Quantitative Computed Tomography of Chronic Obstructive Pulmonary Disease[1]

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Chronic obstructive pulmonary disease (COPD) is described as airflow limitation that is not fully reversible. Quantitative assessment of structural changes within the lung that are responsible for this airflow limitation has relied on the examination of tissue obtained from surgical or postmortem specimens. However, in the past two decades, researchers have developed novel and robust tools to measure the structure of the lung parenchyma and airway wall by using computed tomographic (CT) scans, which do not require the removal of lung tissue. These techniques are extremely important because they allow longitudinal studies of the pathogenesis of COPD and the assessment of therapeutic interventions. Another application of this approach is that it potentially allows phenotyping of individuals who predominately have emphysema or small-airway disease, which may be important for the evaluation of pathogenesis and prescription of treatment options. This review describes some of these CT techniques for quantitative assessment of lung structure.

Key Words. Emphysema; airway wall; computed tomography; quantitative assessment; noninvasive.

Chronic obstructive pulmonary disease (COPD) currently is the 12th leading cause of disability in the world and is predicted to be fifth by 2020 (1). In the United States alone, the annual cost of morbidity and early mortality caused by COPD was estimated to be approximately $4.7 billion (2). COPD is a complex genetic disorder in which environmental factors interact with genetic susceptibility to cause disease. Tobacco smoke is the most important environmental risk factor, and in susceptible individuals, it causes an exaggerated inflammatory response that ultimately destroys the lung parenchyma (emphysema) and/or increases airway resistance by remodeling of the airway wall. It has long been known that the pathway varies among individuals; some patients have predominant emphysema, whereas others can have similar degrees of airflow obstruction caused by severe small-airway disease with relatively preserved parenchyma. The need to separate these two subgroups of patients with COPD has been emphasized by studies of the genetics of COPD and because of the possibility of specific therapeutic interventions. It is likely that different gene polymorphisms impart susceptibility to one or other of these processes. In any study of the genetics of COPD, it will be important to include this phenotypic distinction in the analysis. Similarly, in any future clinical trials, it will be important to stratify by predominant pathophysiologic process because therapy aimed at forming new alveolar walls or preventing their destruction will have little effect in patients for whom the predominant disease is in small airways. Similarly, therapy aimed at inhibiting matrix remodeling in patients with predominant airway disease could be ineffective or even contraindicated in those who have predominant parenchymal destruction.

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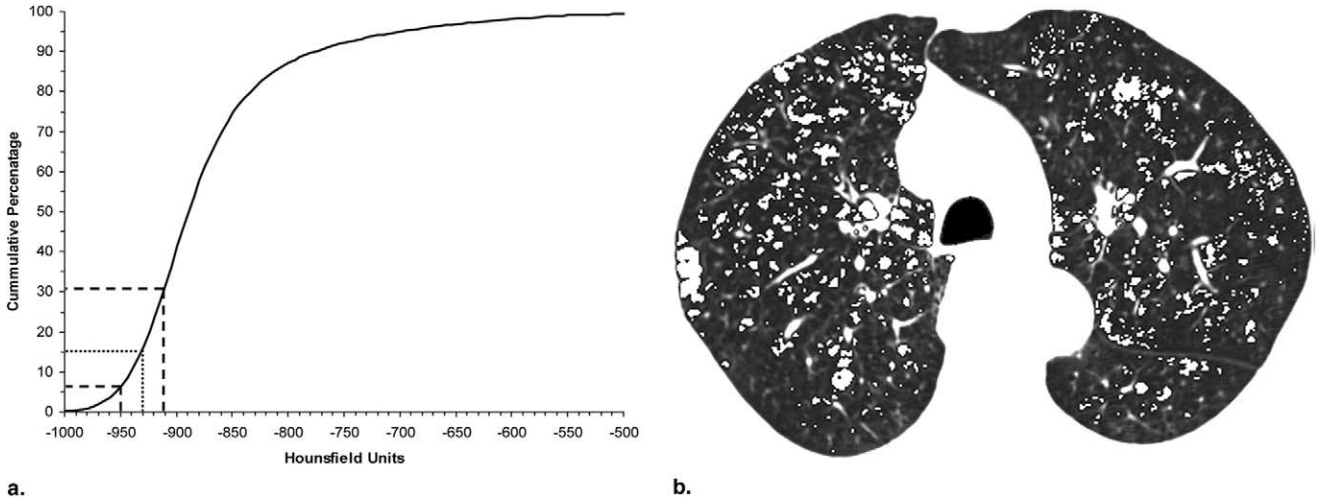


Figure 1. **(a)** Cumulative distribution of X-ray attenuation values from a CT scan. Cutoff values of –910 HU (5) and –950 HU (8) are shown in dashed lines (— — —). The intersection of these lines on the Y-axis indicates the percentage of emphysema in the CT scan using this technique, and this percentage of emphysema is used to compare between or within subjects. The 15th percentile technique (23) is indicated by the dotted line (▪▪▪▪▪). Thse intersection of this line with the X-axis indicates the HU value of the 15th percentile. To compare between or within subjects, the difference in HU at the 15th percentile is examined. **(b)** Voxels with attenuation values less than –950 HU are highlighted in white on the CT scan.

Computed tomography (CT) has the potential to allow the separation and quantification of these two processes in individual patients. The aim of this review is to summarize new trends in quantitative CT assessment of patients with COPD, with emphasis on obtaining quantitative measurements of lung structure that may allow us to separate emphysema-predominant patients from those with predominantly airway disease.

EMPHYSEMA ANALYSIS

Emphysema is defined as abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls, without obvious fibrosis (3). Therefore, assessment of emphysema requires lung tissue, usually obtained from postmortem or resection specimens, effectively limiting studies to cross-sectional analysis of older subjects. For this reason, considerable effort has been invested in developing noninvasive quantitative imaging techniques for the analysis of emphysema.

In the first study to use CT to assess the extent of emphysema, Hayhurst et al (4) found that patients with pathologically defined centrilobular emphysema had more voxels within the −450- to −500-EMI (equivalent to −900 to −1000 Hounsfield units [HU]) range (4). Müller et al (5) and Miller et al (6) extended this analysis by showing that the percentage of lung that absorbed X-rays below a specific value (−910 HU) correlated with the extent of holes greater than 5 mm in diameter on gross pathological specimens (Figure 1). Subsequently, Gould et al (7) found significant correlations between the lowest fifth percentile of HU distribution and both the mean value of the surface area of the alveolar wall per unit volume and extent of emphysema measured pathologically. These techniques are the foundation of quantitative parenchymal analysis, and although there have been modifications to the HU or percentile cutoff value used, the basic analysis approach is still the same.

The first modification was introduced by Gevenois et al (8), who compared quantitative pathological measurements of emphysema with density-mask measurements by using high-resolution CT scans (1-mm sections reconstructed with an edge-enhancing algorithm) and showed that a threshold cutoff value of −950 HU had the best correlation with extent of emphysema (Figure 1). In another pathological study, Coxson et al (9) found that a second density-mask cutoff value representing the patient's maximal lung expansion at total lung capacity (measured in milliliters of gas per gram of tissue) could identify holes in the 2- to 5-mm range. Other groups modified the percentile method and reported that the lowest 15th percentile of the frequency distribution provided a reproducible estimate of the extent of emphysema in α_1-antitrypsin–deficient individuals (10–15) (Figure 1).

Although the threshold cutoff value or percentile techniques yield valuable data about the extent of emphysema, they do not produce information on the size or location of the emphysematous hole or the effect the destruction has on the gas-exchange surface of the lung. Mishima et al (16) used an elastic spring model to show that as emphysematous holes grow in size, they decrease in number, and the relationship between hole size and number can be expressed as a fractal dimension. Coxson et al (17) applied fractal analysis to patients undergoing lung-volume reduction surgery and showed that patients with large emphysematous holes in the upper regions of the lung had better outcomes, measured by means of cardiopulmonary exercise capacity after lung-volume reduction surgery, than patients with smaller holes or disease distributed throughout the lung. Nakano et al (18) divided the lung into apical and basal regions, as well as an inner core and outer rind, and reported a correlation between extent of emphysema in the upper-outer region and lung-volume reduction surgery outcome.

In an attempt to describe the remaining lung tissue instead of just the emphysema, Coxson et al (9) developed a lung-surface area prediction equation using median lung inflation and showed that the predicted surface area correlated with diffusing capacity of the lung (9). Uppaluri et al (19) took the analysis one step further by examining multiple features of the CT images and X-ray attenuation values to describe the lung. This "texture" technique has been shown to have very good sensitivity for lung analysis and has even been able to separate smokers from nonsmokers in the absence of other disease; however, this technique has not been validated with pathological assessment.

The application of quantitative CT techniques to clinical studies has been used predominately to assess the outcome of lung-volume reduction surgery. Rogers et al (20) showed that preoperative volume of severe emphysema predicts improved exercise capacity after surgery, and Flaherty et al (21) showed that emphysema distributed in the upper compared with lower regions of the lung was the best predictor of an increase in forced expiratory volume in 1 second (FEV_1), measured by means of spirometry after surgery. Results of the National Emphysema Treatment Trial confirmed these finding and showed that outcome after surgery is best for patients with both predominately upper-lobe emphysema and low baseline exercise capacity (22).

Applications of these techniques to pharmaceutical studies of disease treatment have been less conclusive. Dirksen (23) used histogram analysis and 15th percentile cutoff value to study treatment effects in α_1-antitrypsin–deficient individuals, but could not show a significant change in lung structure or function with treatment (23). Mao et al (24), in a pilot study of all-trans-retinoic acid treatment of human emphysema, similar to other studies, could not measure a difference in emphysema defined by a density mask using a small group of subjects and a short study design.

On the positive side, Dirksen (23) commented that although he could not show a change in disease with treatment, power analysis indicated that to reach significance, 550 patients would be needed to measure a functional change compared with only 130 patients assessed by using CT. To further establish the use of CT in longitudinal and multicenter studies, this group tested the reproducibility of the percentile method and the density-mask technique by using both a phantom and human subjects. They reported that the 15th percentile and density-mask value of −910 HU showed significant variation among the different manufacturers of single-slice CT scanners, but are very reproducible when using multislice scanners (14). The reproducibility of these metrics using low-radiation-dose CT scans of humans showed that the 15th percentile differed by an average of only −1.29 HU, whereas density-mask measurements showed an average variation of 1.02% (13). Subsequently, Parr et al (25) noticed a drift in density-mask measurements that was related directly to a difference in air calibration of CT scanners. They stressed that although water calibration of the scanner was performed routinely, there was no attempt to calibrate the scanner to air. Therefore, they stressed that proper air calibration must be performed to obtain reliable densitometry results. They even developed a correction factor to apply to analysis of CT scans to correct for drift in X-ray attenuation values of air (25). The conclusion from their studies is that lung densitometry values obtained by using properly calibrated multislice CT scanners is within the variation observed for measurement of FEV_1, but with a smaller variance, and therefore should be used for longitudinal analysis of emphysema progression (13,14,25).

In another recent study, Boedeker et al (26) found that even when all other aspects, such as scanner type and size of breath, were carefully controlled, the reconstruction algorithm could make up to a 15% (average, 9.4%) difference in the extent of emphysema measured by using a density-mask technique (26). These investigators carefully measured the modulation transfer function of four different CT scanners by using various reconstruction al-

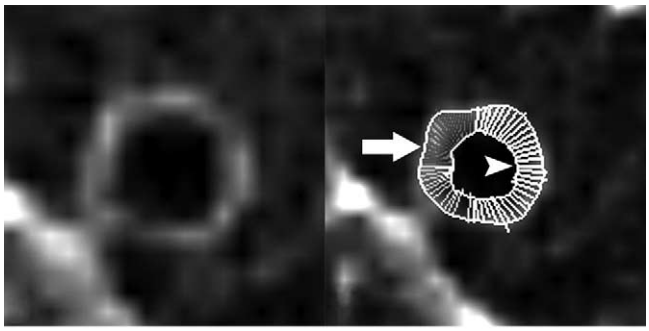
gorithms. Their data showed that some reconstruction algorithms, described as "overenhancing," improved spatial resolution by overenhancing the difference between lung voxels; thereby changing the frequency distribution of the apparent X-ray attenuation values within the CT image and, ultimately, the number of voxels below a certain cutoff value (26). Their conclusion is that special attention must be given to the reconstruction algorithm used to create CT images, and data obtained using different reconstruction algorithms may not be comparable (26). These data also suggest that use of these high-contrast algorithms, although producing an image with superior edge detection, produces images that are not appropriate for densitometry measurements.

In another group of studies designed to evaluate the difference in lung-analysis programs, Leader et al (27), Hoffman et al (28), and Nakano et al (29) compared their different lung segmentation and analysis techniques. Although there are some fundamental differences in lung-segmentation algorithms among centers, results are very similar, and differences in data are less than differences reported for sequential CT scans and reconstruction algorithms.

Therefore, although quantitative analysis of the lung parenchyma provides a consistent and reproducible assessment of lung structure and the density-mask and histogram techniques provide well-validated hallmarks of disease activity, careful attention to detail must be followed to ensure that CT values can be compared among institutions and studies.

AIRWAY ANALYSIS

The lung parenchyma has received the greatest attention in the literature; however, there are numerous reports and techniques, in various stages of development, to measure airway wall dimensions. Initially, these attempts tried to reproduce histological methods and involved manually tracing the airway on the printed image by using a digitizer (30–33). Although this technique seems straightforward, investigators showed that measurements were very dependent on display parameters of the printed image (32,33), which often made the image unusable for diagnostic purposes. Even more important, this technique is tedious, time consuming, and associated with considerable intraobserver and interobserver error. Therefore, attention turned to automatic image analysis, in which the airway lumen was measured by using threshold cutoff values of



a. b.

Figure 2. **(a)** Magnified view of an airway from a CT scan and **(b)** measurement of the airway wall dimensions using the full-width-at-half-maximum method. Ray length is determined by choosing the halfway point between the minimum X-ray attenuation value in the lumen or lung parenchyma and maximum value within the airway wall. Lumen area and internal perimeter of the airway wall are measured by using the internal boundary of the rays (arrowhead), and the wall area and outer perimeter are measured by using the external boundary of the rays (arrow).

−500 or −577 HU (34,35), similar to the density-mask analysis described. This threshold approach only works on airway lumen and does not provide information on airway wall dimensions.

The most commonly reported method for measuring lumen and wall areas relies on the "full-width-at-half-maximum" (or "half-max") technique (Figure 2). This technique evaluates the pixel value distribution of measured x-ray attenuation shown in a CT image (as apparent attenuation) along a ray that is projected from a central point of the lumen to the parenchyma. The magnitude of this attenuation is greater in the airway wall than in the lumen or lung parenchyma because x-ray absorption is greater in soft tissue than air. The shape of this curve is dependent on various parameters, including the reconstruction algorithm used to create the image, partial-volume averaging because of field of view and orientation of the airway within the CT image, and the inevitable blurring of edges that occurs because of the point spread function of the CT scanner. The distance between the point at which the attenuation is half way between the local minimum in the lumen or parenchyma and the maximum within the wall is considered to be wall thickness (36,37). However, validation studies using phantoms and anatomic specimens (37) showed that CT scans consistently overestimate airway wall area and underestimate lumen area, and these errors become very large in small airways. These systematic errors are caused by a combination of the technical and noise propagation factors

listed plus the inability to visualize the folding of the epithelium.

For these reasons, investigators developed different techniques to attempt to overcome these limitations. Reinhardt et al (38) showed that wall thickness can be predicted with greater accuracy by using the "maximum-likelihood method," in which the attenuation threshold along each ray is matched to an ideal calculated ray. King et al (35) developed a technique known as "score-guided erosion algorithm," in which airway wall edges are found by using an edge-finding algorithm that assumes that airways are circular and have a relatively high density compared with the surrounding parenchyma. The image then is shifted and subtracted from the previous image, and a pixel that has a large change after this shift is assumed to be along an edge of the wall.

King et al (35) further attempted to correct for errors caused by orientation of the airway by defining the angle of deviation of each airway from the perpendicular by using the centroid of the same airway on sequential images immediately preceding and following the airway on which measurements are made (35). Saba (39) developed an alternate technique for measuring airways that are not cut in cross-section. This method involves fitting an ellipse to the airway lumen and wall and shows great promise in correcting errors in measurement of obliquely cut airways (39). These techniques claim to be more accurate than the more commonly used techniques, but have not been applied generally, presumably because of the limited availability of the complex algorithms involved.

These techniques have been developed and validated using single-slice CT scanners, but with the introduction and proliferation of multidetector row CT scanners, it now is possible to acquire (volumetric) thin-slice images of the entire chest with 0.5- to 1-mm slice thickness. This is an important advance because it allows researchers to identify and track an individual airway at a specific location within the bronchial tree over time to study the natural history of a disease and effect of an intervention. Additionally, probably the most important advance of these scanners is that they produce true isotropic voxels, in which Z resolution (slice thickness) is the same dimension as X and Y (in plane) resolution, thereby making it possible to measure airways in true cross-section at any location by using a retrospective reconstruction of the images (40–42). This is a major improvement in the study of airways because, to date, investigators have had to rely on random samples of airways or large central airways to compare serial measurements of airway structure before and after treatment (43).

Although there is great interest in airways within the pulmonary community, applications of these techniques to COPD have been very limited. Nakano et al (36) evaluated the right apical segmental bronchus of 114 smokers by using the half-max method. The investigators chose this airway because it usually is cut in cross-section on CT and is identified consistently and reliably on CT. Data from this study showed that thickening in this large airway correlated with FEV_1 percent predicted, forced vital capacity percent predicted, and residual volume/total lung capacity. Furthermore, multiple regression analysis suggested that for a given FEV_1, subjects with more extensive emphysema had less airway-wall thickening than those with less extensive emphysema. However, all symptomatic smokers had thicker walls than asymptomatic smokers (36). A criticism of this report is that the important site of airflow obstruction in patients with COPD is the small airways (44,45), but, as mentioned, there are large errors associated with measurement of airways this small (37). To answer this question, Nakano et al (46) recently compared airway measurements from CT scans and histological examination of excised lungs of smokers who had various degrees of airway obstruction. They compared the wall area of small airways (1.27-mm diameter) measured histologically with the wall area percentage of larger airways with a mean internal diameter of ~3.2 mm. These data show a significant association ($R^2 = 0.57$; $P = .001$) between dimensions of the small and larger airways. The investigators concluded that, at least for patients with COPD, measuring airway dimensions in the larger bronchi, which are assessed more accurately by means of CT, can provide an estimate of small-airway remodeling. It is likely that the same pathophysiologic process that causes small-airway obstruction also takes place in larger airways, where it has less functional effect.

CONCLUSION

During the last decade, quantitative CT has become an important research tool to assess lung structure. Furthermore, with increased awareness that careful phenotyping of subjects with COPD is critical in our understanding of the pathogenesis and effect of therapeutic interventions, CT is poised to have an even more central role. There already are data that suggest CT is more sensitive than

traditional pulmonary function measurements in interventional studies, which has led for calls to include CT as an end point in new trials. However, CT imaging has inherent limitations, particularly concerning radiation exposure to the subject and the standardization and quality control of CT scan parameters. Plus there still is controversy about which are the best CT measurements to use to assess small changes in lung structure. Nevertheless, CT is the only readily accessible, relatively noninvasive technique that provides quantitative structural data in vivo, and with an awareness of these limitations, studies can be designed that minimize their impact while producing valuable data on this devastating disease and how it can be alleviated.

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