The Role of Chest Computed Tomography in the Evaluation and Management of the Patient with Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease (COPD) exhibits significant heterogeneity in its clinical presentation and rate of disease progression among affected individuals, owing at least in part to differing pulmonary morphologic abnormalities. Symptom assessment, spirometric evaluation, and frequency of respiratory exacerbations have traditionally been used to determine disease severity and guide management. Chest computed tomography (CT) is a noninvasive imaging modality that provides additional insight into structural and pathophysiologic pulmonary parameters, leading to a better understanding of disease variability and further characterization of COPD phenotypes (1, 2). Many patients with and at risk for COPD undergo a chest CT in the outpatient setting for lung cancer screening, evaluation of pulmonary nodules detected on chest X-ray, assessment of concurrent interstitial lung disease, or planning for surgical options such as lung transplantation and lung volume reduction surgery (LVRS). In the acute setting, chest CT scans are frequently ordered in patients with COPD for the clinical workup of dyspnea and chest pain to rule out pulmonary embolism,

cardiovascular disease, or infection. However, despite the increasing use and widespread availability of chest CT scans (3), the wealth of data they contain is not consistently used in routine practice and has not yet been incorporated into clinical guidelines for COPD diagnosis, prognosis, or management. In this article, we review available chest CT quantification methods and clinical implications of several pulmonary parameters (emphysema, airway disease, air trapping, and pulmonary vasculature) and highlight the potential value of assessing nonpulmonary structures (coronary arteries and vertebral bone) to provide better comprehensive care for patients with COPD.

Pulmonary Parameters

Emphysema

Pulmonary emphysema is characterized by permanent dilatation of air spaces and destruction of their walls distal to terminal bronchioles (4). It can be visually identified on CT by areas of low attenuation as well as vascular distortion and thinning (Figure 1). Emphysema is

classically categorized into three anatomic subtypes depending on its location within the secondary pulmonary lobules: centrilobular, panlobular (also known as panacinar), and paraseptal. Centrilobular emphysema is the most common form of smoking-related emphysema. It begins in the central portion of the secondary pulmonary lobules, initially appearing as small holes that become more confluent as the disease progresses. It is typically upper lung predominant and characterized by the obliteration or narrowing of distal bronchioles. Panlobular emphysema is classically found in the lower lobes of individuals with alpha-1 antitrypsin deficiency, involves each secondary lobule diffusely, and is accelerated in severity and age of onset in the presence of cigarette smoking. Pure panlobular emphysema is characterized by the preservation of bronchiolar lumens (1) and is not, in the classic (5) or contemporary (6) literature, associated with smoking exposure. Paraseptal emphysema affects the secondary pulmonary lobules along the mediastinal, costal, and fissural pleural surfaces, most commonly in the upper lobes. Although

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Figure 1. (A and B) Coronal (A) and coronal maximum intensity projection (B) chest computed tomography of a smoker with lower zone–predominant emphysema. Note the distorted and obliterated vasculature in the lower zones. In contrast, the vascular architecture is preserved in the upper zones, which are mostly spared from emphysematous destruction. (C and D) Coronal (C) and coronal maximum intensity projection (D) chest computed tomography of a smoker with severe diffuse emphysema. Note the paucity of distal vessels as well as the elongation and narrowing of the more central pulmonary vasculature. Images courtesy of Dr. Philippe Grenier, Paris, France.

individuals with paraseptal emphysema tend to be male and asymptomatic and may have unremarkable pulmonary function tests, those with centrilobular emphysema experience more dyspnea, have less exertional tolerance, and show evidence of hyperinflation and decreased diffusion capacity (6).

Although the visual assessment of CT allows the determination of emphysema subtype and is a validated tool for the estimation of emphysema extent, it is time consuming and limited by interobserver variability (7–9). Automated densitometry methods provide a more reliable quantification of emphysema (10) and are more sensitive for homogeneous changes in the lung parenchyma. The clinical utility of CT densitometry has been well demonstrated in alpha-1 antitrypsin deficiency. The upper lung zone emphysema score on chest CT was found to be an independent predictor

of mortality in this patient population (11, 12). In addition, the annual rate of CT lung density decline has been shown to be significantly lower in patients on alpha-1 antitrypsin augmentation therapy in clinical trials (13, 14). Most scanner manufacturers now provide automated densitometry software, making emphysema quantification a potentially broadly available metric. These programs calculate the percentage of lung voxels at or below a given attenuation threshold, which is referred to as the percent emphysema or percent low attenuation area. The optimal cutoff is estimated to be between –950 and –970 Hounsfield units (HU) on the basis of comparisons with macroscopic and microscopic morphometry of pathologic specimens (15, 16). A complementary but less widely used approach to quantify emphysema is the “15th percentile” method or “Perc 15,” which reports the

HU at the lowest 15th percentile of a cumulative frequency distribution for all HU values (17, 18). Quantitative measurements are not yet capable of distinguishing between emphysema subtypes. For example, centrilobular emphysema may be present in subjects without quantitative emphysema; similarly, panlobular disease may be missed by visual inspection but detected on quantitative analysis (9). Therefore, visual assessment and quantitative evaluation of emphysema on CT are currently considered to be complementary.

Lung densitometry can be affected by both patient and CT-related factors, including obesity, adequacy of deep inspiration, and CT model and calibration. Accounting for these variables becomes particularly important in research studies with multiple study sites and serial monitoring, where intrasubject and intersubject comparisons are required. The reproducibility of CT measurements can be maximized through rigorous imaging protocols that address parameters such as spatial and temporal resolution, inspiratory and breath-holding techniques, consistent field of view, scanner calibration, and radiation exposure (19). Minimizing radiation exposure, particularly as part of research protocols that use serial monitoring, is always a goal. The recent use of dose optimization protocols and the development and propagation of new iterative reconstruction techniques has allowed investigators to obtain thoracic CT scans at a fraction of the standard clinical dose, while still producing quantitative assessments of emphysema, air trapping, and airway dimensions (20, 21). The rapidly evolving scanner technology has provided optimism that radiation exposure from a quantitative chest CT can be reduced to that of an anterior-posterior and lateral digital chest radiographic examination (22).

Airway Disease

The radiologic assessment of airway disease severity is more challenging and has been less well-studied and validated than the quantification of emphysema. Similar to emphysema, visual analysis of airway wall thickness is subject to significant interreader variation (9). Recent advances in CT technology on the basis of whole lung imaging at a slice thickness of

less than 1 mm within a single breath hold have allowed the development of three-dimensional models of the central airway tree and the determination of mean segmental and subsegmental airway wall thickness and luminal area. However, one challenge affecting these measurements is the substantial variability in airway size within and between subjects, even among healthy individuals. To facilitate comparisons between individuals, a useful measure known as Pi10 takes advantage of the known linear relationship between the square root of the airway wall area and the internal perimeter of the airway (23); it represents the square root of the wall area for a hypothetical airway with an internal perimeter of 10 mm. This measure, in combination with quantitative emphysema and air trapping measurements, has been shown to be a useful predictor of the presence of COPD on lung cancer screening scans (24). Until the reproducibility, clinical validity, and ease of use of airway measurements can be further demonstrated, these quantitative methods are primarily limited to the research arena at this time; qualitative visual inspection of airways, including assessment of bronchial wall thickening, bronchiectasis, and expiratory central airway collapse, remains the standard in routine clinical practice.

Air Trapping and Functional Small Airway Disease

Both increased compliance from emphysema and increased resistance from small airway disease contribute to airflow limitation in COPD. Because the narrowing and loss of terminal

bronchioles occur before the development of emphysema, assessment of small airway disease severity has the potential to identify COPD at an early stage (25). Although airways less than 2 mm in diameter are the main site of airflow obstruction (26), they fall below the resolution limit of chest CT for direct evaluation. For this reason, investigators have used different measures of air trapping on expiratory CT as surrogates for the estimation of functional small airway disease. These include the ratio of expiratory to inspiratory mean lung density (27, 28), the expiratory to inspiratory relative volume change of voxels with attenuation between -860 and -950 HU (29), and the percentage of voxels below -856 HU in expiration (30). However, each of these imaging techniques has its advantages and limitations, and it remains to be determined which one correlates best with clinical outcomes. One promising application, parametric response mapping, detects attenuation changes for individual voxels between coregistered volumetric inspiratory and expiratory CT scans to classify each voxel as normal lung, emphysema or functional small airway disease (Figure 2) (31). Not only does this technology allow for radiologic components of COPD to be geographically mapped but it also has the potential to further characterize COPD phenotypes, monitor disease progression, and assess response to therapy (32, 33). Another application, the air trapping index, relies on the attenuation difference detected per voxel on coregistered inspiratory and expiratory CT scans

(34, 35). Software programs for the detection of functional small airway disease are becoming increasingly clinically available and are more sensitive than the routine practice of visual assessment of air trapping on expiratory CT scans, especially in the presence of emphysema.

Pulmonary Vasculature

Pulmonary vascular damage is prevalent in patients with COPD and may manifest as pulmonary hypertension, especially in those with advanced disease (36). However, little is known about pulmonary vascular changes early in COPD pathogenesis. New quantitative CT methods are being developed to better understand the relationship between these changes and emphysema. Smokers with early emphysema display increased heterogeneity in pulmonary perfusion compared with never-smokers and smokers without emphysema when assessed by multidetector-row CT perfusion imaging (37). In a study by Estépar and colleagues, volumetric chest CT scans of smokers revealed pulmonary vascular remodeling through the distal pruning of small intraparenchymal blood vessels (38). These findings suggest that inflammation associated with patches of emphysematous tissue may cause endothelial dysfunction and damage or promote local areas of hypoxic vasoconstriction, thereby resulting in perfusion heterogeneity. More recent work further demonstrated that this pulmonary blood flow variability can be reversed with the

Figure 2. Coronal computed tomography images of a patient with chronic obstructive pulmonary disease in inspiration (A), expiration (B), and parametric response mapping (C). On the parametric response mapping image, green represents normal lung tissue, yellow represents functional small airway disease, and red represents emphysema. This patient has predominantly functional small airway disease involving both lungs.

administration of sildenafil (39). Although the clinical significance of these findings still needs to be clarified, continued investigation in that area is warranted, as it may open the door for new therapeutic options for patients, particularly those with mild or early disease. In clinical practice, many radiologists measure and report central pulmonary artery size, but software that can quantify the entire intrapulmonary vascular volume is not currently routinely available.

Clinical Correlations of CT Pulmonary Parameters

Emphysema, airway disease, air trapping, and pulmonary vascular abnormalities are common in smokers with and without COPD (40) and are associated with a number of clinically important outcomes.

Respiratory symptoms and health status. Increased dyspnea has been independently associated with both emphysema and airway disease identified on chest CT scans of subjects with COPD (41, 42). Even among individuals without COPD, emphysema on chest CT has been associated with dyspnea (43), and airway wall thickening has been associated with higher COPD Assessment Test scores (44). When examined together, however, the relative contribution of airway disease to worse health status seems to be greater than that of emphysema when adjusted for FEV₁ percent predicted (45). Hence, although assessing symptoms in smokers clearly does not require a CT scan, if one is available, clinicians should be aware that even among patients without spirometrically defined COPD, emphysema and airway wall thickening can be associated with increased respiratory symptoms and poorer health status.

Lung function and disease progression. In patients with COPD, FEV₁ percent predicted on spirometry inversely correlates with emphysema and air trapping on chest CT (46, 47). The relationship between lung function and airway disease identified on CT is more ambiguous due to inconsistent results that are influenced by the specific airway measure used and the size of the assessed airways (46–48). Longitudinal studies designed to evaluate lung function decline found that emphysema detected on chest CT is independently associated with

the rate of annual FEV₁ decrease (49, 50). Although Bhatt and coworkers confirmed this relationship, they also found that functional small airway disease on parametric response mapping was even more correlated with lung function decline than emphysema, especially in individuals with Global Initiative for Chronic Obstructive Lung Disease stage I or II COPD (32). Furthermore, increased small airway abnormality was found even among current and former smokers without airflow obstruction. These results suggest that subjects with mild to moderate COPD and smokers with preserved pulmonary function who have evidence of emphysema or air trapping on chest CT may be at increased risk for disease progression. Total lung capacity (TLC) is another metric commonly available from inspiratory CT. Although CT-based measures of TLC demonstrate good correlation with TLC measured by plethysmography, the former may be underestimated, particularly in the presence of air trapping (51). Thus, a normal TLC on chest CT suggests the absence of restrictive lung physiology, and a high TLC likely indicates the presence of hyperinflation.

COPD exacerbations. A multivariate analysis of the COPDGene cohort demonstrated that a 5% increase in emphysema in subjects with at least 35% total emphysema and a 1-mm increase in bronchial wall thickness were associated with an increase in annual COPD exacerbations by 1.18 and 1.84 times, respectively, regardless of the degree of airflow limitation (52). Similar findings were observed in a prospective cohort of smokers for both qualitatively and quantitatively defined emphysema (53). In other analyses, subjects with COPD with visually identified bronchiectasis on chest CT were found to have more frequent severe respiratory exacerbations when assessed by the need for hospitalization (54) or the duration of symptoms (55). In a study of current and former smokers, central airway collapse greater than 50% on expiration was associated with a higher frequency of respiratory exacerbations (56). Moreover, a ratio of the pulmonary artery diameter to the aorta diameter greater than 1 has also been demonstrated to be a strong and independent predictor of severe exacerbations (57), even when adjusted for lung function and prior history of

exacerbations. For the clinician, these findings suggest that CT-quantified emphysema, airway disease, and pulmonary artery dilation provide additional information regarding increased COPD exacerbation risk beyond other readily available clinical and physiologic metrics. It still remains to be determined whether the exacerbation mechanisms differ between those three phenotypes and what implications this would have on prevention and treatment.

Lung cancer. Low-dose chest CT screening has been shown to decrease lung cancer mortality (58) and improve the detection of early-stage malignancy (59). Subjects enrolled in the National Lung Screening Trial (NLST) were 55 to 74 years of age, with at least a 30 pack-year smoking history, and were either current smokers or former smokers who had not quit more than 15 years ago. Multiple studies have validated the independent association between visually assessed emphysema on chest CT and the risk of lung cancer in current, former, and never smokers (60–62). Moreover, lung cancer was found to have a predilection for lobes with more severe emphysema (63). This relationship has important clinical consequences, as the addition of emphysema to the NLST screening criteria led to fewer missed malignancies (64).

Mortality. Although the presence of bronchiectasis on CT portends a worse survival (65), airway wall thickness as measured by Pi10 has not been related to increased mortality (66). On the other hand, both visual and quantitative assessments of emphysema have been shown to be independent predictors of all-cause, respiratory, or cardiovascular mortality in smokers with and, notably, without COPD (66–69). This association further supports the known relationship between worse emphysema and higher scores on the body mass index, airflow obstruction, dyspnea, and exercise capacity (BODE) index, which is a well-validated predictor of mortality in subjects with COPD (41, 45, 70). In terms of therapy, LVRS confers a survival advantage in selected patients with predominantly upper-lobe emphysema and poor exercise capacity (71). A chest CT to assess emphysema distribution and fissural integrity is required to evaluate a patient's candidacy for LVRS and advanced

bronchoscopic interventions, respectively. Even though endobronchial coils and valves can improve lung function, exercise tolerance, and quality of life in patients with either homogeneous or heterogeneous emphysema, their long-term outcomes and safety still need to be determined (72–76). None of these devices are currently approved for use in the United States.

Nonpulmonary Structures

Coronary Arteries

Ischemic heart disease is a common comorbidity in COPD (36). Myocardial infarction occurs more frequently and carries a worse mortality in patients with COPD, even after accounting for shared risk factors like age and smoking (77, 78). Therefore, the early identification of coronary artery disease and the institution of appropriate preventive strategies have the potential to improve outcomes in this patient population. The measurement of coronary artery calcium (CAC) on chest CT provides a noninvasive and accurate assessment of coronary atherosclerosis. An elevated CAC score has been shown to be an independent predictor of future cardiovascular events and deaths in both symptomatic and asymptomatic patients (79–81). CAC scores were found to be higher in subjects with COPD than in nonsmokers and smokers with normal spirometry and were associated with increased mortality (82). Visual assessment of CAC (classified as mild, moderate, or severe calcification) performed as well as quantitative measurements such as Agatston scoring with respect to predicting cardiovascular death (83). Although an electrocardiographically gated CT is usually the study of choice to measure CAC, Budoff and colleagues showed low-dose ungated CT scans to be a reliable alternative (84). Thus, chest CT scans performed in patients with COPD for noncardiac reasons, such as lung cancer screening or pulmonary embolism exclusion, provide an opportunity to evaluate coronary atherosclerosis. However, because CAC is typically recommended for screening of asymptomatic adults with intermediate cardiovascular risk, the clinical implications of this measurement reported on chest CT scans ordered for other reasons in an unselected population

need to be further elucidated. At this time, when available, a CAC score should be integrated with each patient's other cardiac risk factors to guide individual management.

Vertebral Bone

Osteoporosis is prevalent in COPD, as the two conditions share common clinical factors such as smoking, low body mass index, physical inactivity, steroid use, and vitamin D deficiency (85). More importantly, a diagnosis of severe COPD was associated with significantly increased 1-year mortality in patients with osteoporotic hip fractures (86). Although dual-energy X-ray absorptiometry (DXA) of the lumbar spine and hip is currently the gold standard for the screening and diagnosis of osteoporosis, quantitative CT (QCT) is emerging as an alternative for assessing bone mineral density (BMD) (87, 88) and predicting future vertebral fractures (89), particularly in smokers who had a chest CT performed for other purposes. Although DXA yields an area measure of BMD (in milligrams per square centimeter) that sums both cortical and cancellous values, QCT uses a three-dimensional technique that reports a volumetric assessment (in mg/cm^3) and provides information on osseous architecture by identifying cancellous versus cortical bone. Because most vertebral compression fractures occur in the mid to lower thoracic region, chest CT provides a good window for evaluation of thoracic BMD and vertebral fractures. Jaramillo and coworkers showed that COPD, and more specifically the emphysema phenotype, was associated with low vertebral volumetric BMD measured on chest CT even after accounting for traditional risk factors of osteoporosis (90). Low vertebral bone attenuation detected on chest CT was also shown to be an independent predictor of increased morbidity in patients with COPD, including higher rates of respiratory exacerbations and hospitalizations (91). In addition, vertebral compression fractures can result in decreased vital capacity (92). More studies are needed to determine whether vertebral BMD assessed on QCT is adequate to predict fractures prospectively and whether it can be used to initiate treatment. At this time, further evaluation of patients with low QCT vertebral bone attenuation values should be considered

using standard DXA measurements to determine T scores and make treatment decisions.

Conclusions

Although chest CT is not currently considered standard of care in the diagnosis and management of mild to moderate COPD, its expanding use for other purposes now demands that clinicians understand how to treat radiologic information that becomes available. For subjects with established COPD, chest CT provides data on risk of lung function decline, respiratory exacerbations, and death, independently and incrementally to routinely used studies, such as pulmonary function tests and symptom measures. In patients with end-stage disease, chest CT has clear utility in identifying those who would benefit from interventions such as LVRS and lung transplant. Chest CT should be more frequently integrated in COPD clinical trials to determine the effect of existing or new therapies on patients with different imaging phenotypes, as has been shown with LVRS (71). In smokers being screened for lung cancer, CT-quantified emphysema and air trapping, along with certain clinical variables, can be used to identify individuals with airflow obstruction (93). Therefore, one could argue that any significant amount of emphysema, airway disease, or air trapping noted by a radiologist on a chest CT performed for any reason should raise the clinician's suspicion for COPD if spirometry has not already been performed. Beyond the assessment of airways and lung parenchyma, images from existing chest CT scans also provide information on extrapulmonary parameters and comorbidities, including coronary artery disease and osteoporosis, which are recognized as an essential aspect of COPD care (94). In that context, chest CT clearly has the potential to become a powerful tool in the quest of personalized medicine in COPD. Whether it is incorporated into routine assessment for patients with COPD will ultimately depend on our ability to demonstrate that this information changes management and improves outcomes. ■

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

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