoring changes in COPD phenotype (Fig. 4). Although we consider these data promising, further validation of the use of PRM to follow COPD progression in subjects will need to be performed in a larger cohort of imaging data collected from a longitudinal study. Nevertheless, our results suggest that PRM provides a tool for improving understanding of the relationship between fSAD and emphysema in COPD progression.

DISCUSSION

In this study we demonstrate the ability of PRM, as a new application of an existing voxel-based image post-processing technique, to serve as a quantitative imaging biomarker to assess phenotypic contributions of fSAD and emphysema in COPD when applied to inspiratory and expiratory CT images\textsuperscript{21}. This is a new application of PRM in that cyclic physiological respiratory states, not changes in biological tissue as a response to disease or treatment, are being captured through imaging and compared on a voxel-by-voxel basis by image co-registration. In this analysis, the registered CT images share the same geometric space, that is, lung tissue at expiration is spatially aligned with the same lung tissue at inspiration. We developed a unique classification scheme based on specific thresholds that allows for spatial information about the disease to be retained. This is accomplished by classifying voxels into discrete zones that can be analyzed as a global metric (that is, relative volumes) but also support the ability to identify local phenomena of the individual PRM metrics. PRM can be used not only as a versatile imaging biomarker to diagnose disease extent and phenotype but also to provide detailed spatial information related to disease distribution and precise location. Moreover, PRM can potentially be used to reveal the nature of COPD progression as it pertains to small airways disease and emphysema.

The natural history of COPD within an individual has been primarily based on pulmonary function tests\textsuperscript{23}. Although the breadth of this knowledge has provided detailed information used to improve patient clinical care, it does not address the progression of the underlying phenotypes of COPD\textsuperscript{24}. Such understanding would allow clinicians to tailor therapeutic intervention to a particular COPD phenotype, as most cases have varying degrees of fSAD and emphysema. A key feature of PRM not easily attained by other methodologies is its potential to localize the disease states and possibly detect and identify the COPD progression pathway. This is made possible through the unique PRM signature for each individual and the sufficiently large population available for such an analysis. When plotting the metrics center of distribution and principle eigenvector for each of the 194 subjects, we observed not a random distribution of values within our inspiration-expiration plot (the Cartesian plot) but a continuous ribbon originating from healthy lung, through fSAD and ending at emphysema (Fig. 3). As each arrow is only a snapshot of disease state, we acquired additional longitudinal data from individuals not accrued as part of the COPDGene study to demonstrate the utility of PRM as an imaging biomarker for monitoring changes in COPD phenotype (Fig. 4). Although we consider these data promising, further validation of the use of PRM to follow COPD progression in subjects will need to be performed in a larger cohort of imaging data collected from a longitudinal study. Nevertheless, our results suggest that PRM provides a tool for improving understanding of the relationship between fSAD and emphysema in COPD progression.
Another potential use of this technique is as a secondary biomarker of therapeutic response in pharmacological trials. Few pharmaceutical advances in COPD have been made over the past few decades, primarily due to the lack of accurate biomarkers of the disease\textsuperscript{25,26}. In an effort to rigorously test potential therapies for COPD, the US Food and Drug Administration has set guidelines for potential biomarkers in specific contexts, which include stratification of patient populations, dose-ranging and use as a disease outcome. Currently, no well-validated biomarker of COPD has been identified other than FEV\textsubscript{1}, which is limited to whole-lung airway obstruction. Inclusion of the PRM approach proposed herein as a secondary endpoint may aid in pharmacological trials by stratifying patients as having ISAD- or emphysema-dominant COPD. For example, the relative volume of ISAD lung tissue (yellow voxels) could be used as a surrogate of treatment efficacy in routine patient care and in drug trials. A change of yellow voxels into green voxels should indicate lung tissue that has been rescued by therapeutic intervention.

The PRM approach differs from previous approaches because the classification process imposed on individual voxels allows the capture of the unique signature specific to the disease state of an individual patient. To date, groups who evaluate the prognostic value of registered data sets typically use statistically based metrics, such as the mean of the Jacobian, differences in HU or dissimilarity measures based on the histograms of the CT images where information from the measure is pooled throughout the lung into a single outcome measure, which forfeits the spatial information that is inherent in the CT images\textsuperscript{9,10,14,27}.

Given the prevalence and impact of COPD worldwide, there is a crucial need to develop quantitative imaging methodologies, which can more objectively characterize the disease and, ideally, define response to therapy. PRM provides a quantitative imaging application that has promise in classifying COPD by disease subtype and can be applied to facilitate individualized treatment strategies. PRM provides for parenchymal analysis as well as analysis of lung airway disease through a systematic algorithmic workflow for quantification of lung function in a high-volume, time-constrained clinical environment.

**METHODS**

Methods and any associated references are available in the online version of the paper.

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**AUTHOR CONTRIBUTIONS**

C.J.G. conducted data and statistical analyses and wrote the manuscript, M.K.H. acquired images, PFT data and clinical information from COPDGene, C.R.M. and J.L.B. optimized and performed image registrations, K.A.C. aided in image registration and performed PRM on image data, T.D.J. assisted with the statistical analysis, S.G. and A.R. contributed to the design of the study and E.A.K., F.J.M. and B.D.R. supervised the project, including data analysis and manuscript preparation.

**COMPETING FINANCIAL INTERESTS**

The authors declare competing financial interests: details are available in the online version of the paper.

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ONLINE METHODS

Subjects from COPDGene study. Subjects (n = 194, 110 male, 84 female) with at least a 10-pack-year history (1 pack-year = 1 pack per day for 1 year of smoking) of cigarette smoking were enrolling as part of the 10,000 total accrued subjects in the previously described COPDGene study (http://www.copdgene.org)3. The COPDGene study research protocol was approved by the University of Michigan Institutional Review Board, and all participants provided written informed consent. Subject characteristics and COPDGene study details are summarized in Supplementary Table 1.

Additional subjects. Additional retrospective longitudinal imaging data outside of the COPDGene study from two subjects who had previously visited the University of Michigan pulmonary clinic and underwent an inspiratory/expiratory CT scan protocol over two time intervals. Acquisition and analysis of these data were approved by the University of Michigan Institutional Review Board. Subjects provided informed consent.

Computed tomography acquisition and analysis. Except for the additional subjects obtained for longitudinal analysis, all CT data were obtained and analysis was performed as part of the COPDGene project. Whole-lung volumetric multidetector CT acquisition was performed at full inspiration and normal expiration using a standardized previously published protocol2. Data reconstructed with the standard reconstruction kernel was used for quantitative analysis. All CT data were presented in Hounsfield units (HU), where stability of CT measurement for each scanner was monitored monthly using a custom COPDGene phantom3. For reference, air and water attenuation values are −1,000 and 0 HU, respectively; the healthy lung parenchyma value is approximately −700 HU. Quantitative analysis of emphysema severity was performed on segmented lung images using Slicer (http://www.slicer.org/). The percentage of emphysema was defined as all lung voxels with a CT attenuation value of less than −950 Hounsfield units (HU) divided by the total lung volume at full inflation, multiplied by 100. The total percent gas trapping (GT) was defined as the fraction of lung with a CT attenuation value of less than −856 HU divided by the total lung volume at expiration, multiplied by 100. Automated airway analysis was performed using VIDA Pulmonary Workstation version 2.0 (http://www.vidadiagnostics.com/) using previously validated segmentation methods (details in Supplementary Methods)28. All analytical measurements not pertaining to the discussed PRM approach were performed by COPDGene personnel. Similar data acquisition and post-processing were performed on the additional retrospective longitudinal data sets, which were not obtained as part of the COPDGene study.

Parametric response mapping. Prior to registration, lung parenchyma and airways were segmented to restrict the focus of the registration process to the lungs only. The expiration CT (floating) image is spatially aligned to the inspiration (reference) CT image using thin-plate splines as the deformable registration interpolant. The registration algorithm is manually initialized using 42 degrees of freedom (DOF) warping of the floating data set. The automatic algorithm then iteratively optimizes the solution using mutual information as the objective function. The DOF of the warping is roughly doubled and the scale space halved in each of three subsequent registration cycles, automatically increasing the warping of the floating data set ultimately to approximately 330 DOF with no folding29.

The PRM of quantitative CT as expressed in HU, a measure of tissue density, was determined by imposing two thresholds: (i) −950 HU on full inspiration scan, with values less denoting emphysema, and (ii) −856 HU on normal expiration scan, with values less denoting gas trapping. These thresholds are applied to a joint histogram formed using all voxel pairs within the registered inspiration–expiration lungs. Three discrete classifications were identified (details in the Supplementary Methods) where voxels were designated as healthy lung parenchyma, color-coded green; fSAD, color-coded yellow; and emphysema, color-coded red. Global measures were also determined and presented as the relative volumes of each class, which are the sum of all voxels within a zone normalized to the total lung volume. To minimize the contribution of airways and vessels in our PRM analysis of parenchyma, only voxels with HU between −500 HU and −1,000 HU in both scans were considered for analysis.

Data and statistical analyses. Bivariate linear and logistic regression models were generated for individual prognostic indices of COPD severity and overall survival to assess the contribution of fSAD and emphysema, as quantified by PRM_EMph and PRMEmph, respectively; P values for the various statistical tests performed are presented in Supplementary Table 2. In addition, multivariate linear regression models were generated for FEV1 and FEV1/FVC to assess the contributions of PRM,sAD, PRM,Emph and airway measurements WAP (wall area percentage), IAI (inner area during inhalation), P10 (internal perimeter of 10 mm) and AWT (airway wall thickness) to the models (Supplementary Table 3). All statistical computations were performed with a statistical software package (SPSS Software Products). Results were considered statistically significant at the two-sided 5% comparison-wise significance level (P < 0.05). All data are presented as the mean ± s.e.m. Details on PRM signature analyses are presented in the Supplementary Methods. All calculations were performed using a mathematical programming software package (MatLab, MathWorks).

Additional methods. Detailed methodology is described in the Supplementary Methods.

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