The Modern Art of Reading Computed Tomography Images of the Lungs: Quantitative CT

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Abstract

Lung diseases are increasing in prevalence and overall burden worldwide. To stem the tide, more and more national and international guidelines are recommending the use of various diagnostic algorithms that are disease specific. There is growing consensus among the respiratory community that although patient histories and lung function testing are the minimum required for clinical examinations, these tests alone are not sufficient for disease characterization. Therefore, the use of computed tomography (CT) imaging is increasing used in clinical decision making for lung diseases. Lung diseases affect various components of lung, including the small airways, lung parenchyma, the interstitial space and the pulmonary vasculature. Quantitative CT (QCT) methods are emerging and are increasingly available using commercial software to quantify the underlying disease components, and a growing body of evidence suggests that QCT is an important tool in the clinical setting to help accurately and reproducibly detect where the disease is located in the lung, and to quantify the extent and overall severity for sev-

eral lung diseases. Furthermore, this growing body of evidence has promoted the use of thoracic QCT to the point that it is now considered by many as an indispensable technology for longitudinal analysis and intervention trials. Many QCT imaging measurements are available to the respiratory physician, and the aim of this review is to introduce and describe pulmonary QCT imaging measurements and methodologies.

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Introduction

The burden of respiratory diseases impacts not only the individuals, but also their families, schools, workplaces, neighborhoods, cities, and states. The number of patients diagnosed with respiratory diseases is rapidly increasing [1]. Respiratory symptoms are among the major causes of consultation at primary health-care centers [2].

Some lung diseases, like asthma and chronic obstructive lung disease (COPD), involve the narrowing or blockage of the airways resulting in poor air flow. Other lung diseases, including pulmonary fibrosis, pneumonia, and lung cancer, are caused by a loss of elasticity in the lungs that produces a decrease in the total volume of air

that the lungs are able to hold. Research has shown that long-term exposure to air pollutants can reduce lung growth and development and increase the risk of developing asthma, COPD, and other respiratory diseases [3].

In addition to the clinical examination, evaluating the patient history and lung function testing, most international disease-based guidelines also recommend imaging. Conventional measurements of lung function are only available at one location (the mouth) and therefore do not provide any regional information. Due to the rapid developments of computed tomography (CT) imaging technology, the dramatic reduction in the radiation burden associated with CT in recent years, and the clear diagnostic improvement of CT compared to classical chest X-ray, CT has emerged as the gold standard imaging modality for lung disease evaluation. However, the information gained by CT imaging is overwhelming, therefore motivating the development of CT imaging analysis software to streamline quantitative CT (QCT) into clinical use.

The quantification of emphysema via lung density thresholding in CT images dates back more than 2 decades [4], and is now accepted for use as an outcome measure in studies of emphysema-modifying therapy in patients with alpha-1-antitrypsin deficiency [5–7]. CT technologies to assess the extent of airway disease have also been developed, and airway wall morphometry is used as a measure of airway remodeling in COPD and asthma [8–10]. Depending on the indications, various other QCT measurements are used by different groups worldwide to diagnose, stage, and control various lung diseases. Therefore, commercially available software solutions can provide quantitative imaging endpoints for assessing the impact of therapies on lung function. However, to facilitate earlier decisions regarding the impact of therapeutic treatments, standardized image acquisition protocols and quality certified and validated image analysis methodology is required to ensure high accuracy and precision of the quantitative information provided.

The purpose of this report is to define QCT measurements, provide evidence of their utility in certain applications where available, and to discuss the potential of these measurements in various applications.

Techniques for QCT of the Lung

Below, we have described a need for a standardized image acquisition combined with core lab analysis to obtain high quality and reproducibility images, and the QCT

measurements that can be derived; a summary of all QCT measurements and their potential application in lung diseases is shown in Table 1.

Standardizing Image Acquisition Protocols

Accurate and reproducible analysis of the lungs using QCT metrics requires a standardized CT image acquisition protocol [11]. CT protocols are dynamic, and technology is rapidly advancing as CT systems are updated and lower-dose options become available [12, 13]. It is important to those in industry providing QCT measures to adapt to these CT technology advancements, and understand how these advancements impact QCT measurements.

It is well-described that CT systems can have both global scanner Hounsfield unit (HU) calibration bias as well geometric and filtration differences, which may impact the density histogram, texture, tissue, and airway measures [14]. Although there are no formal standards yet for CT imaging of the lung, there are new working groups that aim to better understand and minimize this interscanner variability, such as the Quantitative Imaging Biomarker Alliance (QIBA) with the Radiological Society of North America (RSNA) [15]. The SubPopulations and Intermediate Outcome Measures In COPD (SPIROMICS) multi-site, cohort study has also recently outlined the best practice for QCT imaging for multi-site studies in which images were acquired using multiple CT scanner makes and models [16]; a standardized imaging protocol was detailed for various CT scanners, where spatial (1-mm slices), temporal resolution, use of a standard CTDvol across body sizes, and a particular reconstruction kernel for the various scanners was provided.

Standardizing image acquisition protocols to minimize nonbiological variability is critical for longitudinal and other serial studies, and for detecting early, subclinical disease changes. In this regard, it was recently demonstrated that using the SPIROMICS standardized protocol, as well as the same protocol and parameters at both baseline and follow-up, QCT was able to detect significant changes in COPD progression only 1 year after follow-up [16]. Another key paper employing the same standardized SPIROMICS image acquisition protocol identified a subgroup of smokers that had normal spirometry and no radiological signs of hyperinflation, but exhibited COPD symptoms [17]. QCT, however, detected very small (sub-millimeter) changes in airway wall thickness, further validating that disease-related changes are subtle, and may only be detected in studies that have robust CT standardized protocols.

Table 1. Overview of QCT measurements and applications

	COPD	Emphysema	Chronic bronchitis	Asthma	ILD	Cancer
<i>Density measurements</i>						
Low attenuation area (%)	×	×				
Low attenuation cluster	×	×		×		
LAC slope	×	×				
Max cluster size (%)	×	×				
15% percentile (HU)	×	×				
Air trapping (%)	×	×		×		
<i>Heterogeneity measurements</i>						
Heterogeneity (%)	×	×				
Heterogeneity weighted (%)	×	×				
<i>Tissue measurements</i>						
Tissue volume (mL)	×	×		×	×	
Lung tissue mass (g)	×	×		×	×	
Thoracic volume (mL)	×	×				
Disease probability map (%)	×	×		×	×	
Fissure integrity (%)	×	×				
<i>Vascular measurements</i>						
Total vascular volume (mL)	×	×	×			
Peripheral vascular volume (mL)	×	×		×		
Bronchoarterial ratio	×	×	×	×		
<i>Airway measurements</i>						
Luminal diameter (max/min)	×	×		×		×
Lumen diameter circle equivalent	×			×		×
Wall thickness (mm)	×	×	×	×	×	
Airway wall fraction	×	×	×	×	×	
Airway circularity	×	×	×	×	×	
Airway concaveness	×	×	×	×	×	×
Pi10 (mm)	×	×		×	×	
Airway labeling		×	×	×	×	×
<i>Airway path planning</i>						
Angle to target		×		×	×	×
Airway extension to target		×		×	×	×
ILD, interstitial lung disease.						

In addition to standardizing image acquisition protocols, QCT imaging software solutions can provide highly accurate and reproducible measurements. It is important to note that although fully automated QCT eliminates inter- and intrareader variation, high-quality QCT requires expert analyst verification, particularly in clinical applications where QCT may be used in diagnosis or impact treatment decisions. Therefore, combining a robust standardized QCT imaging protocol and ISO quality certified and validated image analysis methodology that includes expert analyst verification is considered the best practice for today's QCT imaging.

Density Measurements

Low Attenuation Areas. The low attenuation areas (LAA) is a measure of lung density, defined as the percentage of voxels in the lung below a certain threshold. Although numerous CT density thresholds have been investigated, the −950 HU threshold is most commonly used [4, 18]. LAA₉₅₀ has been validated using histology and therefore serves as a surrogate measurement of emphysema [19]. An important advantage of QCT imaging is the ability to localize these LAA to specific regions of the lung (i.e., lobes and sublobes) as shown in Figure 1a. Another advantage of QCT measurements is the high

Fig. 1. QCT density measurements. **a** Low attenuation areas below -950 HU are highlighted in green for the right lung and red for the left lung (Apollo software; VIDA Diagnostics Inc., Coralville, IA, USA). **b** 3D representation of the low attenuation clusters below -950 HU (color coded for the different lung lobes) (Apollo software). **c** 3D representation of fissure completeness, where the green and blue areas represent the incomplete and complete portions of the fissure surfaces (Apollo software).

reproducibility. There is significant variability within and between observers for visual radiology assessments [20, 21]. Studies have also suggested that visual scoring may underestimate emphysema extent in mild disease [18] and overestimate emphysema in more severe disease [18, 20]. Furthermore, there is evidence to suggest that quantitative emphysema is better correlated with morphological measures of emphysema than visual scoring [20, 22].

High Attenuation Areas. The high attenuation areas (HAA) is a measure of the percentage of voxels in the lung between -600 and -250 HU. HAA has been shown to be associated with cigarette smoking [23] and increased odds of interstitial lung abnormalities [24]. HAA has also been shown to be associated with biomarkers of inflammation, extracellular matrix remodeling, reduced lung function, and a higher risk of death [25].

Low Attenuation Cluster Analysis. Low attenuation cluster (LAC) provides a visual representation of emphysema as spheres or “clusters,” as shown in Figure 1b. The clusters show lung regions defined by connected voxels below a specific threshold, grouped into spheres for ease of visualization. Using CT acquired at full inspiration and a LAA density threshold (e.g., -950 HU), these clusters can indicate the size of the “emphysematous hole.” These clusters can also indicate regions of gas trapping when performed using expiratory CT, and can be used globally or regionally to find LAA in specific regions of the lung

(i.e., lobe or sublobe). Quantitative measurements derived from the LAC analysis are described below:

LAC Slope. Quantitative LAC analysis can be performed by plotting the number of LAA clusters against the size of clusters and taking the slope [26]. A steep slope indicates fewer “big clusters” or more small emphysematous holes, possibly indicating early disease or diffuse pan-lobular emphysema. Conversely, a less steep slope indicates more “big clusters.” This analysis can be performed on the whole lung or regionally. It has been suggested that the LAC is less sensitive to other potential causes of low attenuation (i.e., image noise), and studies suggest that LAC correlates better with radiologist visual scoring than LAA [18].

LAC Max Cluster Size. This represents the volume of the largest “sphere” (low density area) in a given lung/lobe, expressed as a percentage; the max cluster size indicates the location of the largest concentration of emphysema (e.g., lung lobe, sublobe).

15th Percentile. This is another well-established density measurement for estimating emphysema that uses fixed percentiles of the frequency distribution of CT density. Gould et al. [27] showed that the lowest 5th percentile correlated with distal airspace size taken in resected lung/lobe from patients that underwent resection for a peripheral lung tumor. More recently, a study by Dirksen et al. [6] in patients with severe alpha-1 antitrypsin deficiency concluded that the decline in CT density percentile

may provide a sensitive measure of emphysema progression. This has led to the recommendation of the lowest 15th percentile as a measurement of emphysema and emphysema progression [28, 29].

Air Trapping. Air trapping provides a percentage of LAA on expiratory CT images, thought to represent hyperinflation or “air trapping,” by location (e.g., lung, lobe, sublobe). Air trapping is a measure of lung density on CT images acquired at full-expiration, defined as the percentage of voxels below a given threshold; several thresholds have been investigated, including the −856HU threshold cutoff on end-expiratory CT images [30], the −850 HU [8] and the −900 HU [31] threshold, although the −856 HU threshold is most commonly used. CT air trapping measurements are significantly correlated with measures of pulmonary function in COPD [32] and asthma [30, 31, 33], and can be used to assess response to therapy [34].

Fissure Integrity. The percentage of the fissure surface with a complete fissure can be measured on CT images [35]. Figure 1c shows a 3D representation of fissure completeness (Apollo software; VIDA Diagnostics Inc., Coralville, IA, USA), where the green and blue areas represent, respectively, the incomplete and complete portions of the fissure surfaces. Fissure integrity has been validated as a minimally invasive surrogate for collateral ventilation [36], which is critical in endoscopic treatment selection for severe emphysema patients.

Heterogeneity Measurements

Emphysema Heterogeneity. The emphysema heterogeneity score is a surrogate measure of the distribution of emphysema in the lung and is considered an important indicator of success when treating emphysema with lung volume reduction devices (e.g., one-way valves). Patients with visual evidence of an upper lobe, heterogeneous pattern of emphysema have been associated with improved outcomes following lung volume reduction surgery [37]. Quantitatively, emphysema heterogeneity has been defined as the difference in the LAA (below −910 HU [38] or −950 HU [36]) between the targeted lobe and the ipsilateral adjacent nontarget lobe, and greater heterogeneity of emphysema between lobes has been shown to identify patients with greater functional and physiological responses to endobronchial valve therapy [38]. Another study, however, indicated that patients with evidence of complete fissure and lobar occlusion benefited from endobronchial valve treatment, independent of emphysema heterogeneity [39].

Heterogeneity Weighted. The heterogeneity measurement in the left lung is the difference in LAA between the

selected lobe and the ipsilateral lobe. However, because there are 3 lobes in the right lung, the difference in LAA between the selected lobe and the 2 ipsilateral lobes is calculated by weighting the LAA in the ipsilateral lobes according to lung volume. For example, to calculate the heterogeneity in the RUL, the difference in LAA between the RUL and the LAA of the weighted ipsilateral lobe is calculated. The weighted ipsilateral lobe is calculated by summing the LAA in the RML and the RLL weighted by the volume of the corresponding lobes, and dividing by the total volume in the RML and RLL. This measurement is especially useful if the middle lobe is being considered for treatment in the indication lung volume reduction.

Tissue Measurements

Tissue Volume. Tissue volume is derived from CT density measurements because the attenuation of X-rays is directly dependent on density [40]. Tissue volume can be reported by thirds, lobes, sublobes, or by lung. A localized increase in tissue volume may indicate more a disease change in patients with lung fibrosis, interstitial pulmonary fibrosis, interstitial lung disease, or represent a change in patients with COPD disease [41].

Lung Tissue Mass. Lung tissue mass (g) is calculated from lung tissue volume. The density of tissue is 1.065 g/mL [42].

Thoracic Volume. Thoracic volume is the volume (mL) of segmented lungs and/or lobes.

Vascular Measurements

Total Vascular Volume. Total vascular volume is the volume of all vessels (arteries and veins combined) [43, 44] (Fig. 2a). The total vascular volume is an important metric to determine vascular destruction compared to hyperinflation in patients with COPD.

Small Vessels Percent Vascular Volume. Small vessels percent vascular volume (SVPVV) is the volumetric fraction of the small vessels relative to overall vascular volume [44]. The small vessels represent the outermost layer of the airway tree and are defined using mathematical morphological erosion, not by airway generation or lumen diameter size [36]. SVPVV is a localized measure of perfusion that separates the peripheral pulmonary vessels from the central or more mediastinal pulmonary vessels. For example, SVPVV has been validated as a predictor of LVR outcome [36].

Bronchoarterial Ratio. Bronchoarterial ratio is calculated by airway segmentation at the segmental level and beyond. For a given airway segment, the corresponding adjacent artery segment is found, and the airway and ar-

Fig. 2. QCT vessel and airway measurements. **a** 3D representation of the vasculature (arteries and veins combined) highlighted in red (Apollo software; VIDA Diagnostics Inc., Coralville, IA, USA). **b** The segmentation of the airway lumen (shown in red) and the outer airway wall (shown in blue) (Apollo software). **c** 3D representation of the airway tree with airway labels (Apollo software).

terial diameters are measured. The bronchoarterial ratio is defined as the airway diameter divided by the accompanying arterial diameter. Healthy subjects typically have a ratio of $\sim 1:1$ [45]. An increased ratio can, for example, occur in bronchiectasis or asthma [46]. CT-measured pulmonary artery diameter, aortic diameter, and their ratios have also been shown to be abnormal in patients with pulmonary hypertension and dyslipidemia [47].

Airway Measurements

Pi10. The Pi10 is the square root of the airway wall area for an idealized airway with the lumen perimeter of 10 mm [48]. Pi10 can be thought of as a standardized airway wall thickness measurement and has been shown to be significantly correlated with histological measures of the small airways [49]. Pi10 is the most commonly used measure of airway wall thickening in the literature and in many phenotyping studies of COPD and asthma, either globally (whole lung) or in a given major airway path or lobe [48, 50–52].

Airway Wall Thickness or Wall Fraction. The thickness of the airway wall or the fraction of the entire airway (lumen and wall) that is airway wall area, also commonly referred to as wall area percent (WA%), can be measured as shown in Figure 2b, and are surrogate measures of airway wall remodeling. In asthma, CT airway walls have been demonstrated to be thicker compared to healthy controls [53, 54] and are significantly correlated with asthma duration and severity [54], airflow limitation [54, 55], and neutrophilic airway inflammation [55]. In

COPD, CT airway wall thickening has been shown to be significantly associated with lung function [56] and the frequency of exacerbations [57].

Functional Small Airway Disease. Registering CT images acquired at full inspiration to CT images acquired at full expiration allows lung voxels that trap gas (hyperinflated) related to tissue destruction (i.e., emphysema) to be differentiated from lung voxels that trap gas related to functional small airway disease. Two approaches have emerged that use CT inspiratory-to-expiratory methods to classify lung voxels as emphysema or functional small airway disease: parametric response map [58] and disease probability measure [59]. In COPD, functional inspiratory-to-expiratory small airway disease has been shown to be reproducible over short periods of time [60] and correlate with pulmonary function [58], and is associated with longitudinal changes in FEV₁ [61].

Luminal Diameter (Max/Min). This represents the largest and the smallest diameter of an airway segment. Airway lumens have varying diameters and may not be circular, e.g. elliptical cross-section. Local disease can affect the luminal max/min and an indicator of various disease states.

Lumen Diameter Circle Equivalent. This is the diameter of the circle with the same area as the cross-sectional area of the lumen.

Airway Circularity. Quantitative assessment of “circle-ness” of airway cross-section. A perfectly circular lumen has a circularity of 1 and a fully collapsed lumen has a circularity of 0. Deformed lumens are in-between (the more deformed the closer to 0) [62]. Airway circularity is

Fig. 3. QCT path planning to target. Path planning to target lesion using VIDA Diagnostics precision software (VIDA Diagnostics Inc., Coralville, IA, USA).

a key metric to define localized disease and fitting of devices into the airway.

Airway Concaveness. Airway concaveness expresses the severity of a cross-sectional concavity (e.g., in case of tracheomalacia) as a value between 0 (circular, no concavities) and 1 (fully concave, i.e. half-moon shape with fully collapsed lumen). Values between 0 and 1 quantify the extent of the concave area(s) relative to the overall cross-sectional area.

Airway Labeling. Airway labeling applies all 32 standard airway labels, and subsegmental labels (“a” and “b” labels in airway generations immediately following segmental airways) typically used by bronchoscopists, as shown in Figure 2c, and is based on common spatial branching patterns across populations [63]. Labeling could facilitate longitudinal comparison of airway measurements and provide a mapping or historical roadmap to a lesion.

Airway Path Planning

For pulmonologists performing transbronchial biopsies for pulmonary nodules, it has been well established that guided bronchoscopy technologies improve diagnostic yield relative to traditional transbronchial biopsy [64]. Therefore, there is motivation for developing virtual bronchoscopy planning software, such as VIDA’s Lung Bronchoscopy Planning (VIDA Vision, VIDA Diagnostics Inc.), to enable path to target identification, automatic labeling of airways, and QCT measurements, as shown in Figure 3. Other bronchoscopy planning software tools are also available, such as the picture archiving and communication system (PACS), Broncus Medical

Inc., and superDimension™. PACS provides 2D CT images for the user to scroll through; however, there is no specialized workflow for path planning. superDimension™ navigation system provides similar 2D planning software, with an additional real-time navigation component. The software generates 3D maps of the airways and registers patient anatomy with the 3D map, thereby enabling real-time navigation to show where the scope is in relation to CT. Broncus Medical Inc., provides real-time path navigation through the 3D CT airway tree reconstruction; side-by-side navigation pairs real-time and virtual images throughout the procedure.

Angle to Target. This refers to the angle of approach vector between exit point in airway tree and target point. The angle to target is a key measure for virtual bronchoscopy to target peripheral lesions. It is important to match the specifications of the device to the architecture of the path.

Airway Extension to Target. This is the distance from the closest airway in a selected path to the target point in the lung parenchyma. The airway extension to target is a measure for virtual bronchoscopy to target peripheral lesions.

Conclusions

QCT provides anatomical and physiological insights into the structure and function of the lung in various lung diseases. QCT is now becoming an established tool to assess the pathological component of lung disease in cross-sectional and longitudinal studies providing a

deeper understanding of how to stratify patients for treatment to improve outcomes. QCT also enables clinicians to visualize and quantify improvement following various therapeutic interventions. Furthermore, with improved image reconstruction methods that reduce ionizing radiation doses, there is potential to apply these QCT methods in longitudinal studies, and in younger patients. Respiratory physicians need to understand the

different measurements and the best uses of these measurements for patient management. It is highly recommended for those who want to use QCT imaging to use standardized image acquisition protocols and quality certified and validated image analysis methodology. Further development and evaluation of CT will determine its value in the clinical management of patients with lung disease.

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