Quantitative imaging of chronic obstructive pulmonary disease—moving towards clinical application

Eduardo J. Mortani Barbosa Jr

Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
Correspondence to: Eduardo J. Mortani Barbosa Jr, MD. Department of Radiology, Perelman School of Medicine, University of Pennsylvania, 3400 Spruce St, Philadelphia, PA 19104, USA. Email: Eduardo.Barbosa@uphs.upenn.edu.

Chronic obstructive pulmonary disease (COPD): clinical relevance and approach to diagnosis

COPD is characterized by progressive, non-reversible airflow limitation, associated with an enhanced chronic inflammatory pulmonary response. It is comprised by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). In addition, large airways inflammation (chronic bronchitis) is also part of the spectrum of COPD. The relative contributions of these components vary substantially, and may affect clinical presentation, frequency of exacerbations, prognosis, and therapeutic response. COPD is strongly related to smoking. It has emerged as the third leading cause of death in the United States, the only one that has been steadily rising in the past decades. The diagnosis of COPD is based on clinical grounds and spirometric [pulmonary function testing (PFT)] evidence of non-reversible obstruction. Classification of severity relies on spirometric parameters, and worsening obstruction correlates with increasing morbidity and mortality (1,2). According to the GOLD practice guideline, imaging does not play a substantial role in the diagnosis of COPD (1,2).

Current status of non-quantitative clinical imaging of COPD

Even though not endorsed by GOLD for diagnosis, in clinical practice patients with COPD are imaged frequently, for a variety of indications, which include clinical exacerbations, pulmonary infections and suspected malignancy. On most clinical imaging, the signs of COPD are described simply as present or absent. Some practices will provide a subjective assessment of severity, using categories such as mild, moderate or severe. Obviously, there is substantial variability of what these terms really mean, giving absence of standardization and the highly diverse background of physicians providing imaging interpretation. In an attempt to standardize semi-quantitative clinical assessment of COPD and harmonize it with published data on quantitative computed tomography (QCT) phenotypes, a statement of the Fleischner Society (3) proposed a visual CT based classification system comprised by five different emphysema predominant subtypes and two distinct airway predominant subtypes, and identified this proposal as a work in progress to drive future research, including outcomes of distinct CT phenotypes.

Current status of QCT of COPD

Even though extensive research has been published on QCT imaging of COPD, since the inception of thoracic CT in the late seventies, clinical application has lagged behind. A summary of relevant concepts and results in the field of QCT of COPD is provided below.

QCT requires strict standardization of CT scanning technique. As a CT scanner is essentially a device that measures voxel density as it relates to the attenuation of X-rays, frequent calibration with test objects (phantoms) to ensure accuracy of CT numbers is paramount. In addition, patient coaching has to be emphasized, in order to scan at consistent lung volumes (such as TLC for inspiration and FRC for expiration) and to minimize motion artifacts. Imaging datasets need to be acquired with near isotropic, sub-millimeter resolution in all three axes and reconstructed

with a small field of view. Computer algorithms are also required to accurately separate the lung parenchyma, central airways, central vasculature, mediastinum, and chest wall structures based upon attenuation characteristics and geometric constraints. A variety of computational methods can then be applied to detect different disease phenotypes and quantitate their relative extent and distribution (4-6).

It has been established that attenuation density masks that separate all low attenuation voxels [low attenuation areas (%LAA)] in the segmented lung parenchyma (e.g., voxels <−950 HU), excluding the central airways, can accurately quantify the volume of emphysema compared with the reference standard of pathological assessment. Such CT measures of emphysema demonstrate strong correlation with functional metrics that denote obstruction (e.g., FEV_1/FVC) (5). In addition, small airways disease can be indirectly measured using expiratory QCT measurement of air trapping, for which the simplest method measures the % of lung voxels measuring less than a given threshold (−856 HU has been proposed as a cut-off) on expiratory CT as areas of air trapping. Our group has proposed more sophisticated computational techniques that utilize non-rigid registration algorithms that track individual voxel motion and regional volume changes between CT data acquired at TLC and FRC, allowing for a one-on-one correspondence between lung voxels in inspiration and expiration. We have shown that the correlation with PFT metrics of obstructive disease is improved if the air trapping volume is measured at certain attenuation change thresholds utilizing co-registration of inspiratory and expiratory CT, and the improvement is most substantial when there is minimal or no emphysema by %LAA, allowing separation of small airway disease predominant and emphysema predominant phenotypes (6).

Volumetric QCT with appropriate software also allows measurement of several airway dimensions and indices, including true orthogonal airway inner and outer diameters, wall thickness, airway areas (inner, outer, wall) and % wall area (%WA, defined as the ratio of airway outer area and WA), to the 6th or even smaller generation of airways. Measurement of airway parameters correlates with severity of airflow obstruction and with frequency of exacerbations (7).

A meta-analysis by Li et al. (8) aimed to assess diagnostic value of QCT for COPD, selecting a small number of high quality studies and noting substantial heterogeneity in study design and summary measures of COPD. Nonetheless, a noteworthy result is that the sensitivity (SE) for COPD diagnosis using a pooled summary measure in the studies

that utilized "standard" radiation dose was higher than in the "low" radiation dose studies (SE =0.85 vs. 0.66), whereas the specificity was similar (SP =0.88). Another meta-analysis by Xie et al. (9) identified fifteen high quality studies to investigate the strength of the association of QCT metrics such as %LAA <−950 HU, mean lung density and airway WA and PFT metrics such as FEV_1 and FEV_1/FVC. It calculated the absolute pooled correlation coefficients, which ranged from 0.48 (95% CI, 0.40–0.54) to 0.65 (0.58–0.71) for inspiratory CT and 0.64 (0.53–0.72) to 0.73 (0.63–0.80) for expiratory CT, concluding that there are significant correlations between QCT measurements and airflow obstruction in COPD, and these are stronger for expiratory CT.

Recent advances of QCT for COPD

In the study by Paoletti et al. (10), 132 COPD patients were prospectively enrolled and CT was obtained with paired inspiratory and expiratory acquisition. Two QCT metrics were calculated: %LAA <−950 in inspiration and %LAA <−910 in expiration. These were initially correlated with a variety of PFT metrics such as FEV_1/FVC, RV/TLC and DLCO. The strongest linear correlation coefficients ranged from −0.59 (%LAA inspiration and DLCO) to −0.74 (%LAA expiration and FEV_1/VC). Multivariate linear regression analysis using %LAA inspiration and expiration as dependent variables and PFT metrics as independent variables selected FEV_1/VC, DLCO and TLC as the best predictors of %LAA inspiration (R^2=0.46) and FEV_1/VC, DLCO and FRC as best predictors of %LAA expiration (R^2=0.63). Analysis of residuals between the predicted and observed values suggested that there was significant non-linearity of the association between QCT and PFT metrics, noting that %LAA was overestimated in patients with %LAA lower than its mean value, and underestimated in patients with %LAA higher than its mean value. Finally, a multiple model estimation approach arrived at two different linear submodels (A for %LAA inspiration ≤21% and %LAA expiration ≤26%, B for %LAA inspiration >21% and %LAA expiration >26%), that retained FEV_1/VC as the best predictor in submodel A and DLCO as the best predictor in submodel B. The performance of this approach was better than the multivariate linear regression model, with R^2=0.75 for %LAA inspiration and R^2=0.83 for %LAA expiration, both statistically significant. The authors conclude that the relationship between lung function, as measured by PFT, and parenchymal destruction, as

measured by QCT, in COPD patients, is nonlinear, and that a combination of two different linear models according to the severity of emphysema provides a better fit for the observed data over its entire range.

The strengths of this study lie in its prospective nature and thorough statistical analysis. The main conclusion is that a single multivariate linear model does not provide adequate predictive accuracy for QCT densitometric metrics in COPD using PFT metrics as predictors, across the entire range of %LAA values. Instead, a combination of two linear models, one for "low" %LAA and another for "high" %LAA is necessary to provide better predictive accuracy, using different PFT parameters and weights. It may be clinically useful to realize that QCT densitometric metrics correlate better with FEV_1/VC for "low" %LAA, but DLCO is the best metric for "high" %LAA.

The main weaknesses of the study lie on the relatively small sample size, absence of a reference standard to verify the extent of emphysema and airway inflammation associated with each COPD diagnosis, lack of control of the level of lung inflation during CT acquisition and absence of quantification of air trapping on expiratory CT, precluding optimal COPD phenotyping. A more fundamental limitation is the fact that the authors did not elaborate their conclusion that the relationship of QCT and PFT metrics is "nonlinear".

What do we need to make QCT of COPD standard of care?

One important conceptual limitation of the manuscript by Paoletti *et al.* is the conclusion that the relationship of QCT and PFT metrics is "nonlinear". As a philosophical digression, I would contend that theories employ mathematical models to describe and predict the behavior of a system, and are useful only insofar as their predictions are accurate. Theories are just representations of reality, not the ultimate truth about reality. The reason many mathematical and statistical models are linear is not because of a fundamental property of real systems, but instead because linear models are much easier to understand, implement and simulate. Linear systems obey the principle of superposition, and certain linear physical theories such as classical electromagnetism can yield remarkably accurate predictions. Nonetheless, most real systems deviate somewhat from linearity. For example, dose response curves and tumor growth in biology are clearly better modelled by nonlinear approaches (e.g., using the logistic

function). Nonlinear mathematical models are much more general and difficult to analyze, and their predictions may not be accurate on a longer time scale (e.g., chaotic systems). Nonetheless, most biological data will still be better "fitted" by a nonlinear model. Scientists continue to use linear models because these are simpler to understand and statistically analyze, not because of a fundamental assumption about the true nature of the relationship. As a corollary, one can speak about how useful a linear model is and how well it fits the data, as well as to what degree and in what range of values any system demonstrates linearity, however it is important to emphasize that most real systems are not truly linear, in the sense that one can almost always devise a nonlinear model that is superior to a linear model in fitting real biological data. Consequently, the conclusion by Paoletti *et al.* is hardly surprising.

In any case, the literature on QCT for COPD is increasingly demonstrating that there is a substantial amount of functional information that can be extracted from CT, in addition to purely anatomical information. PFT metrics constitute a global assessment of lung function, however do not allow phenotyping as the relative contributions of emphysema, large and small airways disease to the overall clinical presentation and functional status can not be discretely ascertained by PFT. Even within the same GOLD COPD stage, patients will present with differences in severity of dyspnea, frequency of acute exacerbations, and response to inhaled corticosteroids (ICS) or bronchodilators, partially because of differences in phenotyping not addressed by the GOLD scheme. If there is no means other than FEV_1 for classifying patients with COPD into specific phenotypic groups in longitudinal studies, the differential effects of certain treatments may not be proved in terms of primary outcomes. Phenotyping COPD with QCT metrics may be able to address this concern.

Beyond QCT assessment of densitometric CT parameters and airway wall thickness, there is data demonstrating the potential usefulness of more sophisticated approaches that calculate second order statistics representing specific image textures, which may allow a more nuanced and more powerful phenotypic classification, for example separating the relative contribution of smoking relative interstitial fibrosis and respiratory bronchiolitis from the components of emphysema and airway disease. A study by our group showed the potential to distinguish emphysema from interstitial fibrosis by use of texture metrics, which are superior to PFTs for that purpose (11).

All these exciting applications are still largely investigational and not widely used clinically. Here comes the crucial question: What does it take to make QCT the standard of care for COPD?

In order to make QCT of COPD the standard of care, the medical and research community must establish a sound scientific basis supporting its clinical utilization. For that matter, it is imperative to learn how relevant and reliable QCT metrics are for assessing disease severity, monitoring temporal evolution and exacerbations, predicting prognosis, as well as defining targets for therapeutic intervention. Furthermore, it is necessary to devise a better understanding of how CT metrics relate with other clinically meaningful parameters, not limited to PFT, including clinically relevant outcomes such as likelihood and frequency of exacerbations and overall prognosis. It is important to demonstrate that QCT derived COPD phenotypes can predict outcomes and response to therapies better than PFT. It is largely accepted that emphysema is irreversible, but large and small airways inflammation may be treatable, therefore early differentiation of phenotypes via QCT may improve patient management and outcomes, even before PFTs become abnormal. Consequently, larger scale prospective studies with standardized technique and evaluation of meaningful outcomes are needed, including therapeutic trials in which QCT metrics are directly correlated with outcomes (12).

Notwithstanding, scientific validation and justification are necessary, but not sufficient conditions to allow clinical implementation. It is just as important to standardize and optimize CT acquisition technique on a clinical environment, including patient positioning, respiratory coaching, calibration of the CT scanner and standardization of scanning parameters, in order to allow reproducible and comparable data for optimal QCT measurements. Moreover, it is equally important to seamlessly integrate QCT into the clinical workflow. Given the busy radiology workloads across many practices throughout the globe, software for QCT evaluation in COPD patients must be able to deliver results in a timely manner, ideally within minutes, before a report is rendered, and these results should be easily and rapidly communicated to PACS and EMR software, necessitating minimal human input. Finally, relevant QCT metrics should be integrated into the radiology report clearly and concisely, such that patients and referring physicians will be able to understand the results and act upon them. Only then will QCT for COPD be able to fully realize its potential.

Irrespective of the many uncertainties and challenges,

I would strongly argue that QCT of COPD has exciting future prospects and will eventually become an indispensable companion to the practicing physician caring for COPD patients, as well as a central component of modern pulmonary medicine.

Acknowledgements

Footnote

Provenance: This is an invited article commissioned by the Guest-Editor Lihua Chen [Department of Radiology, Taihu Hospital (PLA 101 Hospital), Wuxi 214044, China].
Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2015. Available online: http://www.goldcopd.org/, accessed Nov 2015.
2. Mortani Barbosa EJ Jr, Gefter WB. Modern Approach to Thoracic Imaging Diagnosis. In: Grippi MA, Elias JA, Fishman JA, et al., editors. Fishman's Pulmonary Diseases and Disorders. 5th ed. New York: McGraw-Hill Education/Medical, 2015:412-67.
3. Lynch DA, Austin JH, Hogg JC, et al. CT-Definable Subtypes of Chronic Obstructive Pulmonary Disease: A Statement of the Fleischner Society. Radiology 2015;277:192-205.
4. Newell JD Jr, Sieren J, Hoffman EA. Development of quantitative computed tomography lung protocols. J Thorac Imaging 2013;28:266-71.
5. Lynch DA, Al-Qaisi MA. Quantitative computed tomography in chronic obstructive pulmonary disease. J Thorac Imaging 2013;28:284-90.
6. Barbosa EM Jr, Song G, Tustison N, et al. Computational analysis of thoracic multidetector row HRCT for segmentation and quantification of small airway air trapping and emphysema in obstructive pulmonary disease. Acad Radiol 2011;18:1258-69.
7. Van Tho N, Wada H, Ogawa E, et al. Recent findings in chronic obstructive pulmonary disease by using quantitative computed tomography. Respir Investig 2012;50:78-87.

8. Li JS, Zhang HL, Bai YP, et al. Diagnostic value of computed tomography in chronic obstructive pulmonary disease: a systematic review and meta-analysis. COPD 2012;9:563-70.

9. Xie X, de Jong PA, Oudkerk M, et al. Morphological measurements in computed tomography correlate with airflow obstruction in chronic obstructive pulmonary disease: systematic review and meta-analysis. Eur Radiol 2012;22:2085-93.

10. Paoletti M, Cestelli L, Bigazzi F, et al. Chronic Obstructive Pulmonary Disease: Pulmonary Function and CT Lung Attenuation Do Not Show Linear Correlation. Radiology 2015;276:571-8.

11. Song G, Mortani Barbosa E Jr, Tustison N, et al. A comparative study of HRCT image metrics and PFT values for characterization of ILD and COPD. Acad Radiol 2012;19:857-64.

12. Mets OM, de Jong PA, van Ginneken B, et al. Quantitative computed tomography in COPD: possibilities and limitations. Lung 2012;190:133-45.