Chronic Obstructive Pulmonary Diseases:
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Review

Progress in Imaging COPD, 2004 – 2014

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Abstract

Computed tomography (CT) has contributed substantially to our understanding of COPD over the past decade. Visual and quantitative assessments of CT in COPD are complementary. Visual assessment should provide assessment of centrilobular, panlobular and paraseptal emphysema, airway wall thickening, bronchiectasis, findings of respiratory bronchiolitis, and enlargement of the pulmonary artery. Quantitative CT permits evaluation of severity of emphysema, airway wall thickening, and expiratory air trapping, and is now being used for longitudinal evaluation of the progression of COPD. Innovative techniques are being developed to use CT to characterize the pattern of emphysema and smoking-related respiratory bronchiolitis. Magnetic resonance imaging (MRI) and positron emission tomography PET-CT are useful research tools in the evaluation of COPD.

Abbreviations: computed tomography, **CT**; magnetic resonance imaging, **MRI**; positron emission tomography, **PET**; Global Initiative for chronic Obstructive Lung Disease, **GOLD**; quantitative CT, **QCT**; Hounsfield Units, **HU**; percentage of low attenuation area, **%LAA**; relative area of lung less than -950 HU, **RA950**; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints, **ECLIPSE**; forced expiratory volume in 1 second, **FEV1**; forced vital capacity, **FVC**.

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Introduction

The morphologic manifestations of the group of obstructive diseases collectively labeled COPD, as seen on CT, vary widely. Individuals with similar levels of physiologic impairment or Global Obstructive chronic Lung Disease (GOLD) stage may have substantial, little, or no emphysema. Discrete subphenotypes of COPD include emphysema of varying morphologic appearance, large airway abnormality and small airway obstruction. Increasing awareness of the heterogeneity of COPD has led to increased use of CT to characterize COPD for purposes of genetic evaluation and identification of specific subgroups which may be amenable to therapeutic trials.[1-3] While visual assessment is important in determining the presence and character of emphysema, the last decade has been characterized by increasing use of quantitative imaging to provide precise estimates of the severity and distribution of emphysema, gas trapping and airway wall thickening. Several large cohorts of cigarette smokers have now been quite extensively characterized by CT, resulting in increased knowledge of the clinical correlates of quantitative CT parameters.[4-6] The purpose of this paper is to present the substantial contribution that imaging has made to our understanding of COPD over the past 10 years.

Imaging Techniques

On the chest radiograph, emphysema, airway wall thickening and hyperinflation are useful signs of COPD, but are neither sensitive nor specific. Therefore, the chest radiograph cannot be used to characterize COPD; its primary role in COPD is to detect complications such as pneumonia. CT is currently the most effective modality for characterizing and quantifying COPD, but there is emerging information on positron emission tomography (PET)-CT and magnetic resonance imaging (MRI), as discussed below.

CT: Optimal Technique

Appropriate CT technique is critical for assessment of COPD.[7,8] The cornerstone of CT assessment is a volumetric acquisition obtained at maximal inspiration. The CT technologist has a pivotal role in ensuring that the patient takes a maximally deep inspiration, and standardized breathing instructions are helpful in this regard.

The CT technique should be tailored for specific tasks. Precise characterization and quantification of emphysema requires thin CT reconstructions (1.25 mm or less in thickness). Although these thin section images are associated with relatively high image noise, particularly at lower CT dose, visual characterization of emphysema may be achieved with relatively low CT dose, as used for lung cancer screening. Emphysema may also be effectively quantified using reduced dose, though the increased image noise at lower CT doses may cause relative increase in threshold-based measures of emphysema. For measuring the airways, higher CT doses may be required, because multiplanar reconstructions, reconstructed from submillimeter sections, are necessary to ensure precise cross-sectional measurements. The higher CT dose is needed to reduce the effect of image noise on the reconstructions.

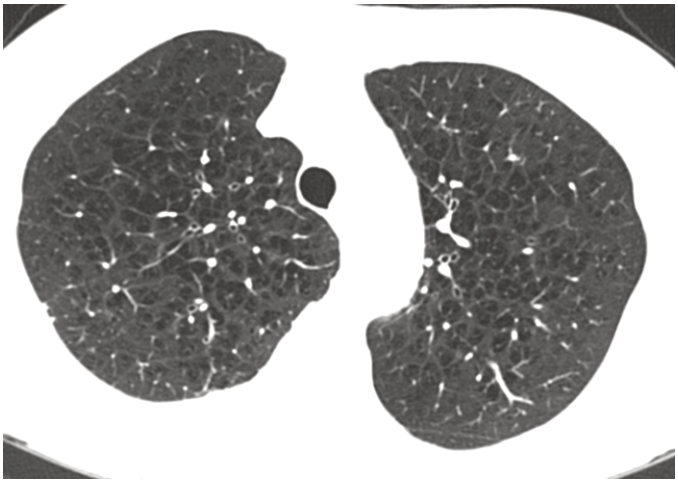

Figure 1. Centrilobular Emphysema in a Cigarette Smoker. Axial CT image through the upper lungs shows numerous well-defined lucencies, many of which are traversed by a central vessel.

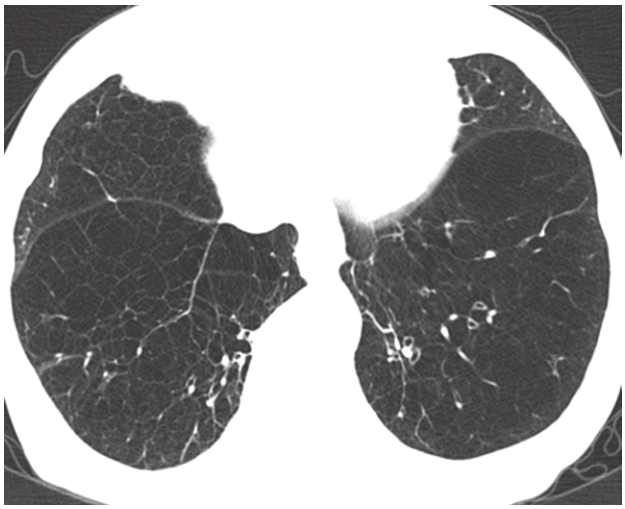

Figure 2. Panlobular Emphysema in a Patient with Alpha-1 Antitrypsin Deficiency. Axial image through the lower lungs shows homogenous decrease in lung attenuation in both lower lobes. Some of the interlobular septa in the right lower lobe are accentuated by the emphysema.

Novel techniques such as iterative reconstruction are increasingly used to optimize CT reconstructions, enabling further reductions in CT dose. However, the effect of these techniques on visual and quantitative evaluation remains unclear.[9-12]

Expiratory CT is increasingly recognized as an important part of the assessment of COPD,[13,14] to facilitate visual and quantitative assessment of the presence and distribution of air trapping. Expiratory images may be obtained at relatively low CT dose. If visual assessment is performed, non-contiguous images spaced at 10 mm or 20 mm will suffice, but volumetric acquisition is generally necessary for quantitative assessment. Coaching by the technologist, and standardized breathing instructions are important to ensure that the patient expires to an appropriate level. The patient may be asked to expire to the end of a normal expiration (functional residual capacity),[1] or to residual volume.[3] There is no clear evidence as to which technique is preferable.

CT: Visual Evaluation

Comprehensive visual assessment of CT in COPD should include assessment of the pattern of emphysema, presence of airway wall-thickening or bronchiectasis, findings of inflammatory and obstructive small airways disease, and pulmonary artery size. For optimal classification, thin section, high resolution CT images should be viewed

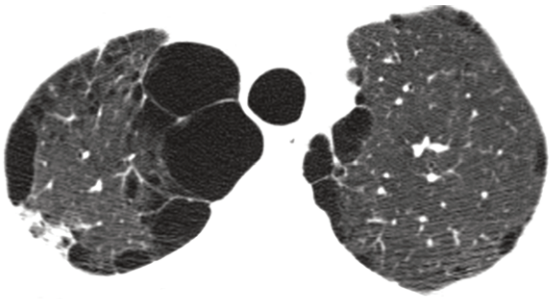

Figure 3. Paraseptal Emphysema in a Cigarette Smoker. Axial image through the upper lungs shows multiple well-demarcated subpleural air-containing spaces.

at standardized window settings, usually with a window level of -700, and window width of 1000 to 1500. Emphysema is classified as centrilobular, panlobular, and paraseptal (Figures 1, 2, 3). (A cicatricial form is also described, which occurs in relationship to lung fibrosis such as progressive massive fibrosis, but this is not relevant to COPD). The patterns of emphysema identified on CT correlate quite well with the patterns recognized on pathology. Visual assessment of severity of emphysema and airway wall thickening correlates quite well with physiologic impairment.[15] However, observer agreement with regard to severity of emphysema on visual assessment has been quite variable and quantitative CT is preferred for assessing disease severity.[16] Bronchial wall thickening is commonly identified in heavy cigarette smokers, and is often a sign of chronic bronchitis. However, identification of bronchial wall thickening is subjective, with considerable observer variation. Bronchiectasis is common in individuals with COPD,[17, 18] and may be a marker for severe airflow obstruction and risk for exacerbation.[19]

CT can show two distinct patterns of small airways disease in cigarette smokers: inflammatory small airways disease (respiratory bronchiolitis) is characterized by poorly defined centrilobular nodularity (Figure 4), while obstructive small airways disease is characterized by expiratory gas trapping (Figure 5). Interstitial lung abnormalities may be seen in up to 10% of heavy cigarette smokers,[20,21] most commonly, ground glass abnormality indicating an inflammatory abnormality, though a fibrotic-appearing abnormality may be found in 1-2% of cases.[21] Evaluation of the pulmonary vasculature is important in individuals with COPD, because enlargement of the central pulmonary arteries is associated with increased risk of exacerbation.[22]

CT: Quantitative Evaluation

The past 10 years have seen substantial increase in our understanding of the use of quantitative CT (QCT) to characterize COPD. Some of the information below is adapted from a recent review of these important advances.[23]

Emphysema

Emphysema results in replacement of normal lung (which has a typical attenuation of about -850 Hounsfield Units [HU] on inspiratory CT) by air-containing spaces, with CT attenuation around -1000 HU. The pioneering work by Müller, et al,[24] validated the density mask technique, in which CT pixels with attenuation below a certain threshold value (initially -910 HU) were defined as emphysema. Quantitative CT measurements were subsequently shown to correlate better than visual CT scoring with macroscopic measurements of emphysema[25]; more recent studies using thin section CT and multidetector scanners showed that the highest correlation between QCT metrics and histology is found when the CT threshold is set at -960 or -970 HU.[26] However, because these higher thresholds may be more sensitive to noise, the threshold of -950 HU is now most commonly used (Figure 6a).[1,6, 27] An alternative approach to emphysema quantification uses the CT attenuation at a given percentile along the frequency histogram of lung attenuation (e.g. first or 15th percentile).[27] The percentile approach may be more robust for longitudinal evaluation of emphysema, and less sensitive to change in lung volumes.[28-30] The first percentile value is optimal for correlation with histology.[26] However, because of concern regarding artifact from image noise and truncation artifact at the first percentile level, most studies have used the 15th percentile threshold.[30, 31]

It is important to remember that the measurement of the percentage of low attenuation areas (%LAA), while it correlates moderately well with histologic severity of emphysema (with r values between 0.5 and 0.6), is not a direct measurement of emphysema. The term *percentage*

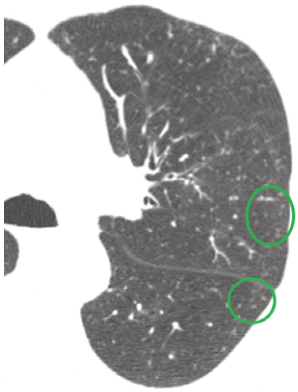

Figure 4. Respiratory Bronchiolitis in a Heavy Smoker. Axial image through the left lung shows numerous poorly defined centrilobular nodules, some examples of which are circled.

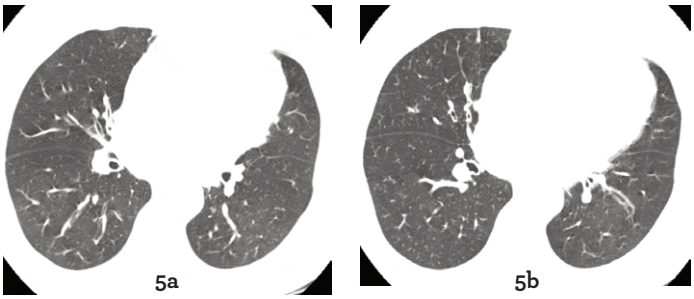

Figure 5. Marked Airway Wall Thickening and Expiratory Gas Trapping in a Patient with GOLD Stage 3 COPD. (a) Inspiratory image shows marked thickening of airway walls. (b) Expiratory image shows that the lung density has not changed significantly, indicating diffuse gas trapping.

of emphysema (% emphysema) is widely used to refer to such CT measurements, but is imprecise and may give rise to confusion. The annotation %LAA$_{-950}$ (or %LAA$_{-910}$, etc.) is preferred because it is more precise. The term RA950 is also sometimes used to indicate the relative area of lung less than -950 HU.

The D value or alpha value represents the slope of the log-log plot of the cumulative frequency-size distributions of the %LAA$_{-950}$, and has been used as an index of the relative size of emphysematous clusters. Mishima, et al, found that smokers with normal %LAA had lower D values than nonsmokers, suggesting that the D value might be a sensitive method for detecting early emphysema.[32] However, Madani, et al, found that the D value did not correlate with macroscopic or microscopic indices of emphysema.[33] More work is needed to identify the best measures of the size of emphysematous clusters or holes (Figure 6b).

Sources of Variation

Major sources of variation in quantification of emphysema include variation in lung volume, technical CT parameters, and cigarette smoking. Measures of emphysema change significantly when scans are obtained at 100%, 90%, 80%, 70%, and 50% of vital capacity.[34] However, the change between 100% and 90% of vital capacity is relatively slight. While several studies have used spirometers to standardize inspired lung volume,[35,36] such systems are not widely available, and the strong physiologic correlations obtained without lung volume control suggest that it may not be necessary. In the absence of a spirometer, careful coaching of the patient by the technologist is important to achieve total lung capacity.

Decreasing slice thickness and decreasing CT dose (tube current) both result in increasing %LAA$_{-960}$, presumably because of decreasing image noise.[37] Differences in reconstruction algorithm (in particular the use of over-enhancing reconstruction algorithms) have a large effect on measurement of low attenuation areas, because they result in increased image noise simulating emphysema.[38] For this reason, a smooth reconstruction algorithm is generally used in quantitative CT evaluation of emphysema (e.g. B35 for Siemens scanners, Standard for GE scanners, B kernel for Phillips scanners, and FC01 for Toshiba scanners).[39]

Several authors have shown that current smokers appear to have lower levels of emphysema than former smokers.[40,41] Even more intriguingly, the extent of *emphysema* appears to increase quite rapidly following smoking cessation, reflecting a fall in lung attenuation.[42,43] This effect is presumed to be due to a smoking-induced increase in inflammatory cells in the lung in current smokers, resulting in increased lung attenuation, so that partial volume averaging masks the areas of low-attenuation emphysema. Therefore, smoking status should always be taken into account when assessing severity of emphysema by quantitative CT.

Longitudinal Evaluation

Several studies have evaluated the ability of CT to detect progression of emphysema on longitudinal evaluation (Figure 7). The main source of variation is related to change in lung volume. Correction for lung volume may be performed using a sponge model, where the % emphysema on the follow-up scan is corrected using the achieved lung volume on the baseline scan.[44] Correction for lung volume reduces the variability in emphysema quantification by a factor of 2.[45] In a randomized controlled study of individuals with alpha-1 antitrypsin deficiency, change in 15th percentile CT density (corrected for lung volume) was found to be more sensitive as an index of progression than measures of physiology or health status.[46] Combined analysis of 2 clinical trials of intravenous alpha-1 antitrypsin augmentation showed that this medication significantly reduces the decline in lung density in individuals with alpha-1 antitrypsin deficiency.[47]

In individuals with smoking-related emphysema, Gietema, et al, evaluated 157 individuals enrolled in a lung cancer screening study, who underwent repeat CT scans within 3 months, and found that the limits of agreement for %LAA$_{-950}$ were from -1.3% to +1.1%, suggesting that CT can detect a change of 1.1% in extent of emphysema with 95% probability. In 1,928 individuals enrolled in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE study) Coxson, et al, found an average annual decline in lung density of 1.13g/L, after correction for lung volume, in a group of 1,928 current and former

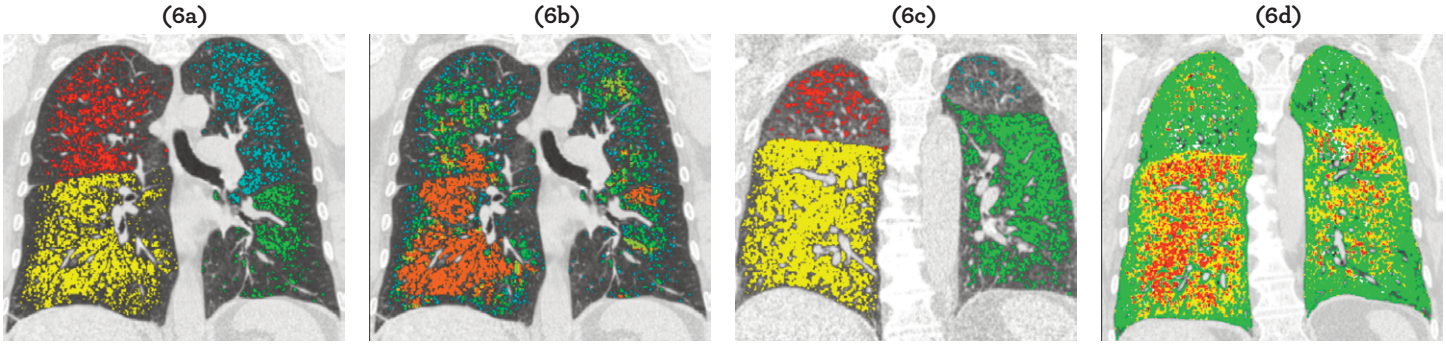

Figure 6. Quantification of Emphysema and Air Trapping in 66 year old Individual with GOLD Stage 3 COPD (FEV1 43% predicted) **(a)** Inspiratory CT: coronal image depicts voxels with CT attenuation less than -950HU indicating emphysema (14% in this case). *Color coding:* Indicates lobes. **(b)** Inspiratory CT: coronal image depicts distribution of sizes of emphysematous clusters, with color coding depending on cluster size. **(c)** Expiratory CT: coronal image depicts voxels with CT attenuation less than -856HU indicating air trapping (38% in this case). **(d)** Image map derived from co-registered inspiratory and expiratory images depicts change in voxel attenuation from inspiration to expiration. *Color coding:* Red indicates voxels that were less than -950 HU on inspiration and less than -856 HU on expiration (emphysema). Yellow indicates voxels that were greater than -950 HU on inspiration, but less than -856 HU on expiration (air trapping). Green indicates voxels that were less than -950 HU on inspiration and less than -856 on expiration (normal). White indicates voxels that were greater than -950 HU on inspiration but less than -856 on expiration. *Images courtesy of Eva van Rikxoort, PhD, Radboud University Nijmegen Medical Centre.*

smokers.[6] The decline was more rapid in women than in men, and in current smokers than in former smokers. Similarly, a study of 3,670 individuals enrolled in the Dutch-Belgium randomized lung cancer screening trial, NELSON (Dutch acronym), showed that former smokers (who had quit more than 5 years before) had an annual rate of progression of emphysema (LAA_{-950}) of 1.07%, compared with 1.12% in current smokers ($p<0.001$).[48] The progression rate was greater in those with more severe COPD at baseline.

Most recently, Staring, et al, have proposed a method to evaluate local changes in lung density using image registration and a modification of the sponge model, and validated it in a pilot study of 21 individuals with emphysema.[49] If this method can be validated in larger populations of COPD individuals, it could prove to be a major advance in measuring the rate of local emphysema progression, independent of changes of lung volume.

Air Trapping

End-expiratory CT, whether obtained at functional residual capacity or at residual volume, is an excellent way to assess gas trapping in COPD. Most studies have evaluated the presence of gas trapping by evaluating the % LAA at a threshold of -856 or -850 HU (LAA_{exp856} or LAA_{exp850}) (see Figures 6c, 7c). This value is chosen because it is the attenuation of a normally inflated lung on inspiration: it is assumed that a normal expiratory lung should always have higher attenuation than this. Murphy, et al, in a study of 216 cigarette smokers showed that LAA_{exp850} provided remarkably high correlations (r=0.85-0.90) with forced expiratory in 1 second to forced vital capacity (FEV_1/FVC) ratio and with FEV_1 percent predicted.[50] Schroeder, et al,[13] found similar levels of correlation in a study of 4,062 COPDGene® participants with and without COPD. Quantitative CT evaluation of severity of emphysema and expiratory gas trapping provides a simple way to assign individual COPD patients to subgroups characterized by predominant emphysema, mixed emphysema and gas trapping, and predominant gas trapping.[23]

Other authors have used other indices of gas trapping, including the ratio of inspiratory to expiratory lung volume, inspiratory-expiratory lung attenuation ratio, and the expiratory to inspiratory relative volume change of voxels with attenuation values between -860 and -950. Mets, et al, found that the inspiratory-expiratory lung attenuation ratio provided the strongest correlation with physiologic air trapping.[51] The same group studied 1,140 individuals enrolled in a lung cancer screening study, and found that a diagnostic model that included $LAA_{-950insp}$, ratio of inspiratory to expiratory lung volume, body mass index, smoking pack years and smoking status permitted accurate diagnosis of COPD.[14] As screening CT becomes more widely implemented for lung cancer detection, it is possible that routine expiratory CT may become part of the algorithm to permit detection of unrecognized COPD, and to evaluate subtle abnormalities of lung function.[52]

One of the challenges with evaluation of expiratory gas trapping in COPD is that a simple threshold measurement does not distinguish between gas trapping due to emphysema and small airways disease. Several authors have used deformation techniques to register the inspiration image to the expiration image, and calculate a voxel-by-voxel ventilation map, based on the change in CT attenuation between expiration and inspiration (Figures 6d, 7d).[50, 53, 54]

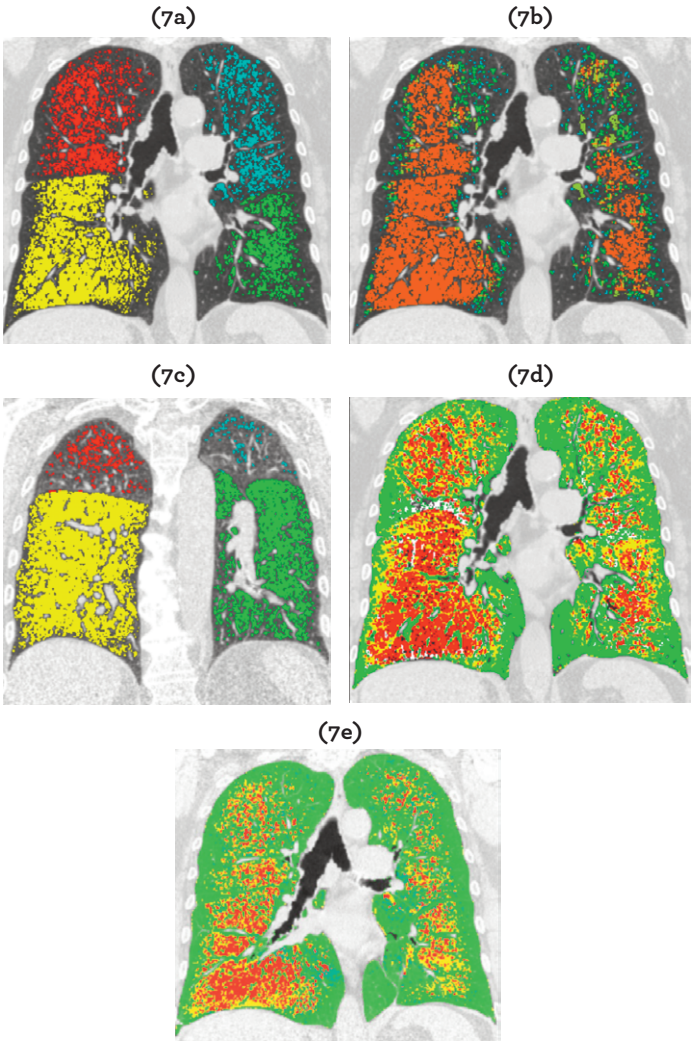

Figure 7. Followup CT Analysis in Same Subject as Shown in Figure 6. *Color coding:* Same as in Figure 6. **(a)** % LAA-950 has increased from 14% to 23%. **(b)** Cluster sizes have also increased. **(c)** Air trapping appears to have increased from 38% to 45%. **(d)** Inspiratory-expiratory registration shows that only the amount of emphysema increased, while the amount of gas trapping remained constant. **(e)** Longitudinal registration of baseline and followup inspiratory scans with micromapping shows areas of stable emphysema in red, new areas of emphysema in yellow, and stable normal lung in green. *Images courtesy of Eva van Rikxoort, PhD, Radboud University Nijmegen Medical Centre.*

Galban, et al, with this technique generated a parametric response map, based on the assumption that voxels of lung with inspiratory CT attenuation less than -950 HU were emphysematous, while voxels that were greater than -950 HU on inspiration, but less than -856 HU on expiration represented non-emphysematous functional small airways disease.[54] Murphy, et al, using a similar technique, found that measures based on expiratory CT provided the best correlations with FEV_1/FVC ratio and with presence or absence of COPD, while measures based on co-registered inspiratory and expiratory images provided better classification of the GOLD stages of COPD.[50]

Airway Abnormality

Radiologic evaluation of the airways is helpful in COPD to provide an index of bronchial inflammation and remodeling, to correlate with exacerbation and other symptoms, and to provide a window into abnormalities of the small airways. There have been substantial recent advances in quantitative evaluation of the segmental and subsegmental airways. Currently, available software permits multiplanar reconstruction of airways from thin section volumetric datasets, permitting measurement of luminal diameter and wall thickness to the level of subsegmental or sub-subsegmental airways. Parameters available for evaluating the airways include absolute measures (bronchial luminal diameter or area, bronchial wall thickness or area, and total bronchial area), and relative measures (e.g. bronchial wall area %). A commonly used summary measure of bronchial wall area is the square root of wall area of a hypothetical bronchus of internal perimeter 10 mm, calculated from linear regression of all measured bronchi, referred to as Pi10.[55]

Nakano, et al, showed that there was a correlation between wall area of the small airways, measured using histology, and wall area of the large airways, measured using CT.[56] Han, et al, showed that CT-quantified bronchial wall thickness and severity of emphysema were independently associated with exacerbation frequency, and could be used to define bronchial predominant and emphysema predominant subtypes of COPD.[5] Grydeland, et al, showed that the Pi10 was independently related to symptoms of dyspnea, cough and wheezing in individuals with COPD.[57] There are modest correlations between airway wall area % and physiologic impairment.[13, 58] Additionally, Washko, et al,[58] showed that on multivariate analysis, wall area % and peak airway attenuation appeared to be independent predictors of FEV_1 % predicted.

Advanced Computerized Analysis Methods

There is increasing interest in using more sophisticated analysis to evaluate smoking-related lung injury, including emphysema. Ginsburg, et al, showed that a texture-based approach could discriminate quite effectively between the lungs of never-smokers, smokers without emphysema and smokers with emphysema.[59] This suggests that textural analysis may be able to identify the early phase of smoking-related lung injury, prior to the development of emphysema. Castaldi, et al, used a local histogram-based technique to characterize and quantify distinct patterns of low attenuation in 9,313 smokers in the COPDGene® Study.[60] They found that these patterns were more predictive than threshold-based emphysema measurement for lung function, dyspnea, quality of life, and health care use, and were strongly associated with pulmonary functional impairment even after adjustment for $\%LAA_{-950}$.

Concordance Between QCT And Visual Evaluation

Although quantitative CT measures correlate with severity of visually assessed emphysema, the level of correlation is not strong. In the COPDGene® workshop, where 58 observers independently scored CT scans of 294 individuals, agreement on pattern and extent of emphysema was poor to moderate, and concordance between visual and quantitative assessment of the presence of emphysema was only 75%.[61] Gietema, et al, found that in those with less severe categories of emphysema, radiologists tended to visually underestimate extent of emphysema compared with quantitative measures, while in those with more severe emphysema, the radiologists tended to relatively overestimate emphysema extent. Thus, QCT and visual evaluation may provide complementary, independent assessments of severity of emphysema, particularly in those with less severe abnormality. Interestingly, although the presence of emphysema on visual assessment is associated with lung cancer,[62, 63] quantitative CT measurement of emphysema has not been shown to be independently associated with lung cancer.[64-66]

Normal Values

A limitation in the implementation of quantitative CT has been the lack of understanding of the normal range of CT parameters,[67] and the factors that influence these measurements. A study of 92 healthy individuals aged between 45 and 80 showed that inspired lung volume was an important determinant of LAA_{-950} and of several airway parameters.[68] Although the parameters also differed by age and sex, these differences did not persist when adjusted for inspired lung volume. Larger studies of healthy individuals are being performed, with the goal of developing prediction equations.[69] It is important to be aware that the range of normal for quantitative CT parameters will vary depending on the CT acquisition technique.

PET-CT

PET-CT using 19F-flourodeoxyglucose can quantify metabolic activity in lungs with COPD. Increased metabolic activity is presumed to be related to neutrophilic infiltration, and correlates with the severity of pulmonary functional impairment.[70] Correction for lung volumes is helpful in quantitative analysis of 19F FDG activity.[71] However, this remains largely a research tool, at least in part because of the relatively large radiation dose associated with PET-CT.

MRI

Hyperpolarized helium-3 is a remarkable tool for imaging emphysema.[72-75] On MRI following inhalation of this gas, its diffusivity can be used to estimate measures of the size of lung microstructure including alveolar ducts and alveoli. In cigarette smokers with absent or mild spirometric abnormality, this technique showed significant decrease in alveolar depth and enlargement of alveolar ducts.[75] Most recently, this technique has shown subtle changes in apparent diffusion coefficient of 11 of 37 individuals who were exposed to secondhand smoke.[76] Despite these unique and valuable properties, use of hyperpolarized helium for research or clinical applications has been limited by increasing scarcity and high cost of this isotope. Because of these limitations, attention is turning to other gases such as 129Xe gas.[77-80] Although this agent is more abundant and less expensive, several technical challenges must be overcome before its role in the evaluation of emphysema can be properly understood.[80] Other potential agents include oxygen, Carbon-13 and perflouropropane.[81]

In addition to the use of inhaled gases, there may be a role for conventional (proton) MRI in evaluation of emphysema.[82-85] Advances in MRI imaging of the lung can result in visualization of low-proton areas of emphysema in at least 50% of cases.[84]

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