Advances in Chronic Obstructive Pulmonary Disease Imaging

Wojciech R. Dolliver, MD and Alejandro A. Diaz, MD, MPH
Division of Pulmonary and Critical Care Medicine, Brigham and Women’s Hospital, Boston, MA, USA

ABSTRACT
Chest computed tomography (CT) imaging is a useful tool that provides in vivo information regarding lung structure. Imaging has contributed to a better understanding of chronic obstructive pulmonary disease (COPD), allowing for the detection of early structural changes and the quantification of extra-pulmonary structures. Novel CT imaging techniques have provided insight into the progression of the main COPD subtypes, such as emphysema and small airway disease. This article serves as a review of new information relevant to COPD imaging.

CT abnormalities, such as emphysema and loss of airways, are present even in smokers who do not meet the criteria for COPD and in those with mild-to-moderate disease. Subjects with mild-to-moderate COPD, with the highest loss of airways, also experience the highest decline in lung function. Extra-pulmonary manifestations of COPD, such as right ventricle enlargement and low muscle mass measured on CT, are associated with increased risk for all-cause mortality.

CT longitudinal data has also given insight into the progression of COPD. Mechanically affected areas of lung parenchyma adjacent to emphysematous areas are associated with a greater decline in forced expiratory volume in one second (FEV₁). Subjects with the greatest percentage of small airway disease, as measured on matched inspiratory-expiratory CT scan, also present with the greatest decline in lung function. (BRN Rev. 2020;6(2):128-43)

Key words: Chest computed tomography. Chronic obstructive pulmonary disease. Emphysema. Muscle mass. Small airway disease.
INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a complex disease with significant heterogeneity in terms of structural and clinical manifestations as well as progression. For instance, subjects with similar severity of airflow obstruction may experience marked differences in symptoms, health-related quality of life, exacerbation prevalence, and exercise capacity. The extent of parenchymal and airway abnormalities, as well as extra-pulmonary manifestations of the disease, also differ between patients with similar levels of spirometric impairment. Chest imaging, particularly computed tomography (CT) and magnetic resonance imaging, provides an in vivo assessment of those processes and enables tangible visualization of COPD pathology. Recent progress in COPD imaging has generated a better understanding of the disease process. This progress has allowed for the improved detection of structural changes in subjects at risk for COPD, the identification of COPD phenotypes, and the additional evaluation of associated extra-pulmonary structures. For example, imaging has demonstrated that airways are not only remodeled but are also completely lost\(^1\,^2\). Airway loss has been shown to precede the development of emphysema, and subjects with the highest airway loss on CT, also experience the greatest decline in lung function\(^3\,^4\).

A myriad of factors have contributed to this progress in COPD imaging, including the increased use of CT scanning; improved computational capabilities; artificial intelligence-based development of algorithms for imaging; and the increased availability of large cohorts of subjects with imaging characterization, such as the Genetic Epidemiology of COPD (COPDGene) Study\(^5\), Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE)\(^6\), Subpopulations and Intermediate Outcome Measures of COPD Study (SPIROMICS)\(^7\), and Canadian Cohort Obstructive Lung Disease (CanCOLD) Study\(^8\).

In this review, we have primarily focused on CT imaging as a modality since it is most widely used, and it provides a tremendous source of information. Three main aspects of imaging are explored: a) imaging of subjects at risk for and with mild COPD, b) imaging of extra-pulmonary structures, and c) COPD progression imaging. Recent reviews on other imaging modalities and aspects of COPD are available\(^9\,^10\).

IMAGING OF SUBJECTS AT RISK FOR AND WITH MILD COPD

The diagnosis of COPD is primarily based on spirometric measures of airflow obstruction (i.e., a ratio of forced volume in one second to forced vital capacity \([\text{FEV}_1/\text{FVC}] < 0.7\)\(^11\); however, substantial clinical manifestations, such as dyspnea, chronic bronchitis, exacerbations, and hospitalizations, as well as structural changes, can occur before susceptible individuals meet the criteria for airflow obstruction\(^12\,^15\).

Lung parenchyma imaging

Imaging studies suggest that smokers undergo a radiographic bi-phasic remodeling process, with a more predominant diffuse parenchymal inflammation in mild disease.
followed by emphysematous destruction in more advanced stages. In a large cohort, investigators demonstrated that CT lung mass (i.e., lung parenchyma Hounsfield Units [HU] +1,000) was higher in smokers with mild disease (i.e., Global Initiative for Obstructive Lung Disease [GOLD] stage 1) than those without COPD and those with GOLD stages 2-416. Although the findings of that study may reflect the effect of cigarette smoking on increasing lung density rather than inflammation, additional studies in smokers have linked high-density lung areas with clinical outcomes and inflammation biomarkers. Investigators explored areas of normal-looking parenchyma and examined their local density to elucidate their potential clinical implications. They then determined the percentage of lung occupied by normal-looking parenchyma with density values at the percentile 95th or above (abbreviated: Norm_HA), — taken from the distribution of local histograms of density in never-smoking subjects. The investigators found that smokers with the highest quartile of Norm_HA had lower exercise capacity and a higher risk of death than did those in the lowest quartile, independent of emphysema and interstitial lung abnormalities. They also found that a higher percentage of regions of lung occupied by Norm_HA was related to higher levels of C-reactive protein, a biomarker of systemic inflammation. Although the study still lacks histological validation, this CT metric has the potential to identify mild lung tissue injury (or inflamed tissue), before the phase of lung destruction (emphysema) becomes apparent.

CT is a non-invasive, in vivo method to identify and quantify emphysema. Emphysema is quantified as percent of low attenuation areas (%LAA) below a selected HU threshold, typically -950 on inspiratory CT scans, whereas gas trapping is defined as %LAA below -850HU on expiratory CT scans. Emphysema is typically thought of as a manifestation of overt COPD: however, in a large CT study, 26% of smokers who do not meet the spirometric criteria for COPD had radiographic evidence of lung disease, encompassing emphysema (defined as > 5% of LAA on inspiratory CT) or gas trapping (defined as > 20% of LAA on expiratory CT), suggesting that spirometry underestimates the effects of cigarette smoking in this population. Moreover, in the general population, the emphysema-like lung was demonstrated to be predictive of incident airflow limitation. This information could prove useful for clinicians, as increased emphysema on CT scans in smokers at risk to develop COPD may warrant closer monitoring and earlier follow-up.

Airways imaging

CT imaging has also demonstrated that in never-smoker subjects, the smallest central airways (i.e., airways visible on clinical CT scans) are associated with the lowest lung function, and central airways in smokers with COPD are smaller than in smokers without COPD, suggesting an interplay of native tracheobronchial structure and environmental exposures such as tobacco smoke. One possible consequence of this interplay is that people with smaller central airways may be more prone to develop airflow obstruction when exposed to tobacco smoke. Moreover, people who have small central airways relative to lung size —a phenomenon called dysanapsis— are more likely to develop COPD over
time. In terms of bronchial structural changes, symptomatic current and former smokers without COPD had higher central airway-wall thickening compared to their asymptomatic counterparts.

Central airways may reflect small airway (i.e., <2mm lumen diameter) pathology, the site of airflow obstruction in COPD. A surrogate measure of small airway disease is air trapping on expiratory CT images. Computational advances have made it possible to match voxel-to-voxel inspiratory and expiratory images, a technique called Parametric Response Mapping (PRM) (Fig. 1). Based on lung density thresholds described above, PRM classifies the paired voxels as normal, emphysema (PRM<sub>EMPH</sub>), and functional small airway disease (PRM<sub>fSAD</sub>), the latter representing non-emphysematous air trapping areas of the

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**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 (reprinted from Bodduluri et al. (Annals of the American Thoracic Society 2018; 15(3): 281-289) with permission of the American Thoracic Society, © 2020 American Thoracic Society). PRM: parametric response mapping.
lung. The metric has been recently validated against microCT measures of small airway disease in lung tissue from COPD patients who underwent a lung transplant. Specifically, a higher percentage of PRM\text{ISAD} was related to lower circularity and luminal area as well as complete obstruction of terminal bronchioles; a higher PRM\text{EMPH} was correlated with larger air space size, lower alveolar surface area, and fewer alveolar attachments per terminal bronchioles. In COPD pathogenesis, small airway disease is thought to precede the emphysematous destruction of the lung. Interestingly, a study in smokers without meeting criteria for COPD, showed that higher PRM\text{ISAD} was associated with a higher residual volume to total lung capacity ratio (RV/TLC), an index of air trapping; a lower transfer factor for carbon monoxide adjusted for alveolar volume; and spirometric measures of small airways. These findings suggest that high PRM\text{ISAD} might be an early indicator of pulmonary pathology in this population.

CT imaging has also helped demonstrate variations in central airway tree branching, which has been identified in over one-quarter of the general population. Investigators have shown that central airway branch variants have strong familial aggregation and increased COPD susceptibility, particularly among smokers. They also found that one airway branch variant—the absence of the right medial-basal airway—was associated with single nucleotide polymorphisms of fibroblast growth factor 10—FGF10, which is involved in a broad range of cellular processes including, lung morphogenesis—supporting a genetically programmed airway structure-function endotype. COPD pathology is characterized by a profound loss of small airways as shown on microCT, up to 40% in mild-to-moderate COPD, and up to 80% in severe-to-very severe COPD when compared to smoker controls. The loss of normal parallel pathways in this setting may explain the increased (4- to 40-fold) resistance to airflow, a central pathophysiologic feature of the disease. The loss of small airway branches seems to extend to central airways as well, as demonstrated in patients with advanced and mild-to-moderate disease. In a Canadian study, the total airway count (i.e., the number of branches counted on a CT-based bronchial tree) of subjects with mild-to-moderate COPD and never-smoking controls and smokers without COPD was compared. The authors found that patients with COPD had a 19% and 17% lower total airway count compared to never-smoking subjects and smokers without COPD, respectively. Furthermore, parent airways with missing daughter branches had smaller lumens and thinner walls than those parent airways without missing branches, which raises the possibility that airways shrink before disappearing. The loss of airways also raises the question as to whether it may have therapeutic implications, particularly for inhalation therapy.

**IMAGING OF EXTRA-PULMONARY MANIFESTATIONS OF COPD**

COPD is considered a systemic disease affecting multiple organs. Advances in imaging have allowed for the identification and quantification of extra-pulmonary structures, leading to a better understanding of their relationships with the lungs and the potential clinical implications. Large vessels such as the pulmonary
artery and aorta, as well as the heart, skeletal muscles, and bones, can be segmented and quantified; and their associations with clinical outcomes determined.
Large vessels

Pulmonary hypertension is frequent in patients with COPD and linked to worse outcomes\(^{29}\). Although the standard method to diagnose pulmonary hypertension is right heart catheterization, imaging modalities such as echocardiogram and CT are non-invasive alternatives to identify this condition\(^{29}\). Enlargement of the main pulmonary artery (PA) has long been recognized as an imaging feature of pulmonary hypertension. On CT images, PA enlargement is measured as the ratio of the diameter of PA to the aorta (PA:A) on a single axial slice. It has been demonstrated that a PA:A > 1 is a better indicator of pulmonary hypertension than echocardiogram in subjects with severe COPD\(^{30}\). This advantage of CT scanning might be due to the poor acoustic windows for the echocardiogram resulting from hyperinflation in severe COPD. Subjects with a higher PA:A or PA:A ratio > 1 (versus those with ratio ≤ 1) had greater right ventricular (RV) end-diastolic and end-systolic volume indices as well as lower RV ejection fraction, as measured with cine cardiac magnetic resonance imaging (cMRI) and echocardiogram\(^{31,32}\). PA:A ratio was also related to PA systolic pressures and pulmonary vascular resistance. Imaging data also has given greater insight into the pulmonary circulation in smokers. Non-contrast CT studies have shown that the enlargement of the main pulmonary artery is associated with the loss of distal pulmonary vessels, measured as the volume of vessels < 5 mm\(^2\) —a measure called BV5. The PA:A ratio correlated inversely with total intra-parenchymal pulmonary blood vessel volume and BV5\(^{31}\). This CT measure also provides prognostic information. In a study using two large cohorts of COPD subjects, a PA:A ratio > 1 was independently associated with COPD exacerbations, suggesting that vascular factors might be considered as a potential etiology of exacerbation episodes\(^{33}\). Since cardiovascular disease accounts for approximately fifty percent of deaths among COPD patients, investigators have also evaluated the relationship between pulmonary artery enlargement and mortality. Several studies have consistently shown that the PA:A ratio is related to increased mortality\(^{34-36}\). These findings suggest that PA:A ratio provides clinically relevant information, is a useful marker of pulmonary vascular changes and has prognostic value.

Heart

Cardiac dysfunction is frequent in COPD and is thought to be due to tobacco smoke exposure, hyperinflation, and pulmonary vascular remodeling. Both enlargements of the RV (i.e., cor pulmonale), as well as decreased RV filling and reduced-end diastolic chamber (i.e., cor pulmonale parvus), are manifestations of cardiac dysfunction described in COPD\(^{37,38}\). To understand the complex relationships between the heart, the pulmonary vasculature, and emphysema, as well as their associations with clinical outcomes, investigators used numerous imaging techniques (Fig. 3). Using mathematical models and cardiac models as a reference, they segmented and quantified the heart in non-contrast CT scans\(^{39}\). This CT method provides epicardial (i.e., myocardium volume plus chamber volume) measures of the RV and left ventricle volumes. The generated CT measurements were correlated with echocardiogram and MRI measurements, imaging modalities typically used in clinical
Figure 3. Pulmonary vasculature and right (blue) and left (red) ventricular reconstructions from computed tomography images for two subjects with approximately 20% emphysema on computed tomography scan. (A, C, and E) Subject 1 with 19% emphysema and relative preservation of the distal arterial vascular volume (arterial volume for vessels less than 5 mm² in cross-section = 131 ml). (B, D, and F) Subject 2 with 18% emphysema and relative loss of the distal arterial vascular volume (arterial volume for vessels less than 5 mm² in cross-section = 70.8 ml). (A and B) Axial images of the epicardial surface of the right ventricle (RV), which is outlined in blue and the epicardial surface of the left ventricle, which is outlined in red. Emphysema is depicted in green. (C and D) Frontal view of the arterial (blue) and venous vasculature and the surface model of the epicardial (myocardium and chamber) RV volume (blue) and epicardial (myocardium and chamber) left ventricular volume (red). The epicardial (myocardium and chamber) RV volume of Subject 1 is 58.9 ml and the epicardial (myocardium and chamber) RV volume for Subject 2 is 140 ml. (E and F) Sagittal views of the arterial (blue) and venous (red) vasculature of the left lung demonstrating the relative loss of distal arterial vascular volume. Emphysema is shown in green (reprinted from Washko et al.38 with permission of the American Thoracic Society, © 2020 American Thoracic Society).
settings to evaluate the heart. The technique was applied to a large cohort of smokers. The investigators found that RV was smaller in subjects with GOLD stage 4 versus stage 1 COPD and that higher arterial pruning (i.e., lower BV5) and emphysema on CT were each independently associated with greater RV sizes. In further analysis, however, arterial vascular pruning was related to greater RV size only in subjects with mild airflow obstruction and in those with a low burden of emphysema (i.e., < 9.1%). RV enlargement was inversely associated with exercise capacity only among subjects in the lowest quartile of emphysema. A greater RV size was also related to increased mortality. However, the effect was modified by arterial BV5, such that death risk was 63% higher in patients with RV enlargement and arterial pruning, with no significant increased risk for death without pruning. Altogether the CT findings on heart, pulmonary vasculature, and lung density suggest a vascular phenotype in COPD that warrants further investigation.

Skeletal muscles

During the natural course of COPD, 15-40% of patients develop muscle wasting. A good measure that reflects skeletal muscle mass is the fat-free mass (FFM), and a low FFM is an independent risk factor for mortality in COPD. Traditional techniques used to measure FFM include bioelectrical impedance, skin-fold anthropometry, and dual X-ray absorptiometry. These three methods are not typically used in COPD clinics, whereas chest CT scanning is increasingly more common, particularly for lung cancer screening in heavy smokers. In the last few years, investigators have used chest CT imaging to evaluate muscle groups such as the pectoralis and paravertebral muscles. CT measurements of the pectoralis muscle area (PMA) are a reproducible measure of muscle mass and are easily obtained on a single axial slice. PMA correlates with bioelectrical impedance measures of muscle mass in healthy individuals and handgrip measures in subjects with COPD. Investigators have been able to derive FFM from CT measures of PMA, using two large cohorts of COPD subjects. The derived measure of FFM (i.e., $\text{FFM}_{\text{PMA}}$) was then used to test the association between muscle mass and all-cause mortality. The investigators found that smokers with COPD and low $\text{FFM}_{\text{PMA}}$ had an increased risk of death. In smokers, muscle changes developed before they met the criteria for COPD. For instance, smokers without COPD have a lower oxidative fiber area and a higher glycolytic capacity than non-smoking controls. However, the prognostic value of muscle mass was unknown until recently. Investigators found that smokers without COPD in the lowest quartile of PMA (versus the highest quartile) had 85% higher risk of mortality. These findings highlight the ability of CT to provide an alternate assessment of skeletal muscle.

Bone mineral density

Osteoporosis is frequent in patients with COPD, and it is associated with an increased risk of bone fracture, which has prognostic implications. For instance, patients with COPD have a 60-70% increased risk of death following hip fracture compared to those without COPD. The potential causes of osteoporosis in this population include smoking,
emphysema, lack of activity, steroid use, and chronic inflammation\textsuperscript{52}. The standard measure to diagnose osteoporosis is bone mineral density (BMD) using dual X-ray absorptiometry\textsuperscript{52}. Since imaging is based on determining tissue density, investigators have also used chest CT scanning to evaluate vertebral density. The method uses calcium calibration rods placed in the scanner pad under the subject and its density data stored within the chest image. A dedicated software determines the volumetric bone density —in mg/cc— (vBMD) for each selected vertebra where a region of interest has been defined\textsuperscript{53}. Using this method, a study in over 3,200 smokers demonstrated that men with or without COPD (versus their women counterparts) have a higher risk of low vBMD and vertebral fractures\textsuperscript{53}. The authors also showed that a higher burden of emphysema and airway disease on CT were each associated with low vBMD. In a short-term longitudinal study, it was found that a high burden of emphysema and greater levels of bone metabolism biomarkers (i.e., type I collagen C-telopeptide) also were associated with hip BMD decline at 2-year follow-up\textsuperscript{54}. Collectively, data on chest CT scanning applied to extra-pulmonary manifestations of COPD offers a unique opportunity to quantify structures concurrently, identify comorbidities (e.g., osteoporosis), and assess prognosis in both smokers at risk for and those already diagnosed with COPD.

**COPD PROGRESSION IMAGING**

FEV\textsubscript{1} change is the traditional measure of COPD progression. Large studies have demonstrated marked variability in FEV\textsubscript{1} changes over time\textsuperscript{55,56}. The number of exacerbations, biomarker levels, such as Club cell protein 15, and CT measures of emphysema are factors associated with disease progression\textsuperscript{55,57}. In the last few years, advances in imaging have allowed for further insight into the pathological features and mechanical factors that contribute to disease progression. In a study in smokers with and without COPD, investigators used PRM\textsuperscript{SAD} and PRM\textsuperscript{EMPH} to assess the relative importance of small airway disease or emphysema in predicting the decline in lung function\textsuperscript{58}. The investigators showed that PRM\textsuperscript{SAD} occurs in a significant number of subjects who do not meet the criteria for airflow limitation. While PRM\textsuperscript{SAD} but not PRM\textsuperscript{EMPH} was significantly associated with FEV\textsubscript{1} decline in subjects without COPD, both PRM\textsuperscript{SAD} and PRM\textsuperscript{EMPH} were associated with FEV\textsubscript{1} decline in GOLD 1-4 COPD subjects\textsuperscript{58}; however, the proportional contribution of the two CT metrics to the FEV\textsubscript{1} decline relative to each other was higher for PRM\textsuperscript{SAD} than for PRM\textsuperscript{EMPH} \textsuperscript{58}. This imaging technique has demonstrated that both small airway disease and emphysema are associated with disease progression. However, small airway disease seems more relevant in mild-to-moderate COPD, which has the highest rate of FEV\textsubscript{1} decline. In another study, different disease processes were determined using factor analysis of 26 spirometric and CT variables. The loading of variables on the axes defined distinct disease processes. Two of these processes —airway-predominant axis and emphysema-predominant axis— resulted associated with increased mortality. The death risk varied based on the deciles of airway-predominant axis and emphysema-predominant axis in that the 9\textsuperscript{th} and 10\textsuperscript{th} deciles had the highest risk. These results allowed the investigators to create 6 groups of subjects as follows\textsuperscript{59}: 1) High-risk airway-predominant
disease only; 2) Moderate-risk airway-predominant disease only; 3) High-risk emphysema-predominant disease only; 4) Combined high-risk airway- and emphysema-predominant disease; 5) Combined moderate-risk airway- and emphysema-predominant disease; and 6) No high-risk pulmonary group. The association between these groups and the GOLD stage progression was examined. The investigators found that the moderate-risk airway predominant disease was associated with the conversion of GOLD 0 to GOLD 2-4, while the high-risk emphysema-predominant disease was associated with the conversion of GOLD 0 to GOLD 1, and GOLD 1 to GOLD 4\textsuperscript{59}.

Biomechanical stress is a conceivable mechanism of lung injury. Based on a proposed lung network model\textsuperscript{60}, initial damage to the alveolar walls (fibers) in emphysema concentrates stress on the remaining adjacent fibers. If local forces exceed fibers yield stress, then fibers can break, leading to the progression of the disease through direct mechanical injury. Imaging studies have now made clear how mechanically stress contributes to COPD progression. Investigators have assessed the mechanical stress of lung parenchyma using matched inspiratory-expiratory CT images. In matched CTs, the investigators measured regional changes of lung volume from total lung capacity (inspiratory CT) to functional residual capacity (expiratory CT), creating a deformation map representing lung areas of expansion and contraction. This metric is a Jacobian determinant, where values higher and lower than 1 indicate local expansion and contraction, respectively; a value of 1 indicates neither local expansion nor contraction (Fig. 1). The investigators also assessed the Jacobian determinant on penumbras of a millimeter each around the emphysematous areas. In patients with COPD, they found that the Jacobian determinant was associated with FEV\textsubscript{1}/FVC and FEV\textsubscript{1} % predicted\textsuperscript{61}. They also demonstrated that the parenchyma within 2 mm of emphysematous areas was mechanically affected lung (MAL\textsubscript{2}) and called it “lung at risk”. They found that, in subjects with mild-to-moderate disease, the Jacobian determinant of MAL\textsubscript{2} at or above versus below the median value was associated with faster FEV\textsubscript{1} decline (56.4 ml/yr versus 43.2 ml/yr), supporting the long-recognized relevance of biomechanical stress in COPD progression\textsuperscript{62}.

The prevailing view of the natural history of COPD proposed by Fletcher and Peto\textsuperscript{63}, that the rapid decline in FEV\textsubscript{1} is caused by tobacco smoking, has been challenged\textsuperscript{64}. Only approximately half of the COPD subjects had a rapid FEV\textsubscript{1} decline. In contrast, the other half never reached normal peak lung function in early adulthood and developed COPD in adulthood with an average rate of FEV\textsubscript{1} decline\textsuperscript{65}. More recently, investigators have added CT phenotypic characteristics to the trajectories that can lead to COPD\textsuperscript{66}. First, lung function trajectory models were derived from a cohort of healthy men aged 21-80 years followed-up for a median of 29 years. These trajectories were then applied to a cohort of smokers, and their COPD phenotypes were compared. The subjects were scanned at two points in time, five years apart. The longitudinal analysis was performed by age (in years) groups, 45-55, 55-65, 65-75, and 75-85. The results demonstrated four distinct trajectories of lung function. 17% of subjects fell in the lowest trajectory (Trajectory 1), and they had the highest CT burden of emphysema.
and small airway disease across all age groups, whereas 36% fell in a low trajectory with evidence of increasing small airway disease and emphysema (Trajectory 2) with increasing age. The rest of the subjects fell in the remaining two trajectories (Trajectories 3 and 4) and tended to have preserved lung function and low burden of emphysema on CT (Fig. 4). These findings and those of prior studies support the notions that lung development abnormalities may contribute to the development of COPD.

In the last few years, imaging has also provided insight into the progression of COPD subtypes (i.e., emphysema and small airways disease predominant). Prior studies have suggested that small airways disease is a precursor of emphysema. The investigators have provided further evidence on this notion by demonstrating that baseline PRM is independently associated with emphysema at 5-yr follow-up. Other investigators have shown that the lobar distribution of emphysema is also related to different patterns of progression. In a cluster analysis study, investigators showed that the cluster most characterized by upper-lobe predominant emphysema at baseline experienced a faster overall progression of emphysema five years later. In the future, distinct patterns of COPD subtype progression may prove useful in the identification of patients for precision therapy; however, the impact of the radiographic changes on patient-specific outcomes still requires further investigation.

A few studies have used imaging as an endpoint to evaluate therapy, particularly in alpha 1 anti-trypsin deficiency COPD to test anti-trypsin therapy replacement. In two consecutive clinical trials of augmentation therapy with an Alpha-1 Proteinase Inhibitor, the primary end-points were CT lung densities measured as TLC, functional residual capacity (FRC), and TLC+FRC combined. In the first trial, the investigators showed that the replacement therapy significantly slowed the progression of emphysema compared with placebo (mean annual rate of lung density loss of −1.45 g/L/year versus −2.19 g/L/year). In the second trial, mean reduction in the yearly lung density between baseline and year 2, was significantly smaller in the early-start group (who received active therapy throughout), compared with the delayed-start group (who received placebo in the first trial; −1.51 g/L/year versus −2.26 g/L/year). Those two trials also showed the therapeutic effect was more prominent in the basal region of the lung, highlighting that CT densitometry is a technically feasible outcome measure to assess the efficacy of emphysema-modifying therapies.

**FUTURE DIRECTIONS**

While the imaging advances discussed here have enabled a richer understanding of COPD as a disease, there are still areas that require more progress. Chest imaging could prove to play a vital role in the clinical assessment of COPD, but further validation is required. Given the detailed information that CT imaging provides to identify COPD subtypes (e.g., emphysema), its role in the selection of patients for therapies, such as lung volume reduction surgery or valve placement; and the improved quantification of disease progression; there is a compelling argument to be made for considering CT imaging as a more routine tool.
Figure 4. Age-stratified average relative composition of emphysema (Emph), functional small-airway disease (fSAD), normal tissue, and “other” (dark yellow portions) for each trajectory, as assessed by parametric response mapping analysis. Rows correspond to age strata, and columns correspond to trajectories; color-coded arrows clarify the direction of increasing age for each trajectory (reprinted from Ross et al. with permission of the American Thoracic Society, © 2020 American Thoracic Society).
in the management of COPD. Although the findings of a few clinical trials using imaging as an endpoint are encouraging, more longitudinal imaging data is needed to provide better insight into disease subtype progression. Following this, there is great potential for the development of new therapies based on specific-disease subtypes.

A primary concern in the more routine use of CT imaging is radiation exposure. Although the current radiation exposure for chest CT is around 7.0 mSv, the further development of technologies to reduce this exposure level is desirable. Ongoing efforts to mitigate radiation exposure include automated exposure control, beam-shaping filters, and iterative reconstruction algorithms.

CONCLUSIONS

CT imaging is a robust in vivo tool that provides detailed information about changes in lung structures in subjects at risk for developing COPD, as well as about the subtype progression in those with COPD. Current advances in CT imaging are also proving useful for the examination of associated extra-pulmonary manifestations of the disease. Translations of these imaging findings into the development of new therapies for COPD is desirable.

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