# Quantitative Computed Tomography of Lung Parenchyma in Chronic Obstructive Pulmonary Disease

## An Overview

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**This article provides a brief overview of the important issues influencing the effective use of quantitative X-ray computed tomography (QCT) in the assessment of the lung parenchyma in patients or research subjects with chronic obstructive pulmonary disease (COPD). This effort builds on an earlier workshop that was done in 2001. The pathologic appearance of emphysema is briefly reviewed. CT scanner, CT phantom, and CT image acquisition parameters are discussed that are important in obtaining high quality CT images of the lungs for image quantitation. Data storage, data transfer and data archival issues are reviewed. Current image processing techniques to derive meaningful quantitative measures of emphysema are also discussed.**

**Keywords:** X-ray computed tomography; quantitative imaging; COPD; emphysema

The purpose of this article is to provide a brief overview of the important issues influencing the effective use of quantitative X-ray computed tomography (QCT) in the assessment of the lung parenchyma in patients or research subjects with chronic obstructive pulmonary disease (COPD). This effort will build on relevant elements of an earlier report describing a previous 2001 workshop entitled "Report of a Workshop: Quantitative Computed Tomography Scanning in Longitudinal Studies of Emphysema" that dealt with similar issues (1). In this review, the reader will also be referred to other manuscripts that were written concurrently with this manuscript in conjunction with the 2008 workshop entitled "Quantitative Chest Tomography in COPD Research."

QCT of the lung parenchyma uses accurate measures of lung density to generate histogram statistics of the lung to detect lower-density areas of the lung that correspond to emphysema on total lung capacity (TLC) scans and can also look at lower-density areas of the lung that correspond to air trapping on CT scans of the lung obtained at functional residual capacity (FRC) or residual volume (RV). The detection of the emphysema is a direct measure of lung remodeling in COPD, and the detection of air trapping is believed to be an indirect measure of small airway disease. There may be overlap in the signal of these two entities, as one might suspect. More advanced quantitative CT scanning and image processing techniques can be used to assess texture and function of the lung parenchyma as described elsewhere in this issue.

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## BACKGROUND

Emphysema is one of the key structural abnormalities in the lung in patients with COPD, and for this reason it is important to understand the definition of emphysema. "Emphysema is defined as a condition of the lung characterized by abnormal, permanent enlargement of air spaces distal to the terminal bronchioles, accompanied by the destruction of their walls, and without obvious fibrosis," (1, 2). Three subclassifications of emphysema are described relative to the involvement of the pulmonary acinus. Centriacinar emphysema is associated with inflammation in the center of the pulmonary acinus with involvement of the respiratory bronchioles and adjacent airspaces (1, 2). Centriacinar emphysema predominates in the upper lobes. Centriacinar emphysema is seen in smoking and in pneumoconiosis from exposure to coal dust or other mineral dust exposure. Panacinar emphysema involves the entire pulmonary acinus uniformly (1, 2). Panacinar emphysema occurs more commonly in the lung bases and is associated with smoking and also with $\alpha_1$-antitrypsin deficiency. It should be noted that as the severity of the emphysema progresses it becomes increasingly difficult to distinguish centriacinar emphysema from panacinar emphysema (1, 2). Distal acinar emphysema involves primarily the alveolar ducts and sacs (1, 2). This form of emphysema is associated with the secondary interlobular septa and is often referred to as paraseptal emphysema. There is early subpleural involvement that may develop into extensive bullous emphysema with little airflow obstruction but with increased risk of spontaneous pneumothorax, particularly in young adults (1, 2). The bullous lesions may require surgical resection when they reach one third to one half the size of the involved lung.

Gould first described a quantitative technique to analyze CT images of the lungs with emphysema using the modal CT attenuation value and the value of the fifth percentile of the histogram. These quantitative CT indices correlated well with a morphometric index derived from pathologic sections of the lung (3). Subsequently, Müller and colleagues used the "density mask" program available on GE CT scanners in the late 1980s to quantify the amount of lung tissue that measured less than −910 HU and showed good correlation with both anatomic measures and pulmonary function measures of emphysema (4). Subsequently, there have been many reports in the scientific literature using CT and image processing techniques to quantitate the amount of emphysema in the lungs (5–16).

There is emerging evidence that CT can be used to phenotype patients with increased genetic susceptibility to COPD, not only in patients with $\alpha_1$-antityrpsin deficiency but also in patients without $\alpha_1$-antitrypsin deficiency (17–24). It will be important to use CT to quantify not only total emphysema burden but also to assess other phenotypic features such as regional distribution (i.e., upper lobe predominant versus lower lobe predominant emphysema), indirect assessment of small airway disease with CT by measuring both emphysema and air trapping on expiratory CT images (7), and directly measuring the airway wall geometry in a quantitative fashion using CT (Coxson, ref. 25, this issue).

There are several important technical parameters that need to be understood and dealt with in Quantitative CT imaging of COPD. These include X-ray CT scanner make and model, CT scanner calibration using CT phantoms, image acquisition parameters, image reconstruction parameters, lung volume at acquisition, intravenous contrast media, quantitative image analysis method(s), CT radiation dose, CT data handling, and CT image processing. The following sections will discuss these important issues.

## CT SCANNER, CT PHANTOM, AND CT IMAGE ACQUISITION PARAMETERS

A multi-detector CT (MDCT) scanner using 16 or more detectors is preferred for quantitative CT studies of COPD because of the shortened scan time over earlier CT scanners with fewer detector channels. It is important to try to scan patients with the same make, model, and particular CT scanner, since there are significant variations in the CT Hounsfield units between make, model, and even between CT scanners of the same make and model. The quantitative analysis of the lungs in COPD is heavily dependent on the reproducibility of the Hounsfield scale and necessitates the above restrictions. Certain makes and models of CT scanners, such as single detector CT scanners, may be unacceptable for quantitative CT of lung parenchyma in COPD.

CT phantoms are devices that are made of inorganic materials simulating lung, water, soft tissue, and bone, and are used to calibrate CT machines periodically so that they provide the best images possible. This process of using CT phantoms to calibrate CT scanners is especially important in quantitative CT of lung parenchyma in COPD. This typically involves complying with the CT manufacturer's recommendation in maintaining CT quality. A CT performance phantom is scanned once a week to comply with the recommended CT manufacturer quality assurance program. CT scanning quality assurance allows for assessment of the accuracy of CT slice thickness, spatial resolution, contrast scale, low contrast detectability, noise, and uniformity in the center and peripheral aspects of the water phantom. Quantitative CT studies of lung parenchyma often require additional measures of CT scanning quality. A study-specific CT phantom can be developed that looks at CT attenuation values of the lung in the range of Hounsfield units that may correspond to normal lung, emphysematous lung, or both. Special foam-type consistency materials are most suitable for simulating lung tissue.

MDCT scanning of the lung requires researchers and physicians to select a number of parameters to optimize image quality and reduce radiation dose to the patient as much as possible. The parameters include tube voltage (kV), tube current (mA), rotation time (s), the product of tube current and rotation time (mAs), scan collimation (mm), pitch, reconstructed axial image thickness (mm), reconstruction interval (mm) (i.e., contiguous, 50% overlap), scan field of view (cm), reconstructed field of view (cm), software reconstruction kernel, patient's lung volume at the time of the scan, use of iodinated intravenous contrast media, and effective (radiation) dose (mSv) to the patient. These CT scan parameters have been extensively evaluated for the COPDgene study mentioned above, and an example of suitable parameters for quantitative CT scanning in the COPDgene study are provided in Appendix E1 in the online supplement.

It should be noted that there is not a universally accepted quantitative CT technique in COPD, though the 2001 workshop mentioned earlier and this 2008 workshop are intended to provide guidance for investigators who require CT COPD phenotyping in their investigations of COPD using quantitative CT of the lung parenchyma. There is reasonable agreement at this time in using 120 to 140 kV, MDCT with 16 or greater channels, pitch of 1 to 1.5, isotropic three-dimensional reconstruction of the entire lung using 0.625-mm axial reconstructed slice thickness, obtaining the CT scan at TLC without respiratory gating, using a medium to low spatial resolution reconstruction kernel (i.e., Siemens B35f), and making sure no iodinated contrast media is administered, as this will increase lung density do to the circulating contrast media in the lungs.

If the assessment of lung density alone is sufficient for the purposes of the individual research project or clinical question, then it may be sufficient to perform the CT examination with a low mAs, (i.e., 20–40 mAs) which results in a low effective radiation dose to the patient but may preclude direct assessment of the airway geometry beyond the fourth airway generation. However, It has recently been noted that the lower-dose CT scan for assessing lung parenchyma for the presence of emphysema will result in a higher emphysema score because of increased noise in the CT images that broadens the image histogram curve. If the threshold for emphysema is set at −950 HU, this results in an increase in percent emphysema from 5% to 10% when decreasing the mA from 118 to 30 mA (26). A similar effect was noted when assessing for emphysema using the fifth percentile point. The lowest fifth percentile point decreased from −938 to −959 HU when the mA was reduced from 118 to 30 mA. The authors of this article emphasize the importance of keeping the reconstruction kernel and effective mAs the same for all subjects for quantitative CT studies of emphysema (26). The authors also showed that if different CT manufacturers were used, but equivalent reconstruction kernel and effective mAs were used, there was little difference between the results of quantitating emphysema using different CT scanners that were manufactured by different companies (26). This low-dose technique may also be sufficient for the indirect assessment of air trapping if the CT scan is obtained with the patient's lung volume at FRC or residual volume (RV). However, the previous discussion of dose-related effects on quantitating low-attenuating areas in the lung still applies.

The direct assessment of airway geometry to seven or eight airway generations may require scans using 100 to 200 mAs, which increases the radiation dose proportionately (i.e., fivefold increase in radiation dose). It is not clear at the present time and is an area of active research whether the higher-mAs CT scans will obtain sufficient additional information regarding airway geometry to add significantly to the CT phenotype profiling of individual subjects or patients. This is discussed in more detail by Coxson, Reference 25, this issue.

## DATA STORAGE, DATA TRANSFER, DATA ARCHIVAL

It is generally agreed that the CT scan image data should be stored in a Digital Imaging and Communications in Medicine (DICOM) format, (i.e., .dcm file format); then it can either be stored on a high-density DVD or directly transferred over the Internet. The simplest option at this point is to have the CT image data archived on a DVD, placed in a special mailing envelope, and transferred to a central image processing facility using express surface mail–type delivery services. Direct Internet transfer is an attractive option but involves a number of additional issues, including setting up the internet transfer computers, software and protocols, providing secure internet data transfer, and receiving and archiving the data automatically at the central data archive and image processing facility. The current complexity of direct Internet data transfer increases costs over that achievable with the use of DVDs.

Once the CT image data arrives at a the central data archival and data processing facility, the CT image data will need to be uploaded into a secure, redundant computerized image archival system and the image data will have to be evaluated for quality by a trained technician. Any problems with CT image quality will

have to be communicated to the specific CT scan site where the subject was imaged, and will have to be addressed by either rescanning the patient or rejecting the patient from the study.

## IMAGE PROCESSING

As suggested above, it is believed to be best practice in multicenter trials to have a designated central image storage, archival, and image processing facility. This appears to be the most cost-effective and efficient way of managing the image storage and image processing parts of a study.

The image processing portion of the study requires special computer hardware and software that represents a significant cost to the study to process the CT images and to extract meaningful measures of lung and airway remodeling in subjects or patients with COPD. Specially trained CT image data handling and processing technicians are required for the study, and these study resources are best deployed by using a central image data handling and processing center for each study.

There are three basic steps in the image processing part of the study. The first step is to load a large three-dimensional CT image dataset of the lungs on a specific patient and CT scan study date into the image processing software environment. The next step is to use the image processing software to extract the lungs from the rest of the cervical, thoracic, and upper abdominal anatomy, a process referred to as image segmentation. This image segmentation process is best accomplished with semiautomatic or fully automatic methods because of the large of amount of data involved in such studies. The third step is to analyze the lung image data using histogram-type statistical methods. More advanced texture processing can be done as a fourth step if required.

There are two generally agreed-upon methods to assess the amount of emphysema present using the CT voxel histogram. The first is a method that can be traced back to the work of Müller using the density mask program described earlier (4). A particular threshold value is selected in Hounsfield units that is thought to be representative of abnormally decreased lung density secondary to emphysema, and the amount of lung less than this threshold value is then calculated and usually expressed as a percent of total lung volume. A number of threshold values have been used, including −900, −910, −960, and −970 HU. Recent publications would suggest that a value of −960, −970, or −980 HU are most accurate for the quantitation of emphysema using CT (7, 27). The second method is the percentile point method that "is defined as the cut off value in Hounsfield units (HU) below which a specified percentage of voxels are distributed" (28). The optimal percentile point recently has been suggested to be 15% (28, 29) and 1% (27).

Additional techniques have also been shown to be useful, particularly the fractal dimension or α technique (30), and texture-based approaches such as the Adaptive Multiple-Feature Method (30).

The next step in the image processing of emphysema is to look at the distribution and types of emphysema present. There are reports of successfully quantitating the cranio-caudal distribution of emphysema in the lungs (31–33). This is an important step in trying to not only quantitate the amount of emphysema, but to classify the emphysema as well. It has been shown that patients with greater basilar distrubution of emphysema have greater impairment of airflow obstruction measured by the forced expiratory volume achieved in the first second of exhalation ($FEV_1$) than they have in gas diffusion as measured by $Pa_{O_2}$ (32). It is not currently possible to classify the amounts of centriacinar emphysema, panacinar emphysema, or distal acinar emphysema on the CT images of the lungs with current image processing techniques. It is hoped that the ability to classify emphysema along accepted pathological appearances will be forthcoming in the future.

Longitudinal studies that are trying to detect small changes in lung emphysema over time require techniques to compensate for variations in lung volume between CT studies of the lung done on the same patient at different time points. This approach uses the CT-determined total lung volume derived from the three-dimensional CT volumetric images of the lungs of all subjects at all time points to apply a correction to the percentile point method described above to obtain more accurate measures of emphysema within the lung over time (5, 29, 34).

## SUMMARY

The use of quantitative CT to evaluate the lung parenchyma in patients with COPD is an exciting, powerful tool to try and phenotype patients with COPD. Quantitative CT is also a very demanding imaging methodology that requires a great deal of attention to specific quality control measures and specific CT scanning details. It also requires excellent CT image data handling and processing facilities complete with the appropriate computers, software, and highly trained technical staff to handle and process the CT images to generate meaningful quantitative CT measures of lung parenchymal disease in COPD.

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