Seminars in
ROENTGENOLOGY

Quantitative CT of Interstitial Lung Disease

John D. Newell Jr., MD,[*,†,‡] Juerg Tschirren, PhD,[*] Sam Peterson, MS,[*]
Madeline Beinlich,[*] and Jered Sieren, BS[*]

Introduction

This is a review paper about the use of quantitative x-ray computed tomography (QCT) of the lungs to assess interstitial lung abnormalities (ILA) present in a variety of interstitial lung diseases (ILD). QCT of ILA is a technique that currently augments visual x-ray computed tomography (VCT) assessment of ILA in ILD.

The use of QCT in the assessment of ILD is still largely done only in research studies though with the rapid advancements in CT technology and machine learning it is expected that this will soon change. The future of the assessment of ILD using CT will bring together both visual and quantitative approaches to the assessment of ILD.

There are differences between VCT and QCT approaches in general and salient differences need to be recognized when assessing ILD. There are increased demands on the CT protocol and CT quality control (QC) in QCT for the assessment of lung disease. There are additional technical issues that need to be addressed in QCT of the lungs that go beyond what is usually necessary to acquire CT studies for VCT of ILD.[1-4] There are important QCT methods needed to perform optimal QCT of ILD. These important methods include standardized CT imaging protocols, CT image QC, CT image data handling, and transmission of image data to a central analysis site, and computer software to extract the relevant quantitative CT imaging metrics (also known as radiomic features or signatures) applicable to QCT of the lungs and specifically for the assessment of ILD patients. The next step is the important computer analysis of the CT image metrics using statistical models and machine learning models to analyze and interpret the extracted QCT metrics across cohorts of subjects with ILD. These QCT metrics could lead to new imaging ILD phenotypes that can provide new insights into disease mechanisms and provide a more targeted or personalized approach to treating lung disease.

A brief review of the studies that have been published including earlier as well as more recent studies will be described. In a brief review of this nature a comprehensive review of the literature is not possible, but key references at the end of this article will aid the reader in delving deeper into the growing body of research into QCT lung imaging of ILD.

*VIDA Diagnostics Inc, Coralville, IA.
†University of Washington, Department of Radiology, Seattle, WA.
‡University of Iowa, Departments of Radiology and Biomedical Engineering, Iowa City, IA.
Address reprint requests to John D. Newell Jr. MD, FACR, Department of Radiology, University of Washington, Box 357115 Radiology/Imaging Services at UWMC, 1959 NE Pacific St., Seattle, WA 98195. E-mail: jdnewell@uw.edu

Visual CT Assessment of ILD Versus Quantitative CT Assessment of ILD

The increased protocol requirements and QC needed in QCT versus VCT center around the need for increased accuracy and precision of the CT number assigned to each voxel in the 3-dimensional (3D) CT image dataset of the lungs in QCT vegtrsus VCT. However, there are many important CT protocol issues common to both VCT and QCT imaging of the lungs including instructing the patient to breathe to the proper lung volume and having the patient remains entirely still, while holding their breath in order for the CT scanner to obtain all of the projection data to accurately reconstruct the images.[5] The patient dose, lung volume, and CT scanner type can affect the accuracy of the CT lung density measurements.[6] The patient should be positioned in the center of the CT gantry and their arms should be above their heads. The x-ray tube kVp is typically 100 kev and set to the fastest gantry rotation time; however, pitch settings of 1.0 are favored for QCT over the larger pitch settings that can be used with VCT to decrease patient dose. The display field of view (DFOV) should be large enough to include all of the lungs but no larger. Typical DFOV diameters range from 32 to 36 cm depending on the size of the patient. The tube current time product, mAs, is very important since it determines the dose to the patient and the signal-to-noise ratio in the reconstructed CT image, all other scanning parameters held constant. QCT lung scanning protocols have traditionally kept the mAs at a constant value for the entire CT acquisition to keep the signal-

https://doi.org/10.1053/j.ro.2018.12.007

to-noise ratio in the image constant when averaged across all subjects, and more importantly, to predetermine the maximum possible dose that any patient would receive in order to follow IRB protocols that demand a dose that is less than a maximum fixed value. VCT studies of the lungs can often be obtained at a lower mAs than QCT studies of the lungs and still provide adequate image quality for the VCT assessment of ILA within the CT images. This results in QCT studies with higher doses to the patient than VCT studies. This is more of an issue for older multidetector CT scanners but not so much for the latest CT scanners.[7] Tube current modulation (TCM) methods can lower the dose to the patient while keeping a more uniform signal-to-noise ratio in the image. However, due to differences in how TCM is implemented by different manufacturers and within CT product lines of a given manufacturer, the effects of the accuracy and precision of the CT number assigned to each voxel can vary based on the TCM method used and not on any change in the density of the tissue within a given voxel. This has precluded the use of TCM in QCT of the lung research studies. Currently, there are efforts to adapt TCM in QCT studies of the lungs and TCM will likely be a part of QCT ILD protocols in the future. TCM methods that also vary the kVp across the x-ray tube during the CT acquisition will definitely change the CT numbers assigned to a given voxel as function of what the kVp was for a given location in the patient. This introduces a variation in the HU scale that currently cannot be corrected within and between subjects. For this reason, TCM methods that vary the kVp are not used in QCT studies of the lung, including QCT of ILD.

Reconstruction kernels and the method of image reconstruction are also an area where the optimal method for VCT and QCT diverge. The optimal reconstruction kernel for QCT is a so-called neutral kernel. This is usually a medium sharp kernel that does not add or suppress the sharpness of the anatomy within the reconstructed CT image of the lung. For example, in the large multicenter COPDGene study the recommended reconstruction kernel across the CT scanners that were used in Phase 1 and 2 of this study recommended a medium sharp kernel, B35 for Siemens Healthineers (Erlangen, Germany) CT scanners, Standard for GE (Chicago, IL) CT scanners and B for the Phillips (Andover, MA) CT scanners.[8,9] This was done to try and achieve the most accurate CT numbers across the 3 manufacturers and within CT scanner models from each manufacturer. The CT scans obtained on subjects need to be visually assessed as well as assessed using quantitative techniques in these research studies so multiple reconstructions of the projection image data are used to generate images that are acceptable for VCT, sharper kernel for the visual assessment of the lungs, and a medium sharpness kernel for the QCT. For a given reconstruction kernel, the method of how the projection data are reconstructed can also affect the accuracy of the CT number. Filtered back projection has been the standard method of image reconstruction for many decades but in the last 10 years or so computing power has increased to the point where iterative reconstruction (IR) methods for reconstructing the CT image data have become practical for both research and clinical CT lung studies. Unfortunately, the IR methods vary significantly between different manufacturers and within manufacturer CT products. While IR methods offer reduced dose to the patient and have been widely used in VCT studies, different IR methods can affect the precision and accuracy of the CT number assigned to each voxel in the image and for this reason they have not been used that much in QCT studies of the lung. Currently, substantial effort is being made to improve the accuracy and precision of IR techniques across manufacturers so research and clinical studies that use IR can be used for both VCT and QCT analysis of the lung CT image data.[10] In summary, QCT studies of the lungs require a different reconstruction kernel than VCT studies of the lungs and QCT studies may not be able to use the latest TCM methods and IR methods used by VCT studies. Hopefully, in the future the use of TCM and IR methods can be used for both VCT and QCT studies of the lungs.

Quantitative CT Imaging Protocols

There are QC parameters that are essential to maintain in QCT imaging protocols of the lung including kVp, mAs, pitch, rotation time, TCM, slice thickness, slice interval, positioning, display field of view, image display matrix, for example, 512 × 512, breath holding at specified lung volumes, for example, total lung capacity (TLC), residual volume, reconstruction kernel, and reconstruction method, for example, filtered back projection (FBP) versus IR.[3,4,11] QCT imaging of the lungs depends on both the precision and accuracy of the CT number assigned to every voxel in the 3D CT acquisition of the lungs. QCT demands both precision of the CT number and that the CT number accurately reflects the tissue density of the corresponding CT voxel. Any change in the CT acquisition parameters in the CT scanning protocol that change the CT number of a given voxel will skew the QCT results. One of the most critical factors is the reconstruction kernel which can vary between CT manufacturers and between CT scanner models within a given manufacturer. There has been considerable effort on the part of the research CT imaging community to come up with a reconstruction kernel that is accurate across manufacturers, as CT values vary significantly between different manufacturer's scanners, different generations of scanners from the same manufacturer, and combinations of specific CT scanner model and reconstruction kernel.[12] This QCT kernel is typically not the optimum kernel for VCT and so at least 2 lung reconstructions are typically necessary if both VCT and QCT are desired. Another critical factor in obtaining precise and accurate CT numbers in QCT is the patient's lung volume during CT scanning. Lung volume variation is usually the biggest contributor to changes in CT numbers assigned to lung voxels in QCT studies. Usually, patients enrolled in research studies that require QCT will also have pulmonary physiology testing before their CT examinations. Patients are coached in the CT scanning suite, using similar methods that pulmonary physiology testing personnel have already used, to produce images of the lungs at full inspiration, TLC, and if required expiratory CT scans obtained at either functional residual capacity, normal breath out, or residual volume, exhaling as much air as possible from the lungs.

QCT Image QC and Image Transmission

After high-quality QCT image data of the lungs have been obtained on the scanner there is the need to perform QC on these images before they are transferred to a central image analysis facility. The process of QC and data transfer to a central imaging analysis facility was very labor intensive in early studies of QCT of ILD and chronic obstructive pulmonary disease (COPD). This process now has largely been automated where computer programs at each CT scanner site scan the DICOM CT image metadata to make sure the scans were obtained with the proper CT scanning parameters and if there is a problem an email is sent to the study coordinator at the site where the CT scan was performed.[4] The CT study may be reconstructed with a different DFOV, reconstruction kernel or reconstruction method to correct the QC issue since this does not involve any additional radiation to the patient. If the wrong mAs or kVp were used then the QCT study may be unacceptable for the QCT analysis. Automated systems to quickly check whether the CT data are in compliance for a particular QCT protocol are very important since the CT projection data may only reside on a given CT scanner for a relatively short period of time and when the projection data are deleted no further image reconstructions can be done to correct issues with the DFOV, reconstruction kernel, and reconstruction method.[4] Once the local image transfer program has verified that the CT data pass initial QC checks, the CT data itself are transferred over the internet through secure (encrypted) channels. When the CT image data are received at the central data analysis facility specialized computer software is used to assess the actual CT image data to make sure the subject's CT study meets the CT image standards for the research study. Feedback to the imaging site is given and the image data will be reconstructed again to correct the quality issue if possible. Quality issues due to motion artifacts, for example, breathing and patient movement cannot be corrected and these scans may be rejected depending on the severity and extent of the artifacts. The most concerning quality issue in QCT scanning protocols is a patient dose greater than the CT protocol allows. This is a critical concern for patient safety, IRB's and research study oversite committees. All research study protocol violations are typically reviewed by a quality committee and recommendations are made to the site where the quality issue was discovered.

Extracting QCT Metrics (Lung Density and Histogram Analysis, Texture, and Mechanics)

The first step in extracting QCT metrics from the lung is to separate the lungs and lobes from the rest of the image data contained in CT studies of the thorax, Figure 1. Today this is achieved by automated software methods that are then checked by image analysts to make sure the lungs were separated from the rest of the included anatomy.

Now that the QCT data have been obtained and meet the QC standards that have been set, this is the point where prior research into the relevant QCT metrics for lung disease are used to select the most meaningful labels of various normal and abnormal structures in the lung. These can include mean lung density, high attenuating areas, histogram analysis,[13,14] texture analysis,[15,16] and lung mechanics, which require an inspiratory and expiratory CT scan,[17] of the lung parenchyma. These parenchymal labels can be assessed at various scales including whole lung analysis, individual lungs, lung lobes, lung segments, and local group of voxels or individual voxels depending on the method used. The airway geometry of the lung is usually assessed separately from the lungs to assess changes in airway wall thickness, and area, luminal area, volume of the airway wall and airway lumen at different generations of the airway tree from the trachea, generation 0 to generation 7 or 8 depending on the quality of the CT image data, Figure 1.

Data Analysis

After extracting the QCT metrics, the process of using the QCT image data to phenotype normal subjects and subjects with lung disease including ILD can begin in earnest where the selected quantitative CT metrics have been extracted from each of the subjects QCT lung image data. By using predictive analytics, for example, statistical modeling and machine learning,[18] new imaging phenotypes can be identified and then compared to other important information about the patients to gain new insight into disease and guide the discovery of new treatments for a particular ILD or in applying the correct existing treatment for a specific ILD such as idiopathic pulmonary fibrosis (IPF).

Quantitative CT of ILD research has been going on for several decades.[19] There are many excellent published reports in the scientific literature describing a number of QCT methods to successfully characterize or phenotype ILD using QCT. These methods include the assessment of high attenuating areas (HAA),[20-24] histogram kurtosis methods,[13,14,25] adaptive multiple features method (AMFM),[26-28] Computer-Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER),[29-43] and data-driven texture analysis (DTA).[44]

In the following paragraphs selected research studies that have used QCT metrics and either statistical modeling or machine learning to learn more about ILD from QCT image data will be discussed.

HAA and ILD

There is a recent report using a straightforward QCT metric of ILA, HAA, Figure 2, and their association with ILA.[22] This study defined the CT metric HAA as the lung density between −600 HU and −250 HU in a group of research subjects that had cardiac CT scans as part of the Multiethnic

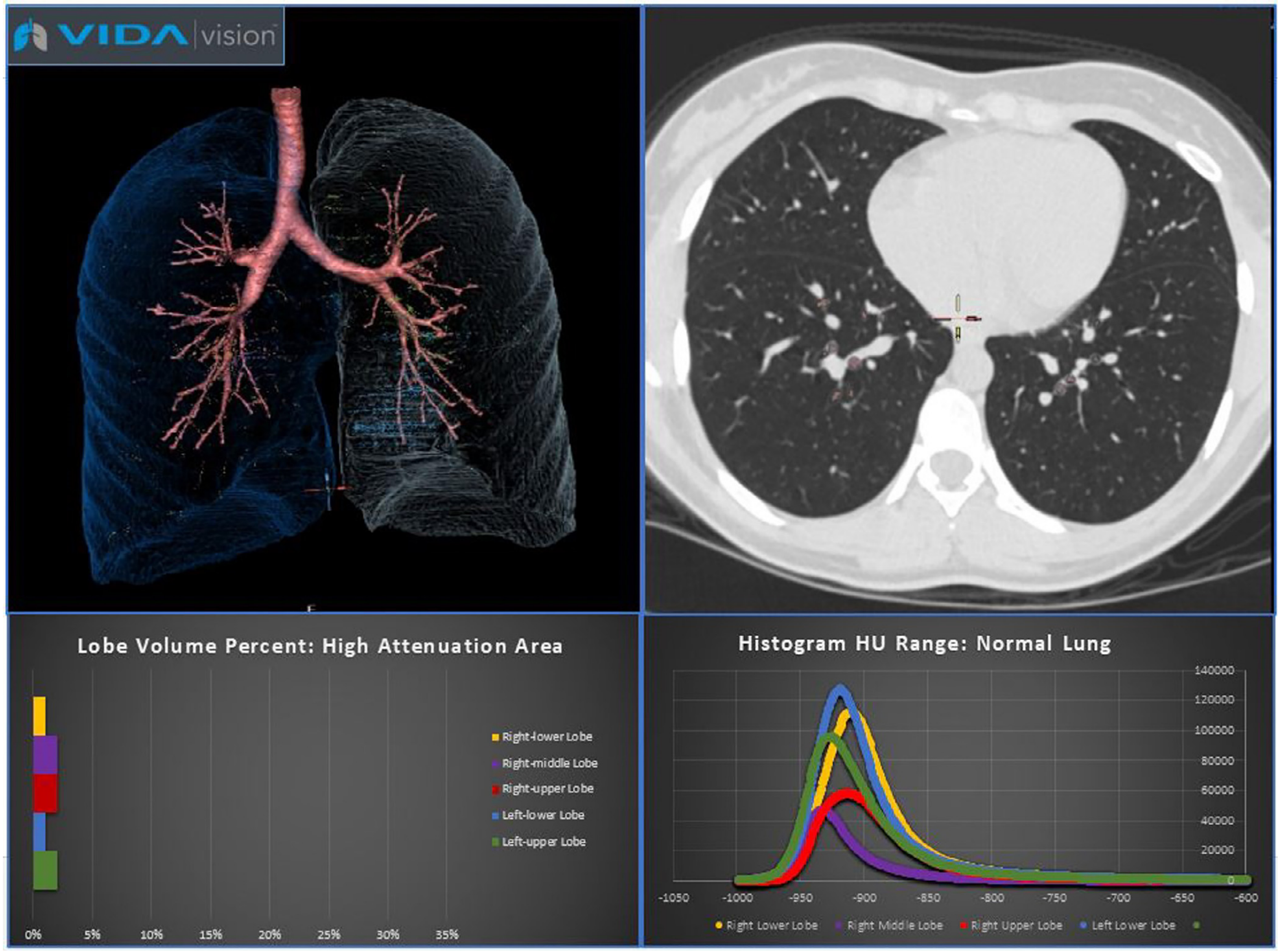

Figure 1 QCT of the lung in a normal subject. The upper left panel shows a 3D segmentation of the lung parenchyma with the 3D segmented airway tree overlaid onto the lung image. The upper right panel shows a representative axial CT image of the lower lobes. The lower left panel shows the percent by volume of high attenuation areas in each of the 5 lobes. The lower right panel shows the histogram plots of the lung voxels for each of the 5 lobes. Each of the lobes in each panel is color coded. QCT, quantitative x-ray computed tomography.

Study of Atherosclerosis (MESA). MESA was an NHLBI multicenter study of subclinical cardiovascular disease. The cardiac CT scans were obtained using a standardized CAC cardiac CT protocol between 2000 and 2002 on 6814 adults who were free of clinical cardiovascular disease and were recruited from 6 different communities. The MESA subjects ages ranged between 45 and 84 years and 53% were male. Inspiratory, noncontrast cardiac CT scans were obtained from the carina to the lung bases and have been shown to include about 65% of the lungs by volume. Between 2010 and 2012 repeat whole lung CT scans were obtained on 2907 MESA subjects using the MESA/SPRIOMICS CT protocol. Increased measures of HAA in this large cohort of middle aged and older adults was associated with elevated levels of the inflammatory biomarkers MMP-7 and IL-6. HAA was associated with decreases in pulmonary function with decreases in forced vital capacity (FVC) and decreased exercise capacity. The subjects with increased HAA were also associated with increased mortality. The authors conclude that these results support HAA as a novel QCT metric to phenotype subclinical ILA in people who may very well go on to develop clinical ILD.

Histogram Analysis and ILD

This approach looks primarily at the distribution of the CT numbers assigned to the voxels in the lungs. It is not concerned about what is going on around each voxel, for example, texture analysis, and is not concerned about lung mechanics, for example, lung stiffness.

The QCT histogram metrics that have been used in assessing ILD include mean lung attenuation, variance, skewness, kurtosis, and the shape of the histogram curve.[13,14,25]

Best et al. reported the results of using QCT assessment of the CT histogram metrics for a group of 144 subjects with IPF that were a part of a therapeutic trial assessing the effects of interferon beta 1a in the treatment of IPF.[13] The histogram metrics of mean lung attenuation, skewness, and kurtosis obtained from whole lung QCT histograms were modeled using single and multiple linear regression models where

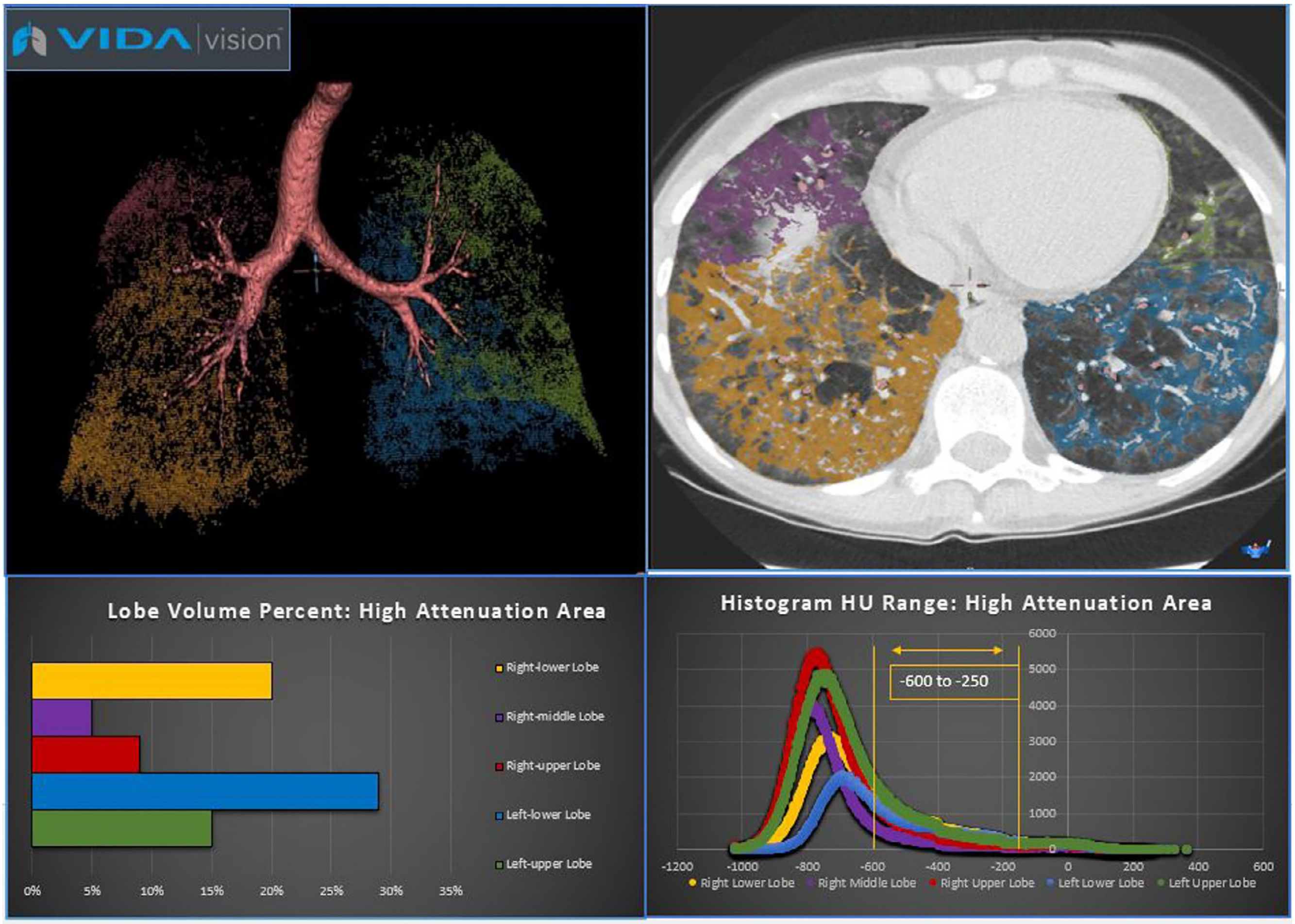

Figure 2 QCT of an ILD subject with Scleroderma. The upper 2 panels show the extensive HAA in both lungs with lower lobe predominance. The lower 2 panels show the percent of HAA by volume in each of the lobes along with the corresponding histograms for the voxels in each lobe. The color coding scheme of each lobe is the same as in Figure 1. HAA, high attenuating areas; ILD, interstitial lung diseases; QCT, quantitative x-ray computed tomography.

greater R^2 values or greater adjusted SD values in the models were used to assess the degree of correlation of mean lung attenuation, skewness, and kurtosis to the corresponding pulmonary function test measures of DLCO, FEV1, FVC, and TLC. The strongest single histogram metric to correlate with FEV1, FVC, and TLC was kurtosis. Compared to a normal subject, patients with ILD from IPF have histogram curves that are skewed to the right, greater positive skewness, toward greater Hounsfield numbers. The kurtosis is decreased, less peaked, in IPF subjects than in normal subjects. The novel observation is the kurtosis measure correlated much better with the physiology measures than did the mean lung attenuation. The statistical model was very helpful in identifying the stronger QCT metric of kurtosis in these IPF subjects than mean lung attenuation.

CALIPER

CALIPER is a computer software system that automatically labels ILA seen on 3D CT scans of subjects with ILD.[30,39] CALIPER identifies and quantitates the amount of ground glass, reticular opacities, honeycombing and vessel-related structures (VRS), and perivascular fibrosis, present in the CT studies of the lungs. CALIPER also generates visual glyphs or "bull size" graphics that aid the radiologist in quantitation of ILD.

CALIPER has been used to successfully assess a number of ILD including connective tissue disease,[33] hypersensitivity pneumonitis,[31,32,35] and IPF.[40]

A recently published study showed that CALIPER VRS scores are especially effective in diagnosing ILA from IPF and assessing progression of IPF over time.[41] This would shorten the length of the trial and decrease the cost of the trial. The CALIPER VRS score is a unique machine learning metric that uses methods to extract and quantify from 3D CT images of the lung.[41]

DTA Analysis of ILD

A recent study of ILA in IPF subjects looked at expert visual assessment, QCT histogram measures, and QCT DTA of 280 IPF subjects with baseline QCT scans and 72 of these subjects had follow-up QCT scans.[44] The QCT histogram analysis was similar to what was described above where the whole lung histograms were derived and then mean lung density, variance, skewness, and kurtosis were determined from each subjects CT scan. This study also used a machine learning strategy that has been labeled DTA. The DTA approach includes not only measures of local voxel intensity, HU value, but also looks at regions around each voxel to try and capture edges and curves in the image and the combination of these methods is referred to as textural analysis. The study used a set of 335 subjects from 3 previous IPFnet trials who had baseline 3D volumetric CT scans done with a minimum slice thickness of less than or equal to 1.25 mm. As is done in machine learning strategies, a number of cases were selected to train the DTA machine learning algorithm, 55 IPF subjects. Thirty-five subjects with 3D-volumetric CT scans done with a minimum slice thickness of less than or equal to 1.25 mm who did not have a diagnosis of ILD or IPF were also included in this training set so the DTA algorithm could be trained on what constitutes IPF and what does not. Two hundred and eighty subjects remained to test the DTA machine learning algorithm. Seventy-two of the 280 test subjects had a follow-up 3D volumetric CT scan so this group of subjects was used to look at how accurate visual, histogram, and QCT DTA methods were in assessing longitudinal change in the fibrosis on the chest CT scans. The DTA training method used an unsupervised approach where thousands of randomly selected 3 mm × 3 mm region of interest (ROIs) were selected from CT scans of subjects with IPF, 55 subjects, and in those who did not have IPF, 35 subjects, and then a k-means clustering algorithm was applied to create a 512-element dictionary of features of interest. An expert radiologist selected ROIs in the CT scans of the 55 subjects with IPF where there was definite evidence of features of ILA from IPF, honeycombing, reticular opacities, and traction bronchiectasis. The 14 mm × 14 mm ROIs from the expert radiologist's visual assessment were then analyzed for the presence of the 512 elements in the data dictionary created above. A support vector machine approach was used in a binary classification of the ROIs into either fibrotic lung or normal lung using the 512-element dictionary. Baseline visual CT assessment of ILD, QCT histogram measures of ILD and QCT DTA measures of ILD showed moderate significant correlation with pulmonary function. The change in DTA between baseline and follow-up significantly correlated with corresponding changes in % predicted FVC and % predicted DLCO. The inclusion of DTA with linear mixed models looking at the outcome variables FVC and DLCO improved the fit of the models compared to visual assessment, QCT histogram assessment, or both. Adding the QCT DTA machine learning assessments improves on the QCT histogram assessment of ILA in these ILD subjects with IPF.

AMFM and Lung Texture Analysis in ILD

The density threshold-based methods, for example, HAA, work well as described above. But they are unable to differentiate between the ILD features of ground glass opacity, reticular opacities, and honeycombing.

The AMFM analysis[27,45,46] was developed to fill this gap. It utilizes statistical and fractal texture features to classify HRCT. The AMFM method was originally designed to work with 2D CT lung images and was shown to have greater ability to distinguish between normal, emphysema, sarcoid, and ILD subjects than the MLD or histogram approaches. 2D AMFM was extended to 3D AMFM using contiguous submillimeter resolution multidetector CT scans in 2006.[28,47]

Both the 2D and the 3D variants of AMFM are quite sensitive to a given CT scan protocol and CT reconstruction methods, and the underlying machine learning algorithms often need to be retrained when these change. New machine learning paradigms based on artificial neural network (deep learning) promise to remedy this situation. A mixture of unsupervised and supervised learning algorithms takes advantage of the vast quantity of CT images available for training today while minimizing the amount of work required by human experts to hand-label training images.

Summary

QCT of ILD requires increased rigor in designing and implementing 3D CT scanning protocols compared to VCT assessment of ILD. QCT of ILD has lagged behind VCT in using dose reduction methods such as TCM and IR, but the gap is closing and though it may never close completely; the latest CT scanners can be used for QCT work that implement some forms of TCM and IR. QCT can provide objective CT image data in subjects with ILD. Objective CT image data combined with the increasing power of machine learning strategies are driving new and exciting rapid advances in the area of QCT of ILD in research and clinical trials. QCT assessment of ILD in clinical practice is likely in the near future.

References

1. Newell JD Jr., Hogg JC, Snider GL: Report of a workshop: Quantitative computed tomography scanning in longitudinal studies of emphysema. Eur Respir J 23:769-775, 2004
2. Newell JD Jr.: Quantitative computed tomography of lung parenchyma in chronic obstructive pulmonary disease: An overview. Proc Am Thorac Soc 5:915-918, 2008
3. Newell JD Jr., Sieren J, Hoffman EA: Development of quantitative computed tomography lung protocols. J Thorac Imaging 28:266-271, 2013
4. Sieren JP, Newell JD Jr., Barr RG, et al: SPIROMICS protocol for multicenter quantitative computed tomography to phenotype the lungs. Am J Respir Crit Care Med 194:794-806, 2016
5. Bakker ME, Stolk J, Reiber JH, Stoel BC: Influence of inspiration level on bronchial lumen measurements with computed tomography. Respir Med 106:677-686, 2012
6. Yuan R, Mayo JR, Hogg JC, et al: The effects of radiation dose and CT manufacturer on measurements of lung densitometry. Chest 132:617-623, 2007
7. Newell JD Jr., Fuld MK, Allmendinger T, et al: Very low-dose (0.15 mGy) chest CT protocols using the COPDGene 2 test object and a third-generation dual-source CT scanner with corresponding third-generation iterative reconstruction software. Investig Radiol 50:40-45, 2015
8. Regan EA, Hokanson JE, Murphy JR, et al: Genetic epidemiology of COPD (COPDGene) study design. COPD 7:32-43, 2010

9. Schroeder JD, McKenzie AS, Zach JA, et al: Relationships between airflow obstruction and quantitative CT measurements of emphysema, air trapping, and airways in subjects with and without chronic obstructive pulmonary disease. AJR Am J Roentgenol 201:W460-W470, 2013
10. Sieren JP, Hoffman EA, Fuld MK, et al: Sinogram Affirmed Iterative Reconstruction (SAFIRE) versus weighted filtered back projection (WFBP) effects on quantitative measure in the COPDGene 2 test object. Med Phys 41:091910, 2014
11. Sieren JP, Newell JD, Judy PF, et al: Reference standard and statistical model for intersite and temporal comparisons of CT attenuation in a multicenter quantitative lung study. Med Phys 39:5757-5767, 2012
12. Boedeker KL, McNitt-Gray MF, Rogers SR, et al: Emphysema: Effect of reconstruction algorithm on CT imaging measures. Radiology 232:295-301, 2004
13. Best AC, Lynch AM, Bozic CM, et al: Quantitative CT indexes in idiopathic pulmonary fibrosis: Relationship with physiologic impairment. Radiology 228:407-414, 2003
14. Best AC, Meng J, Lynch AM, et al: Idiopathic pulmonary fibrosis: Physiologic tests, quantitative CT indexes, and CT visual scores as predictors of mortality. Radiology 246:935-940, 2008
15. Korfiatis PD, Karahaliou AN, Kazantzi AD, et al: Texture-based identification and characterization of interstitial pneumonia patterns in lung multidetector CT. IEEE Trans Inf Technol Biomed 14:675-680, 2010
16. Hoffman EA, Reinhardt JM, Sonka M, et al: Characterization of the interstitial lung diseases via density-based and texture-based analysis of computed tomography images of lung structure and function. Acad Radiol 10:1104-1118, 2003
17. Bhatt SP, Bodduluri S, Newell JD, et al: CT-derived biomechanical metrics improve agreement between spirometry and emphysema. Acad Radiol 23:1255-1263, 2016
18. Goodfellow I, Bengio Y, Courville A: Introduction. Deep Learning. Cambridge, Massachusetts: The MIT Press, 1-26, 2016
19. Rodriguez LH, Vargas PF, Raff U, et al: Automated discrimination and quantification of idiopathic pulmonary fibrosis from normal lung parenchyma using generalized fractal dimensions in high-resolution computed tomography images. Acad Radiol 2:10-18, 1995
20. Bernstein EJ, Barr RG, Austin JHM, et al: Rheumatoid arthritis-associated autoantibodies and subclinical interstitial lung disease: The Multi-Ethnic Study of Atherosclerosis. Thorax 71:1082-1090, 2016
21. Kliment CR, Araki T, Doyle TJ, et al: A comparison of visual and quantitative methods to identify interstitial lung abnormalities. BMC Pulm Med 15:134, 2015
22. Podolanczuk AJ, Oelsner EC, Barr RG, et al: High attenuation areas on chest computed tomography in community-dwelling adults: The MESA study. Eur Respir J 48:1442-1452, 2016
23. Sack C, Vedal S, Sheppard L, et al: Air pollution and subclinical interstitial lung disease: The Multi-Ethnic Study of Atherosclerosis (MESA) air-lung study. Eur Respir J 50. https://doi.org/10.1183/13993003.00559-2017, 2017
24. Sack CS, Doney BC, Podolanczuk AJ, et al: Occupational exposures and subclinical interstitial lung disease. The MESA (Multi-Ethnic Study of Atherosclerosis) air and lung studies. Am J Respir Crit Care Med 196:1031-1039, 2017
25. Obert M, Kampschulte M, Limburg R, et al: Quantitative computed tomography applied to interstitial lung diseases. Eur J Radiol 100:99-107, 2018
26. Salisbury ML, Lynch DA, van Beek EJ, et al: Idiopathic pulmonary fibrosis: The association between the adaptive multiple features method and fibrosis outcomes. Am J Respir Crit Care Med 195:921-929, 2017
27. Uppaluri R, Hoffman EA, Sonka M, et al: Interstitial lung disease: A quantitative study using the adaptive multiple feature method. Am J Respir Crit Care Med 159:519-525, 1999
28. Xu Y, van Beek EJ, Hwanjo Y, et al: Computer-aided classification of interstitial lung diseases via MDCT: 3D adaptive multiple feature method (3D AMFM). Acad Radiol 13:969-978, 2006
29. Arcadu A, Byrne SC, Pirina P, et al: Correlation of pulmonary function and usual interstitial pneumonia computed tomography patterns in idiopathic pulmonary fibrosis. Respir Med 129:152-157, 2017
30. Bartholmai BJ, Raghunath S, Karwoski RA, et al: Quantitative computed tomography imaging of interstitial lung diseases. J Thorac Imaging 28:298-307, 2013
31. Jacob J, Bartholmai BJ, Brun AL, et al: Evaluation of visual and computer-based CT analysis for the identification of functional patterns of obstruction and restriction in hypersensitivity pneumonitis. Respirology 22:1585-1591, 2017
32. Jacob J, Bartholmai BJ, Egashira R, et al: Chronic hypersensitivity pneumonitis: identification of key prognostic determinants using automated CT analysis. BMC Pulm Med 17:81, 2017
33. Jacob J, Bartholmai BJ, Rajagopalan S, et al: Evaluation of computer-based computer tomography stratification against outcome models in connective tissue disease-related interstitial lung disease: A patient outcome study. BMC Med 14:190, 2016
34. Jacob J, Bartholmai BJ, Rajagopalan S, et al: Unclassifiable-interstitial lung disease: Outcome prediction using CT and functional indices. Respir Med 130:43-51, 2017
35. Jacob J, Bartholmai BJ, Rajagopalan S, et al: Automated computer-based CT stratification as a predictor of outcome in hypersensitivity pneumonitis. Eur Radiol 27:3635-3646, 2017
36. Jacob J, Bartholmai BJ, Rajagopalan S, et al: Likelihood of pulmonary hypertension in patients with idiopathic pulmonary fibrosis and emphysema. Respirology 23:593-599, 2018
37. Jacob J, Bartholmai BJ, Rajagopalan S, et al: Serial automated quantitative CT analysis in idiopathic pulmonary fibrosis: Functional correlations and comparison with changes in visual CT scores. Eur Radiol 28:1318-1327, 2018
38. Jacob J, Bartholmai BJ, Rajagopalan S, et al: Functional and prognostic effects when emphysema complicates idiopathic pulmonary fibrosis. Eur Respir J 50. https://doi.org/10.1183/13993003.00379-2017, 2017
39. Jacob J, Bartholmai BJ, Rajagopalan S, et al: Automated quantitative computed tomography versus visual computed tomography scoring in idiopathic pulmonary fibrosis: Validation against pulmonary function. J Thorac Imaging 31:304-311, 2016
40. Jacob J, Bartholmai BJ, Rajagopalan S, et al: Mortality prediction in idiopathic pulmonary fibrosis: Evaluation of computer-based CT analysis with conventional severity measures. Eur Respir J 49. https://doi.org/10.1183/13993003.01011-2016, 2017
41. Jacob J, Bartholmai BJ, Rajagopalan S, et al: Predicting outcomes in idiopathic pulmonary fibrosis using automated computed tomographic analysis. Am J Respir Crit Care Med 198:767-776, 2018
42. Salisbury ML, Xia M, Murray S, et al: Predictors of idiopathic pulmonary fibrosis in absence of radiologic honeycombing: A cross sectional analysis in ILD patients undergoing lung tissue sampling. Respir Med 118:88-95, 2016
43. Ungprasert P, Wilton KM, Ernste FC, et al: Novel assessment of interstitial lung disease using the "Computer-Aided Lung Informatics for Pathology Evaluation and Rating" (CALIPER) software system in idiopathic inflammatory myopathies. Lung 195:545-552, 2017
44. Humphries SM, Yagihashi K, Huckleberry J, et al: Idiopathic pulmonary fibrosis: Data-driven textural analysis of extent of fibrosis at baseline and 15-month follow-up. Radiology 285:270-278, 2017
45. Uppaluri R, Hoffman EA, Sonka M, et al: Computer recognition of regional lung disease patterns. Am J Respir Crit Care Med 160:648-654, 1999
46. Uppaluri R, Mitsa T, Sonka M, et al: Quantification of pulmonary emphysema from lung computed tomography images. Am J Respir Crit Care Med 156:248-254, 1997
47. Xu Y, Sonka M, McLennan G, et al: MDCT-based 3-D texture classification of emphysema and early smoking related lung pathologies. IEEE Trans Med Imaging 25:464-475, 2006