Recent Advances in Computed Tomography Imaging in Chronic Obstructive Pulmonary Disease

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Abstract

Lung imaging is increasingly being used to diagnose, quantify, and phenotype chronic obstructive pulmonary disease (COPD). Although spirometry is the gold standard for the diagnosis of COPD and for severity staging, the role of computed tomography (CT) imaging has expanded in both clinical practice and research. COPD is a heterogeneous disease with considerable variability in clinical features, radiographic disease, progression, and outcomes. Recent

studies have examined the utility of CT imaging in enhancing diagnostic certainty, improving phenotyping, predicting disease progression and prognostication, selecting patients for intervention, and also in furthering our understanding of the complex pathophysiology of this disease. Multiple CT metrics show promise for use as imaging biomarkers in COPD.

Keywords: computed tomography; imaging; image registration; emphysema; small airways

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The diagnosis of chronic obstructive pulmonary disease (COPD) has traditionally relied on spirometry. This reliance on spirometry for diagnosis and severity assessment has led to modest advances in our understanding of underlying pathophysiology. COPD is increasingly recognized as a complex heterogeneous disease, and recent advances in computed tomography (CT) have enabled extensive phenotyping of COPD by allowing morphologic characterization of parenchymal and airways disease (1, 2). CT enables visualization of structural derangements and hence anatomic localization of disease, in contrast to spirometry, which is a more global measure. Indeed, substantial disagreement can exist between spirometric assessment of airflow obstruction and quantitation of structural lung disease (3). Visual analysis

can provide semiquantitative estimates of overall degree of emphysema, as well as of emphysema subtypes (4). In combination with qualitative estimates of airway disease, visual analysis has enabled phenotyping of COPD into emphysema and airways-predominant disease, with implications for respiratory morbidity and disease outcomes (5).

Automated density mask analyses have facilitated quantitation of low-attenuation areas on inspiratory scans to measure the percentage of lung parenchyma affected by emphysema (4). Using differential thresholds for lung density can provide estimates for mild and severe emphysema (4). Airway segmentation and measurement of segmental and subsegmental airway wall thickness allow quantification of airways disease, although these measurements are limited to

the first few generations of airway branching, due to limitations in CT resolution. Details of these advances in CT image-based quantification and assessment of COPD have been discussed elsewhere (1, 2, 6–8).

Recently, several large, multicenter studies combined information from both inspiratory and expiratory CT scans to extract clinically relevant measures of COPD. Inspiratory scans are obtained at total lung capacity (TLC) and expiratory scans at functional residual capacity (FRC) or residual volume. Expiratory scans allow quantification of gas trapping, an indirect measure of small airway disease that cannot be directly visualized with existing CT resolution. Inspiratory and expiratory images can be matched voxel to voxel, and assessments of regional lung expansion can be made. Using image post-processing tools,

paired CT scans obtained at two different lung volumes allow a rich and diverse range of measurements that substantially add to our understanding of disease pathophysiology. These techniques have highlighted the heterogeneity of disease processes in COPD, especially in early disease stages, where intervention may be more fruitful. In this Focused Review, we provide an overview of recent advances in using combined inspiratory and expiratory CT images for assessment of parenchymal and airways disease in COPD. We summarize the strong correlations of the new metrics with existing spirometric measures for disease diagnosis and severity assessment, and portray the value of these new measures by showing that these novel metrics explain respiratory morbidity and outcomes, independent of spirometry measures.

Computed Tomography Densitometry

Emphysema

Visual estimates of emphysema are semiquantitative and rely on estimates of lung density as well as visual patterns (4). Emphysematous lung can also be objectively quantified by commercially available computer software using selected thresholds of tissue attenuation measurement (Hounsfield units [HU]) on inspiratory images obtained at TLC. The number of voxels below this threshold expressed as a fraction of the total number of voxels provides a measure of emphysema. Thresholds of -910 HU and -950 HU have been used to quantify mild and severe emphysema, respectively (9–11), and both thresholds have been validated with histopathology (12–15). Multiple clinical studies have adapted these thresholds, providing data on patient selection for interventional studies (16), gene associations (17), and associations with respiratory morbidity (5).

Small Airway Disease

The small conducting airways less than 2 mm in internal diameter are the major site of airflow obstruction in COPD, but these cannot be directly visualized on CT. Density mask analyses of expiratory scans can quantify gas trapping, which reflects

increased air, and hence lower lung density at end expiration, resulting from a combination of decreased elastic recoil due to emphysema and increased small airway resistance. Densitometric results are substantially different in chronic bronchitis compared with controls on CT scans obtained at 90% and 10% of vital capacity, respectively (18). The most accepted threshold for gas trapping, assessed on expiratory scans, is -856 HU, although other thresholds have also been used (19). Gas trapping quantified using the -856 HU threshold correlates strongly with spirometric airflow obstruction ($r = -0.82$) (20).

A major limitation of the -856 HU fixed-density threshold on expiration is the inability to distinguish low-density regions due to emphysematous tissue destruction from gas trapping in more normal-appearing lung regions resulting from small airways disease. A number of investigators have attempted to account for the emphysema part and derive more specific measures of small airways disease (20, 21). Matsuoka and colleagues (21) excluded all voxels less than -950 HU as emphysematous voxels, and then calculated the percent change of relative area, with attenuation values from -860 to -950 HU between inspiratory and expiratory CT scans. They showed that this relative volume change strongly correlated with FEV_1/FVC (-0.78) and $FEV_1\%$ predicted (-0.80) (21). Hersh and associates (20) studied an alternative measure of gas trapping adjusted for emphysema by calculating the ratio of the expiratory to inspiratory mean lung density (E/I). The E/I ratio correlated with both FEV_1/FVC ($r = -0.62$) and $FEV_1\%$ predicted ($r = -0.73$), as well as with patient outcomes, such as dyspnea, respiratory quality of life, and 6-minute walk distance. They found that, especially in subjects with more severe emphysema, the E/I ratio, as well as the relative volume change from -856 HU to -950 HU, yielded more predictive associations with outcomes than measures using fixed thresholds, suggesting that these metrics provided additional information on small airway disease by adjusting for emphysema measures. Although these represent advances in assessing small airway disease, these measures provide adjustments for the global presence of emphysema, and lack the anatomic

localization to truly adjust for emphysema by region.

Large Airway Disease

In contrast to small airways, large airways above the sixth generation can be easily visualized on both inspiratory and expiratory scans. Segmental and subsegmental airway wall thickness has been used to quantify airway disease, with the assumption that changes at this level reflect more distal changes in the airway tree. Common measurements include airway wall thickness, airway wall area percent ($WA\% = [\text{outer area of airway} - \text{lumen area}] / \text{outer area of airway} \times 100$), and square roots of the wall areas of hypothetical airways with internal perimeters (P_i) of 10 and 15 mm (P_{i10} and P_{i15} , respectively) (22–25). The P_{i10} and P_{i15} measurements were devised to avoid bias due to between-subject differences in airway sizes. The square root of the airway wall thickness was plotted against the P_i of each airway, and the regression line was used to derive the square root of the wall area for a “hypothetical airway” with P_{i10} or P_{i15} . These metrics correlate with FEV_1 (26, 27), bronchodilator responsiveness (28), paradoxical response to bronchodilators (29), and respiratory morbidity independent of emphysema (30), and also are associated with subsequent lung function decline (26). P_{i10} has been reported to be greater in patients without evident airflow obstruction, but with respiratory symptoms (31), and a greater P_{i10} can predict the development of airflow obstruction on longitudinal follow-up (26). Wall area thickness expressed as a percentage of overall $WA\%$ increases with increasing disease severity, but, at each airway generation, luminal diameter decreases disproportionately with worsening disease compared with wall area itself, and recent studies show progressively thinner airway walls with worsening disease severity (32, 33). Washko and colleagues (34) assessed the density of airway walls and showed that wall attenuation is associated with lung function, even after adjustment for emphysema and $WA\%$, suggesting that this measure offers additional information on the characteristics of the larger airways.

In addition to changes in wall thickness, airway walls are also frequently

less rigid and more collapsible in patients with COPD, and the degree of airways collapse on expiration can be assessed on expiratory CT. Expiratory central airway collapse (ECAC) includes expiratory dynamic airway collapse due to weak posterior membrane of the larger airways, as well as tracheomalacia due to cartilaginous weakness. Although the small conducting airways offer the most resistance to airflow in COPD, collapse greater than 50% of the larger central airways during exhalation likely causes additional airflow obstruction. Traditionally diagnosed on bronchoscopy or using dynamic CT during exhalation, ECAC visualized on dual-volume static CT is common in COPD, and is present in about 5% of patients with COPD (35). In a large study of 8,820 current and former smokers, Bhatt and colleagues (35) showed that the presence of

ECAC is associated with worse respiratory quality of life, greater dyspnea, and a higher frequency of exacerbations.

Image Matching

To improve anatomic localization and enhance the separate assessment of emphysema and small airway disease, spatial alignment of inspiratory and expiratory images is necessary. This can be achieved by image matching, also referred to as image registration, which performs the task of spatial alignment or voxel-by-voxel mapping, either between two-dimensional images or three-dimensional volumes. Image matching is usually performed between inspiratory and expiratory CT scans, such that one image is spatially deformed to match the other using defined

anatomic landmarks, such as airways (Figure 1). The procedure can also be performed between baseline and follow-up scans in longitudinal studies to track regional disease progression. Multiple algorithms for image registration exist, the technical details of which have been described previously (36). There are two fundamental approaches to extract clinically relevant information from the image registration process (Figure 1). The first approach is to perform a voxel-by-voxel anatomic comparison and assess the corresponding CT density change from expiration to inspiration, with compensation for lung deformation through image registration. The second approach is to use the lung deformation between inspiration and expiration to derive mechanical and functional measures of lung parenchyma.

Figure 1. The technique of image registration and two fundamental approaches to extracting clinically relevant information from image registration. Inspiratory and expiratory images are matched voxel-by-voxel. Structural measures can be obtained by performing a voxel-by-voxel anatomic comparison and assessing the corresponding computed tomography (CT) density change from expiration to inspiration, with compensation for lung deformation through image registration. The top right shows a representative axial section with localization of emphysema (red), functional small airways disease (yellow), and normal (green) voxels in a patient with moderate chronic obstructive pulmonary disease (COPD). The bottom right depicts functional changes on the same slice. Here, the amount of lung deformation between inspiration and expiration is used to derive a measure of regional ventilation, termed the Jacobian determinant, a measure of local volume change from full inspiration to end expiration. The Jacobian determinant ranges from 0 to infinity; values greater than 1 indicate local expansion, and values less than 1 indicate local contraction. PRM = parametric response mapping.

Structural Lung Disease

Small Airway Disease

Parametric response mapping (PRM) is a recently introduced application of image matching, whereby inspiratory and expiratory images are matched on a voxel-by-voxel basis to examine the differences in density between inspiratory and expiratory images (37). For all voxel pairs within the registered inspiration–expiration lungs, PRM classifies individual voxel pairs based on the commonly used fixed CT density thresholds that represent emphysema (−950 HU on inspiratory CT) and gas trapping (−856 HU on expiratory CT). Voxels with density less than −950 HU on inspiratory CT and less than −856 HU on expiratory CT are deemed emphysematous voxels (PRM^{Emph}), and voxels with density greater than −950 HU on inspiratory CT and less than −856 HU on expiratory CT scan represent areas of “pure” gas trapping without contribution from emphysema, and thus a measure of functional small airways disease (PRM^{fSAD}). The term “functional” is used, as this metric does not directly visualize small airway disease, but instead provides a more homogeneous measure of nonemphysematous air trapping.

As seen with earlier density threshold-based gas trapping metrics, PRM measures correlate strongly with lung function, and PRM^{fSAD} is inversely related to FEV_1/FVC ($r^2 = 0.545$) and to FEV_1 ($r^2 = 0.517$), independent of emphysema (37). In mild to moderate COPD (GOLD [Global Initiative for Chronic Obstructive Lung Disease] stages 1–2), density-based CT gas trapping and PRM^{fSAD} show similar correlations with FEV_1 ; however, the two measures show differential trends in higher disease stages (GOLD stages 3–4), as increasing emphysema adds to the gas trapping fraction (37). It should be noted that density-based CT emphysema and PRM^{Emph} provide identical measures of emphysema, as they do not account for expiratory changes.

PRM provides spatial information on disease location and subtype, and PRM metrics can serve as imaging biomarkers for disease progression. Studies using PRM^{fSAD} as a measure of small airway disease appear to corroborate micro-CT data, suggesting that small airways disease precedes emphysema development in COPD (37,

38). In a large study of 1,508 current and former smokers with and without COPD, Bhatt and associates (39) showed that both PRM^{fSAD} and PRM^{Emph} were associated with FEV_1 decline in patients with COPD; however, in those at risk, but without overt airflow obstruction, PRM^{fSAD} , but not PRM^{Emph} , was associated with FEV_1 decline. Using sequential, paired CT scans at baseline, 30 days, and 12 months, Boes and colleagues (40) showed that PRM metrics are reproducible. They evaluated temporal changes in emphysema and small airways disease across a range of disease severity over a 12-month period and found that there is an early increase in PRM^{fSAD} in mild disease followed by a decrease in PRM^{fSAD} even as PRM^{Emph} increases with increasing disease severity. Some of the PRM^{fSAD} appears to be reversible, and may represent airway inflammation, mucus plugging, or bronchospasm as opposed to airway fibrosis or disappearance (40). The anatomical localization provided by image registration can prove useful to track disease progression locally. Correlations of these metrics with histopathology are currently underway.

Emphysema

Lung density measurement remains the best available metric to track structural disease progression in clinical studies (41), and this has been used to track response to augmentation therapy in patients with α_1 -antitrypsin deficiency (42, 43). A major challenge in the assessment of disease progression on CT is variability in the lung volume at which serial CT scans are acquired, as changes in TLC can affect lung density measurements. Measurements of disease progression are also influenced by scanner variability. Change in smoking status between scans can also affect lung density, with active smoking resulting in higher lung density than not smoking (44). Efforts are being made to standardize lung volumes during CT acquisition, and phantoms are being used to ameliorate scanner variability (25). A further limitation of these density measures is that they are global assessments of disease, with incremental changes over time. Image registration can be employed to match inspiratory scans obtained serially to assess emphysema progression (45, 46). Gorbunova and colleagues (47) used image registration in a small study of 27

patients with severe emphysema to match serially acquired images at baseline, and at 3, 12, 21, and 24–30 months, and found that measurement of local disease progression could be consistently demonstrated. Image registration–based algorithms have been proposed for the measurement of local progression of emphysema that is minimally affected by changes in lung volume between baseline and follow-up (48, 49).

Functional Measures

The heterogeneity of disease initiation and progression implies that there is no uniform trajectory from an absence of disease to the development of airflow obstruction, and that there are trajectories in disease progression beyond that measured by FEV_1 alone. FEV_1 alone is likely not sufficient to measure disease progression. In addition to structural changes in the lung that precede the development of airflow obstruction, there are likely local functional changes that may initiate or aid progression of disease (50), changes that can be assessed by CT image registration at a regional level. Functional measures based on the deformation of the lung during respiration may enhance our understanding of the pathophysiology of COPD, and may result in more sensitive measures for detection of emphysema (51). Two classes of registration-based measures of regional function of lung parenchyma can be derived: regional ventilation measures (local volume change) and measures of lung tissue mechanics (Figure 2).

Regional Ventilation

Density difference. Spirometry provides a global measure of volume change from inspiration to expiration. It is increasingly apparent that a substantial amount of functional loss at the regional level can exist before detection of disease by spirometry (31, 52). Given that lung tissue remains constant during the respiratory cycle, and disregarding vascular volume changes, there is a normal increase in CT attenuation from end-inspiration to end-expiration, and the change in lung density from inspiration to expiration reflects change in air volume. Air trapping

Figure 2. Differences in detection of structural lung disease using lung density measures (top panel) and after image registration with separation of emphysematous voxels and nonemphysematous gas trapping (middle panel). The bottom panel shows local volume change with respiration measured using the Jacobian determinant. Representative computed tomography (CT) scans from an individual without chronic obstructive pulmonary disease (COPD) and two individuals with moderate and severe COPD, respectively, are displayed. The figure demonstrates the differences in the three metrics for the same individuals using different tools for measuring parenchymal lung disease in COPD. PRM = parametric response mapping.

manifests as regions that do not show the expected increase in attenuation, reflecting either a reduced or absent change in gas volume during respiration. Dougherty and colleagues (53) subtracted matched inspiratory density maps from expiratory images and estimated the volume change in the areas of gas trapping. To improve spatial localization of volume change, Kim and associates (54) classified areas of the lung with density difference less than 50 HU as having gas trapping on paired inspiratory–expiratory scans (air trapping index), and assessed the degree of regional gas trapping in areas of normal, emphysematous, and hyperinflated lungs on baseline inspiratory scans. They found

that this air trapping index correlated with FEV_1/FVC ($r = -0.74$) and $FEV_1\%$ predicted ($r = -0.73$), with stronger correlations for the diseased regions of the lungs than normal lung regions. Unlike the gas trapping measures based on global density differences measured by the E/I ratio, these metrics have the advantage of spatial localization, and hence can measure regional heterogeneity.

Specific volume change. Simple density difference metrics are confounded by the influence of the baseline inflation of the lung region of interest. Simon (55) described specific volume change (sVol), which is the ratio of density change between inspiration and expiration over a tidal

breath to the initial gas volume at inspiration. sVol has been validated against regional ventilation with xenon-CT in sheep, with a linear relationship between the two measures (56). Images acquired during tidal breathing can be substituted by images acquired at TLC and FRC, and the resultant sVol will reflect the regional volume change over that pressure and volume gradient. Coxson and colleagues (15) introduced another surrogate measure of regional ventilation, the specific regional gas volume (ΔSVg), by estimating the change in quantity of gas per gram of tissue between inspiration and expiration. They demonstrated a homogeneous distribution of ΔSVg in healthy subjects and

heterogeneous distribution in patients with COPD, with regions showing evident gas trapping associated with ΔSVg . All these metrics can be affected by the gravitational dependence of lung density, with dependent areas showing greater lung density. A comparison of the three metrics of regional ventilation (density difference, sVol, and ΔSVg) showed that ΔSVg is least affected by gravity, and thus the heterogeneity seen in COPD is more directly related to the underlying pathology (57). These functional measures can detect additional heterogeneity over simple density maps. A possible explanation for the greater heterogeneity of functional measures in COPD than in normal subjects is difference in tissue compliance. An additional plausible reason is the presence of collateral channels and collateral airflow. In the healthy lung, collaterals have a minor effect on ventilation distribution, as they have up to 165-fold greater resistance to airflow than normal airways. However, in emphysematous lungs, collaterals can significantly impact regional ventilation as a result of decreased collateral resistance and increased airway resistance (58). Indeed, studies of regional ventilation have

demonstrated an increase in local volume from inspiration to expiration in some areas, likely due to air entering from collaterals, and quantifying these areas has been proposed as a way of measuring collaterals (57).

Jacobian measures of volume change. Lung deformation with respiration can be used to derive an alternative CT registration-based measure of regional ventilation termed the Jacobian determinant, a measure of local volume change from TLC to FRC (3, 59). The deformation map created using registration represents pointwise expansion and contraction of lung areas, and has values ranging from 0 to infinity (Figure 3). A Jacobian determinant value greater than 1 indicates local expansion, less than 1 indicates local contraction, and a value of 1 represents neither local expansion nor contraction. Reinhardt and colleagues (60) estimated the Jacobian determinant-based local volume change, and showed good agreement with sVol measured on xenon-CT. In patients with COPD, the Jacobian determinant has been shown to correlate strongly with FEV_1/FVC ($r = 0.76$) and $FEV_1\%$ predicted ($r = 0.80$) (3, 59), and is more strongly associated with airflow

obstruction and respiratory quality of life than density measures of emphysema. Although there is strong correlation between CT emphysema and CT gas trapping with airflow obstruction, there is also substantial discordance in a number of patients with COPD (61). Values for the mean Jacobian determinant in life-long nonsmokers range from 1.3 to 2.5, with an average of 2.0 (62). Bhatt and colleagues (3) showed that, in patients with substantial discordance between spirometric airflow obstruction and the degree of emphysema visualized on CT, the mean Jacobian determinant considerably improved prediction of spirometric airflow obstruction and also concordance between CT and spirometry measures of disease. Bodduluri and associates (63) showed that the mean Jacobian determinant for the entire lungs is independently associated with the body mass index, airflow obstruction, dyspnea, and exercise capacity index, (BODE) and thus offers additional prognostic information over that provided by traditional CT measures of structural disease (64). On follow-up, the mean Jacobian determinant approached statistical significance for predicting mortality (adjusted hazard ratio = 4.26; 95%

Figure 3. Image matching and derivation of the Jacobian determinant. CT = computed tomography, D = deformation field; J = Jacobian.

confidence interval = 0.93–19.23; $P = 0.064$) (63). Bhatt and associates (65) used Jacobian metrics to show that normal voxels within 2 mm distance of emphysematous areas are mechanically influenced by the emphysematous areas, and this “mechanically affected lung” can be used to predict lung function decline.

Lung Mechanics

Although the density-based and Jacobian-based measures of regional ventilation quantify local volume change in the presence of disease, lung mechanics involve more than just volume change with respiration. Certain regions of the lung might undergo significant deformation, but no substantial volume change, especially when expansion in one axis is compensated by contraction along another axis. This is especially likely in the presence of heterogeneous adjacent lung. Based on this concept, Amelon and colleagues (66) developed the anisotropic deformation index, which captures the direction of lung deformation between inspiration and expiration using CT image registration. The lung deformation field can also be used to derive strain tensor, which is the ratio of the length of the deformed region of interest to the initial length of that region in the lung. Bodduluri and colleagues (59) combined the strain information, anisotropic deformation index, and Jacobian measure of volume change to create a lung biomechanical feature set. They compared the lung biomechanical feature set with CT density and texture-based measures of emphysema and gas trapping in identifying the presence and severity of COPD, and found that the biomechanical feature set was more accurate in COPD diagnosis and in severity classification. Estimation of mechanical forces can be useful in predicting disease progression over time (65).

Practical Considerations and Limitations

Although CT imaging can provide a rich source of information for the diagnosis and

phenotyping of COPD, certain limitations exist. Considerable variability can occur between scans obtained at different time points, due to a number of potential sources of error, including scanner miscalibration, differences in reconstruction kernels used, and variability introduced by manufacturer-determined reconstruction algorithms. Image comparison can also be affected by the lung volumes at which the images are acquired. Patient characteristics, such as obesity and active smoking, can influence lung density. Recently, reference equations were published for normative data for CT density parameters that can alleviate some of these sources of bias. Understandably, there remain concerns about radiation exposure with additional expiratory CT scans. Expiratory CT scans add an additional one-third to one-half of the inspiratory CT radiation exposure (25). Although the current radiation dose exposure for chest CT is approximately 7.0 mSv, multiple recent technological advances, including automatic exposure control, automatic tube potential selection, dynamic z-axis collimators, and beam-shaping filters, as well as advances in iterative reconstruction algorithms and noise reduction methods, are likely to reduce radiation exposure two- to fourfold. It is anticipated that “submillisievert” scans will be possible in the near future, accounting for only one-third of the average background radiation exposure (67).

Clinical Applications and Future Directions

Although CT scans are not routinely obtained for patients with COPD in clinical practice, we believe CT imaging can be useful in a number of clinical scenarios. Patient selection for lung volume reduction procedures for severe emphysema, both surgical and bronchoscopic, is based on heterogeneity of emphysema on volumetric CT (16, 68, 69). Fissure integrity can be assessed in an automated fashion, and at least 90% of fissure integrity is associated with better outcomes for bronchoscopic

lung volume reduction (70). CT densitometry can be used as a surrogate end point for disease progression in patients with α_1 -antitrypsin deficiency receiving augmentation therapy (42, 43). Density-based and mechanics-based measures are also associated with respiratory morbidity, disease progression (39, 65, 71), and mortality (5, 39, 72), independent of lung function, thus providing additional information over and above that provided by spirometry alone. There is no definitive therapy to slow FEV₁ decline. It is possible that the variability of FEV₁ makes it less sensitive to changes induced by medications, and studies are underway to assess whether medications can influence the rate of progression of disease as measured by CT density (NCT00720226, available from www.clinicaltrials.gov) (73). A first step in targeting disease progression is detecting patients at risk, and CT has enabled identification of a number of biomarkers for disease progression, including assessment of functional small airways disease and mechanically affected lung (39, 65). Whether these CT biomarkers are modifiable remains to be investigated in future studies.

Conclusions

In summary, obtaining expiratory CT scans in conjunction with novel tools of image registration and parametric response mapping can add considerable anatomic and functional information in selected patients at risk for, or with, COPD. Measures of functional change in the lung parenchyma are likely to detect disease before becoming manifest on visual examination by a radiologist, and can also shed light on parenchymal heterogeneity that might aid patient selection for therapies, such as lung volume reduction. More research is needed to evaluate whether these emerging metrics can be used as intermediate end points for assessing response to pharmacotherapy. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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