Imaging Advances in Chronic Obstructive Pulmonary Disease: Insights from COPDGene

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ONLINE DATA SUPPLEMENT

Appendix

Scanning protocol

Volumetric CT scans were acquired in all participants with the subject in supine position during a carefully coached breath hold to either full inspiration (total lung capacity, TLC) or end tidal expiration (functional residual capacity, FRC); at one center, expiratory CT scans were acquired with subjects coached to hold their breath at full expiration (residual volume, RV).(1) The scans were acquired with the following protocol: collimation, 0-5mm; tube voltage, 120kV; tube current 200mAs; gantry rotation time of 0.5s; and pitch, 1.1. The images were reconstructed with a standard kernel with a slice thickness of 0.75 mm and a reconstruction interval of 0.5 mm.

Standardization of measurements

Despite the significant advances made in CT imaging of the lung for the diagnosis and characterization of lung disease and comorbidities, there are certain limitations. These include variability induced by the scanner manufacturer/model, scanner calibration, reconstruction kernel, reconstruction algorithms which all vary by manufacturer and the lung volume at the time of CT acquisition. The variability induced by technical factors is important for inter- and intra-subject comparisons of CT measurements across centers and over time. A number of studies that sought to alleviate these concerns were performed in COPDGene.

To account for scanner type variability and to homogenize CT measurements within the attenuation range of lung, the COPDGene CT phantom was developed, including lung equivalent foam (−856 HU), water (0 HU), air (−1000 HU), and acrylic (120 HU).(2). The phantom was scanned at all sites monthly on 12 different scanner models from 3 manufacturers, using the COPDGene human subject protocol. The findings suggested that a standard test object

that includes a range of HU densities should be used throughout the course of multicenter trials to adjust for scanner make, scanner model, and reconstruction kernel type.(2) The COPDGene phantom has also been used to improve spatial resolution of airways, especially those less than 3 mm in internal diameter, using a combination of higher frequency kernels with reduced display field of view (DFOV) reconstructions.(3, 4) Whereas traditionally attempts were made to reduce noise, new methods were proposed in COPDGene that involve statistical characterization of noise in reconstructed CT scans resulting in statistical models that characterize different doses, reconstruction kernels, and devices, enabling comparisons between different CT acquisition protocols.(5)

Emphysema measurements are also sensitive to the reconstruction filter kernel used, with sharper reconstruction kernels resulting in greater emphysema scores because of relatively increased noise. In 369 participants scanned across multiple centers and scanner types, using a normalization method to change the appearance of data resulting from different reconstruction kernels such that they have characteristics similar to a selected reference reconstruction, the difference in mean emphysema between kernels decreased from a range of 7.2 to 7.7 across scanner types to a range of -0.1.(6) Emphysema measurements are substantially decreased in current cigarette smokers, presumably due to increases in inflammatory cellular infiltration. Emphysema measurements also increase with increasing BMI. Therefore longitudinal analysis of emphysema must adjust for both smoking status and BMI both of which may change over time. (7, 8)

Dose reduction

With increasing emphasis on reducing radiation exposure, COPDGene has also enabled advances in the application and interpretation of reduced dose CT scans for the quantification of emphysema. Application of progressively lower radiation dose index by volume on the COPDGene 2 phantom from 11.94 to 0.74 mGy showed that there were no differences in median density values using the older weighted filtered back projection versus the newer sinogram-affirmed iterative-reconstruction in materials with CT density 120 to -856 HU; however, there were substantial differences for materials in the emphysema range, with density -937 to -1000 HU.(9) A subsequent application of third-generation advanced modeled iterative reconstruction methods have enabled acquisition of accurate quantitative CT images with acceptable signal-to-noise ratio with just a 1 to 3 HU shift in density at ultralow radiation dose (0.15 mGy).(10) This is one-half of the radiation dose from a standard postero-anterior and lateral chest radiograph. These advances have major implications for research studies as well as clinical practice, but further understanding of the effect of different iterative reconstruction methods implemented by different manufacturers will be required before these techniques can be routinely used in quantitative CT measurements of the lung and airways. In the meantime, COPDGene investigators have collaborated with the RSNA Quantitative Imaging Biomarkers Alliance in the creation of a draft standardized profile and claim for quantitative CT of emphysema.(11) This profile includes parameters for performing reduced dose quantitative CT, with scanner-specific protocols that meet American College of Radiology criteria for lung cancer screening.

Summary of CT measurements

3D Slicer software (www.airwayinspector.org) was used to measure emphysema and gas trapping. Pulmonary Workstation 2 (VIDA Diagnostics, Coralville, IA, USA) was used to measure airway dimensions.(1) Emphysema was quantified by using the percentage of voxels at end inspiration with attenuation less than -950 Hounsfield Units (HU) (low attenuation area, $\%LAA950_{insp}$), and air trapping as the percentage of voxels at end expiration with attenuation less than -856 HU ($\%LAA856_{exp}$). Lung mass was calculated using the formula Lung Mass (g) = [(HU+1024)/1024] x Voxel volume x Number of voxels.(8) Airway segmentations were done in an automated fashion with manual over-read and corrections. The wall thickness of segmental and subsegmental airways was calculated using the wall area percentage [(Total area of airway – Area of airway lumen)/Total area of airway × 100], the Pi10 [the square root of the wall area of a theoretical airway with internal perimeter 10 mm], and the Pi15 [the square root of the wall area of a theoretical airway with internal perimeter 15 mm].(12) The E/I ratio, a measure of small airway disease was calculated by the ratio of mean lung attenuation at end inspiration to mean lung attenuation at end expiration.(13) The Normal Density E/I ratio (ND-E/I), a measure of small airways disease below traditional thresholds, was measured by the ratio of the mean lung density at end-expiration to the mean lung density at end-inspiration calculated in lung regions with normal density (ND) by traditional thresholds for mild emphysema (-910HU) and air trapping (-856HU). Visual subtypes of emphysema were also estimated in COPDGene according to the Fleischner Society guidelines.(14) This was subsequently automated using local histogram analysis. Regions of interest were labelled by expert radiologists as one of the emphysema subtypes and local histogram analysis was applied to each region of interest to discern distinct emphysema subtypes.(15)

In addition, multiple metrics were derived using image matching with registration of inspiratory and expiratory images to obtain a voxel-pair. By applying separate density thresholds to the inspiratory and expiratory voxel measurements, Parametric Response Mapping (PRM) enables discrimination of emphysema from non-emphysematous air trapping, a measure of small airway disease.(16) PRM^{fSAD}, defined as areas of lung that are >-950 HU on inspiration but also <-856 HU on expiration, is a measure of non-emphysematous air trapping and thus a more homogenous measure of small airway disease. PRM^{emph} is defined as areas of lung that are <-950 HU on inspiration and <-856 HU on expiration. The Jacobian determinant is an estimate of lung mechanics, and measures voxel level volume expansion and contraction during the deformation of the lungs from end-inspiration to end-expiration.(17) The Jacobian determinant ranges from 0 to infinity. A Jacobian determinant value >1 represents local expansion, <1 indicates local contraction and a value of 1 indicates neither local expansion nor contraction.

In addition to emphysema and airway disease, multiple other measures were calculated in COPDGene. Interstitial lung abnormalities (ILA) were defined on visual inspection as non-dependent abnormalities that affected >5% of any lung zone, including one or more of reticular, ground-glass changes, centrilobular nodularity, non-emphysematous cysts, honeycombing and traction bronchiectasis.(18) Pulmonary vascular disease was assessed using the ratio of the pulmonary artery to the aorta at the level of the bifurcation of the pulmonary artery.(19) In addition, the pulmonary vasculature was segmented from the parenchyma using automated tools using the space scale method.(20) Pulmonary vasculature was assessed using the total blood vessel volume in the combined intraparenchymal pulmonary arteries and veins as well as the total blood vessel volume in pulmonary vessels less than 5 mm^2 in cross-section (BV5). The

pectoralis major muscle size was used to estimate cachexia, by quantifying the cross sectional area of the muscle on a single on a single axial slice above the aortic arch.(21)

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