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Development of Quantitative CT Lung Protocols

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Abstract

The purpose of this paper is to review the process of developing optimal CT protocols for quantitative lung CT. This will include discussions of the following important topics; QCT derived metrics of lung disease, QCT scanning protocols and quality control and QCT image processing software.

We will briefly discuss several QCT derived metrics of lung disease that have been developed for the assessment of emphysema, small airway disease and large airway disease.

The CT scanning protocol is one of the most important elements of successfully performing QCT. We will provide a detailed description of the current thinking on optimizing the QCT protocol for the assessment of COPD and Asthma. Quality control of the CT images is also a very important part of the QCT process and we will discuss why it is necessary to use CT scanner test objects (phantoms) to provide frequent periodic checks on the CT scanner calibration to assure precise and accurate CT numbers are obtained.

We will discuss the use of quantitative CT image processing software to segment the lung and extract the desired QCT metrics of lung disease. We will discuss the practical issues of using this software. The data obtained from the image processing software is then combined with other clinical information, health status questionnaires, pulmonary physiology and genomic data to increase our understanding of obstructive lung disease and to improve our ability to design new therapies for these diseases.

Keywords

CT; computed tomography; quantitative; quantitative CT protocol; lung; pulmonary; COPD; asthma

Introduction

The purpose of this paper is to review the process of developing optimal CT protocols for quantitative lung CT. This will include discussions of the following important topics; QCT derived metrics of lung disease, QCT scanning protocols and quality control and QCT image processing software.

QCT derived metrics of lung disease are based on using CT derived measures of intensity/density, texture, volume, perfusion, ventilation and mechanics of lung tissue. It is also based

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JDN and JS are paid consultants for VIDA Diagnostics, Inc. EAH is co-founder and shareholder in VIDA Diagnostics, Inc. which is a company that makes lung image processing software.

on looking at airway geometry to assess thickness of the airway walls and also narrowing or enlargement of the airway lumen.

QCT imaging of the lung has been used to quantitate lung intensity/density and airway geometry in the normal adult human lung¹. QCT has been used to assess smoking related lung disease including emphysema and large airway disease²⁻⁷. QCT has been used to assess air trapping in asthma patients^{4, 5, 8-10}. QCT has also been used to assess Interstitial lung disease¹¹⁻¹⁵, lung nodules¹⁶⁻²², radiation induced lung injury²³⁻²⁶, and both lung perfusion and ventilation²⁷⁻³⁰, but for the purposes of this review we will focus on QCT intensity/density and airway geometry measures of smoking related lung disease and asthma.

There have been several large multi-center trials that have used QCT to assess the effects of smoking induced emphysema, small airway disease and airway remodeling of large airways. These include the following NIH-NHLBI funded multi-center research studies; Genetic Epidemiology of COPD (COPDGene) phase 1 and phase 2, Multi-Ethnic Study in Atherosclerosis (MESA), Subpopulations and intermediate outcome measures in COPD (SPIROMICS). Severe Asthma Research Program (SARP) I, II and III are multi-center research trials that have studied severe asthma patients for using QCT assessments of large and small airway disease.

There have been many iterations of the CT scanning protocol thought to be optimal for QCT assessment of COPD and asthma but the most recent widely accepted QCT protocol for COPD and asthma was designed for the SPIROMICS study and is called the SPIROMICS CT protocol. The important issues that need to be considered in building a robust QCT scanning protocol will be discussed in this review. We will also discuss QCT scanning quality control procedures using manufacturer supplied test objects/phantoms and the COPDGene 1 test object.

QCT image processing software available for the analysis of CT images include PASS (University of Iowa), Apollo Workstation 2 (VIDA Diagnostics, Inc.), Airway Inspector for SLICER (Harvard University). There are several other packages available. We will illustrate the kind of image processing that is output from these programs to provide the QCT metrics necessary to phenotype lung disease.

Quantitative CT Metrics of Lung Disease

The images that are obtained from single breath hold MDCT images of the lungs are made up of individual voxels each assigned an average value for the linear attenuation of lung tissue within that voxel. The linear attenuation values are expressed in a practical unit called the Hounsfield Unit (HU). The CT attenuation values expressed in HU's have a range from -1000 HU to +3095 HU on 12 bit CT scanners. -1000 HU is the value for pure air. 0 HU is the value for pure water. 40 HU is the value for blood. +1000 HU or greater is the value of cortical bone. Analysis of the linear attenuation values assigned to the lung voxels provides the basis for quantitative CT assessment of different tissues including lung tissue.

Several quantitative CT derived metrics of obstructive lung disease have been published in the literature. These include the percent of lung tissue having a density less than -950 HU on a TLC CT scan which is a marker of emphysema^{2, 3, 31, 32}. The percent of lung tissue having a density less than -856 HU on a FRC/RV CT lung scan which is a marker of air trapping and by inference small airway disease^{8, 9}. The ratio of the mean lung density at FRC to the mean lung density at TLC, E/I mean lung density ratio, is also a valuable measure of air trapping and possibly better than the -856 HU threshold method just mentioned³³. The percent bronchial wall area for a given generation of lung airway is a

measure of large airway remodeling, usually thickening, and has been used in a number of QCT studies of COPD and Asthma subjects with success in predicting large airway abnormalities^{2, 18, 20, 32, 34}. These example indices provide CT derived quantitative imaging metrics of certain features of obstructive lung disease. In order to reduce radiation dose to subjects or patients a new method of CT image reconstruction has been introduced that is known as iterative reconstruction. These techniques have come out from multiple CT manufacturers and have been readily accepted by the broad qualitative 3D lung imaging community. There has been concern in the QCT scanning community that these new techniques may introduce inaccuracies in the CT number measurements. Recent work suggests this may not be the case³⁵. Further work is ongoing in this area by multiple QCT research groups including our own.

The value of these QCT metrics of obstructive lung disease can only be assured if precise and accurate measurements are made on each subject or patient. QCT is much more rigorous than qualitative 3D visualization of the lung since the quantitative indices can vary in value based on lung volumes, CT scan parameters and CT scanner calibration. In the next section we will discuss in detail the important aspects of QCT scanning protocols, CT scanner calibration and ways to assure the patient is scanned at the desired lung volume, e.g. TLC or FRC/RV.

Quantitative CT Scanning Protocol and Quality Control

QCT of the lung provides exciting new metrics of lung disease that are not available in qualitative 3D CT visualization of lung disease. The two are complimentary, but QCT is much more rigorous than qualitative 3D visualization CT since we are relying on accurate and precise measures of lung density to derive a number of metrics as mentioned in the last section. Ideally, there would be one CT scanner and software system using exactly the same parameters specified in the QCT scanning protocol to reconstruct images of the lungs on all subjects in a clinical trial to study COPD or Asthma. Unfortunately, this is not possible because in order to recruit the necessary number of subjects to adequately power the research goals of the trial multiple centers must be involved. Also, CT technology is rapidly evolving so over the period of a multi-center trial, 4–5 years, the participating centers will upgrade their CT scanners to new machines with different methods of generating the attenuation values assigned to the individual voxels. These two issues make the development of a robust quantitative CT scanning protocol a challenge.

The approach to designing an optimal QCT protocol for a particular study is as follows:

- Scan at a known lung volume, e.g. TLC, FRC or RV
- Position the patient in the center of the CT scanner gantry, isocenter,
- Acquire a 3D dataset of the lungs with sub-millimeter near isotropic resolution in the x, y, and z axis
- Use an optimal reconstruction kernel
- Use as short a single breath hold as possible.
- Use a reconstruction field of view that includes just the lungs.
- Do all of this accurately and precisely across multiple CT manufacturers and CT scanner models
- Use the lowest possible x-ray dose that meets the needs of a given research study.

We will now discuss each of the above points in more detail. The largest variation in lung attenuation is not driven by differences in CT scanner hardware or software but is driven by

the ability of the patient to inspire or expire to a given lung volume, maintain that lung volume for the duration of the CT scan, 12 seconds or less, and not physically move while the CT scanner is acquiring image data. There are three lung volumes that are commonly used for QCT studies of the lung, total lung capacity (TLC), functional residual volume (FRC) and residual volume (RV). The two approaches that are used are 1) use a volume controller to physically determine at what lung volume the patient is holding their breath and 2) carefully coach the patient to the desired lung volume before beginning the scan. The first approach is the most precise and accurate. The second approach is the most practical. Depending on the goals of the particular research study either method may be used^{36, 37}. Figure 1 shows a technologist carefully instructing a research subject. Table 2 shows the written breathing instructions that are used in the SPIROMICS protocol which is designed for use in large multi-center trials where most of the study sites do not have access to lung volume controllers.

Patient positioning in the CT scanner is also very important. This is not as big an issue in qualitative 3D CT imaging but is essential in QCT. The CT scanner performs a number of calibration procedures including scanning without anything in the scanner imaging volume and also scanning manufacturer provided test objects (phantoms) to correct any drift in the CT attenuation values based on temporal variations in x-ray tube beam, x-ray detectors and associated electronics. This calibration process assumes that a patient will be positioned in the center of the CT gantry or isocenter when they are scanned. The corrections that the calibration process builds into the raw image data will not work properly if the patient is not in the center of the CT scanner aperture. Figure 2, illustrates the correct positioning of the patient in the CT scanner aperture.

The scan time is picked to be as short as possible so that the likelihood that the patient will be able to hold their breath is increased. Shortest scan time can be achieved by using the fastest gantry rotation time, maximum number of channels present and the highest pitch available which is a function of table speed and gantry rotation time. There are limitations if we want the very best quantitative data from the CT images. The accuracy of the CT attenuation values are dependent on having adequate sampling of the entire volume scanned. To insure accurate CT attenuation values the pitch setting needs to be no greater than 1, 1 is usually prescribed. The rotation time is as short as possible usually no greater than 0.5 seconds and often less than 0.3 seconds on the latest scanners. The most important factor is to be sure to have 64 channels or more available on the multi detector CT (MDCT) scanners included in the trial since this determines how much z axis coverage there is for a given pitch and rotation time.

The signal to noise ratio desired in the acquisition of the CT image data is inversely proportional to the radiation dose the patient receives, e.g. more radiation provides greater signal to noise ratio. There is clearly a need to keep the patient radiation dose to a minimum but also provide adequate signal to noise ratio for the study so that meaningful CT attenuation values are obtained and can be used to further research that may help the individual subjects/patients as well as other people with conditions like COPD or Asthma. For a given CT scanner hardware and software configuration the x-ray radiation dose is determined by the product of the tube current and total exposure time and also the maximum voltage, kVp, applied to the x-ray tube. Typically the QCT lung scanning protocol for a single x-ray tube source uses a kVp of 120 keV. This is the most common value chosen in studies of COPD and Asthma. It is important that all subjects/patients are scanned at the same kVp since changing the kVp will change the linear attenuation properties of matter and so change the values of the measured CT linear attenuation values assigned to the lung voxels independent of any other factor. The value of the tube current exposure time product, mAs, is very important in determining signal to noise ratio as well as radiation dose to the

patient. The value of the mAs used is proportional to the amount of photons generated by the x-ray tube anode and so mAs is directly proportional to the patient x-ray radiation exposure from the CT scan. Increasing the mAs will increase the radiation exposure to the patient being scanned. Typical mAs values used in various QCT studies of the lung vary from a low value of 40 mAs for lower dose scans to 200 mAs for moderate dose scans. The radiation dose for a 40 mAs QCT lung scan is approximately 1.5 mSv and for a 200 mAs QCT lung scan is approximately 8 mSv assuming a 64 channel MDCT is used with weighted filtered back projection type image reconstruction. The larger the patient's BMI the greater the mAs needs to be provide enough x-ray photons to the x-ray detector since the larger mass of the patient results in greater attenuation of the x-ray photons produced. This can be achieved by increasing or decreasing the mAs given a certain range of BMI values for the patients that are being scanned. The SPIROMICS CT scanning protocol adjusts the mAs based on the value of the patients BMI, Table 1. Small BMI subjects get less radiation but still achieve the desired signal to noise ratio in the CT images. Large BMI subjects receive more radiation so that the signal to noise ratio in the acquired QCT images are comparable to the values in the small and normal BMI subjects.

The reconstruction process is very important to insure that the CT data obtained accurately represents the true attenuating properties of the lung tissue that has been scanned. The most common reconstruction process in medical x-ray MDCT is the weighted filtered back projection method. The weighting factor is unique to each reconstruction kernel. This kernel needs to have no edge enhancement or image smoothing. Typical qualitative CT images of the lungs use a reconstruction kernel that has edge enhancement to bring out the small details of lung anatomy but at the expense of increased image noise and reduced accuracy of the CT attenuation values. Similarly, if a reconstruction kernel is used that smoothed the image than there is a decrease in the accuracy of the reconstruction kernel. The major CT manufacturers at this time have agreed that they will provide a neutral kernel that does not introduce edge enhancement or image smoothing and so will provide the most accurate values for the CT attenuation values that are obtained. Siemens HealthCare calls this the B35 kernel and GE Healthcare calls this the Standard kernel. Phillips Healthcare calls this the B kernel. For Toshiba scanners, the kernel FC01 is considered the standard kernel for quantitative lung imaging. A neutral kernel is used for QCT Lung studies of COPD and Asthma patients.

The next important issue in the QCT scanning process is CT scanner calibration. Quality control of the CT images must use CT scanner test objects (phantoms) to provide frequent periodic checks on the CT scanner calibration to assure precise and accurate CT numbers are obtained. This is done using manufacturer supplied test objects or phantoms and, in the case of QCT research into COPD and Asthma, the COPDGene 1 test object³⁸, Figure 3. Typically CT calibration is done on a daily or weekly basis using the manufacturers test object and procedures. A dedicated test object that looks closely at the CT scanner's ability to produce accurate CT attenuation values for the lung are also important and typically this sort of test object is scanned at the start of the study on every CT scanner to be used in the study so that accurate and precise CT attenuation values are obtained on all subjects right at the start of a study. This specialized test object is then scanned at monthly intervals on each CT scanner in the study. The results of these test objects scans are immediately sent to a central image processing facility that has special expertise and software to analyze the results and make sure that all the CT scanners in the study are functioning properly. If anomalies are detected in the test object CT image data the center is notified and the CT scanner in question is not used until it is re-calibrated.

Imaging Processing Software

Once the QCT image data is obtained using the procedures outlined above it is necessary to extract the quantitative information out of the 3D QCT image dataset using specially trained image analysts and specialized image processing software.

Typically the image analyst will access a central image archive to load a given subjects CT image data for analysis. This image data has been acquired and stored in the medical imaging standard data format, DICOM 3.0 Part 5. The image analysts will quality control the image data. It is important for trained image analysts to provide comprehensive quality control of the acquired image data, with rapid communication of quality defects to the submitting site. This includes evaluating all of the following important components:

- Inspiratory or expiratory images were acquired at the appropriate lung volume
- Motion artifact is absent
- All of the lung anatomy was imaged.
- The reconstructed image's field of view includes all of the lungs, but as little of the adjacent chest wall and surrounding air as possible.

The next step is to use the specialized image processing software to segment the central airways and the lungs from the rest of the thoracic anatomy, Figure 4. The image analyst will check the segmented lung data output from the image processing software to make sure the boundaries of the lungs and corresponding airways were accurately identified. If there are any discrepancies than the image analyst will make the corrections and save the updated image data. The remainder of the process is done automatically by the image processing software. This includes determining the amount of lung that is less than -950 HU in density on TLC QCT scans. It also may include determining the amount of lung that is less than -856 HU in density on the FRC/RV QCT scans. Central airway wall thickening is also determined automatically by the software and includes values such as luminal area, luminal diameter, wall area, wall area percent and wall thickness. All of these important image parameters can be determined for whole lung, individual lungs and individual lung lobes. This information is then exported to an Excel spreadsheet for further analysis.

Summary

QCT imaging of the lung can provide important metrics or phenotypic measurements of lung disease. In order to obtain accurate and precise image based quantitative CT metrics it is important to design and follow a standardized CT scanning protocol and to adhere to a robust CT scanning quality control program using standardized CT scanner test objects. Suitable image processing software must be used to extract the necessary information from the CT images. QCT imaging derived metrics of lung disease can then be combined with other measures of lung disease to increase our understanding of lung disease and increase our ability to design effective therapies.

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Figure 1.
This is a figure of the technologist carefully instructing on the imaging technique and breathing instructions.

Figure 2.
This figure illustrates the proper positioning of a patient in the CT scanner so that they are in the center of the scanner aperture.

Figure 3.
The COPDGene 1 phantom is illustrated in this figure.

Figure 4.

This figure illustrates the user interface and segmented lung and airway tree output from a typical image processing program that is used for QCT of the lung.

Table 1

The ranges of BMI for patients in the SPIROMICS QCT scanning protocol and the corresponding mas, CTDIvol and effective radiation dose are illustrated in this table.

Effective mAs Range	BMI Range	CTDIvol (mGy)
~150	>30	11.4
~100	20 to 30	7.6
~50	<20	4.2

Table 2

<p>SCANNING: Use the breathing instructions to perform:</p> <ul style="list-style-type: none"> • A practice breathing session • Scouts – as needed- to position the FOV to cover the entire lung and as little soft tissue as possible • The inspiration CT scan (TLC) <p>Inspiratory CT (TLC)</p>	<p>SCANNING: Use the breathing instructions to perform:</p> <ul style="list-style-type: none"> • A practice breathing session • Scouts as – needed- to position the FOV to cover the entire lung and as little soft tissue as possible • The inspiration CT scan (TLC) <p>Expiratory CT (FRC)</p>
<p>BREATHING INSTRUCTIONS: For this scan, I am going to ask you to take a couple of deep breaths in and out before we have you breathe all the way in and hold your breath</p> <p>Ok, lets get started, Take a deep breath in (watch chest to ensure a deep breath in) Let it out (watch chest to ensure air is out) Take a deep breath in (watch chest to ensure a deep breath in) Let it out (watch chest to ensure air is out) Now breathe all the way IN...IN...IN(watch chest to ensure a deep breath in as far as possible) Keep holding your breath – DO NOT BREATHE! At end of scan or practice – Breathe and relax</p>	<p>BREATHING INSTRUCTIONS: For this scan, I am going to ask you to take a couple of deep breaths in and out before we have you breathe out and hold your breath</p> <p>Take a deep breath in (watch chest to ensure a deep breath in) Let it out (watch chest to ensure air is out) Take a deep breath in (watch chest to ensure a deep breath in) Let it out (watch chest to ensure air is out) Take another deep breathe in (watch chest to ensure a deep breath in) Now release your breath out and stop breathing (make sure subject is holding out before starting the scan) Keep holding your breath – DO NOT BREATHE! (count 10 seconds or Scan) Breathe and relax (Give the patient a few relax breaths. After the practice session, talk to the patient to ensure they understand and will tolerate the breath hold. If they cannot hold their breath instruct them to do the best they can and set scanner to scan base to apex.</p>