QIBA Lung Density Biomarker Committee:

Harmonization CT Density Measures Across Platforms

SM Humphries[1], A Rodriguez[2], HH Chen-Mayer[3], MK Fuld[4], BE Hoppel[5], JP Sieren[6], PF Judy[7], D Crotty[8], SB Fain[2], DA Lynch[1], for the QIBA/RSNA Lung Density Biomarker Committee

[1]National Jewish Health, [2]University of Wisconsin; [3]National Institute of Standards and Technology; [4]Siemens Medical Solutions, Inc. USA; [5]Toshiba Medical USA; [6]VIDA Diagnostics, Inc. USA; [7]Brigham and Women's Hospital; [8]GE Healthcare, Inc. USA

Quantitative Imaging Biomarkers Alliance® RSNA®

Background

- We seek to define standard methodology for measuring longitudinal change in lung parenchymal density, specifically markers of emphysema, by image processing of CT scans acquired at different time points.
- Biomarkers of emphysema considered are the threshold of -950 Hounsfield Units (HU) (RA -950 HU), and the HU below which falls 15% of the lung relative area (Perc 15). The literature supports RA -950 HU [1] and Perc 15 [2] as the measures that have undergone the greatest degree of empirical validation and shown to be highly correlated to lung function.
- Modern CT scanners can achieve sub-HU standard deviations for intra-scanner repeat scans in the lung density region, but previously published data has shown vendor inconsistences using these QCT measures [5]
- Differences in lung inflation volume are a major source of variation between time points. Volume adjustment (VA) is included to improve repeatability.

Progress in Profile and Claims

- The CT Lung Density Biomarker Committee is working to harmonize and define Quantitative CT (QCT) protocol requirements to obtain repeatable, robust measures of RA-950 HU and Perc15 [1,2] through a published profile. The Profile is currently in the form of a working draft.

- The requirements specified in the Profile provide guidance intended to achieve the claims.
- The claims state the estimated bias and repeatability for the RA-950 HU and Perc15 biomarkers of emphysema determined from a meta-analysis of repeatability studies in the literature.
- Steps in the workflow summarize the means to achieve the claims (**Fig. 1**).

Claim 1: Without lung VA, an increase in RA -950 of at least 3.7%, or a decrease in Perc 15 of at least 18 HU, is required for detection of an increase in the extent of emphysema, with 95% confidence.

Claim 2: With lung VA, a decrease in Perc15 of at least 11 HU, is required for detection of an increase in the extent of emphysema, with 95% probability.

These claims hold when:
- The thoracic cavity is fully represented in the field of view and readily segmented from the chest wall.
- Contrast agent is not present. Contrast agents shall not be used in the CT assessment of parenchymal lung density.
- Lung inflation at followup is within 10% of lung inflation at baseline (**Fig. 2**).
- The lung parenchyma is sufficiently clear and uncorrupted by motion due to loss of breath-hold (cardiac motion is acceptable and unavoidable).

The confidence intervals defined for the claims, e.g. -18 and +18 HU in Claim 1 for the Perc15 measure, define boundaries that can be thought of as "error bars" or "noise" around the measurement of lung density. If you measure change within this range, you cannot be certain that there has really been a change. However, if lung density changes beyond these limits, you can be 95% confident there has been a true change in lung density, and the perceived change is not just measurement variability.

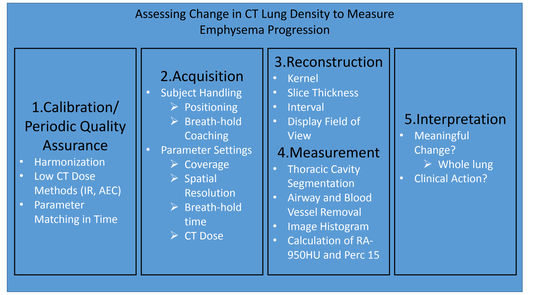

Figure 1: Sequence of activities described in the profile.

Reducing variation due to lung volume

- A balanced approach of prospective attention to protocol details, including proper coaching of the patients to the correct lung volume, combined (when necessary) with retrospective data correction provide the best steps in achieving the most accurate quantitative analysis of the lungs [3,4]
- As part of the QIBA profile, careful instructions are given by the technologist to the subject to assure that scanning is carried out with the lungs held at full inspiration and full expiration.

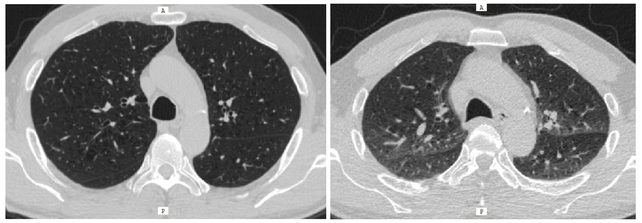

Figure 2: Scan 1 (left) shows 6L liters of air in the lung, a rounded trachea demonstrating adequate breath hold at full inspiration. Scan 2 (right) shows a smaller, 2.2L air volume, and dense lung indicating less air. Also, the trachea on the RV (full expiration) scan is malformed at the base, indicating the subject was breathing out and holding.

Prior to scanning
- Practicing the breath holds just prior to and during scanning is critical to success.
- Verify that the subject is not moving or arching their back while breathing in or out.
- Assure a constant lung volume history by coaching the subject to total lung capacity at least three times just prior to scanning.
- Assertively coach subject during breath holds. After the subject is told to hold their breath, wait a second or two to assure that the subject is compliant and not moving and to give time for stress-relaxation of the lung parenchyma.

Standardizing automated exposure control (AEC) across vendors

AEC has two important advantages for qCT in the lungs:
- Appropriate AEC selection can adapt tube current for patient size and accommodate the anatomy of the chest and thorax to create a more equivalent noise performance over the entire volume.
- The modulation of tube current can reduce CT dose, especially in the thorax, because less tube current is needed to produce equivalent signal to noise ratio (SNR) within the lung anatomy.

- However, AEC methods differ significantly across different scanner makes and models, particularly in the weighting of patient dose vs. noise performance (Fig. 3A and B)
- Therefore an empirical approach for the harmonization of AEC across different scanner makes and models has been developed by the Committee.
- The method requires qualifying a scanner with different sized water-equivalent phantoms to determine the dependence of CT dose on AEC parameter.
- The slope (k) of this dependence will vary depending on scanner make and model and available settings.
- The water equivalent diameter [6] for a range of patient chest sizes is then used to obtain equivalent slope to match noise performance across systems.

$$k_{QRmAs} QRmAs = k_{NI^{-2}} NI^{-2}$$

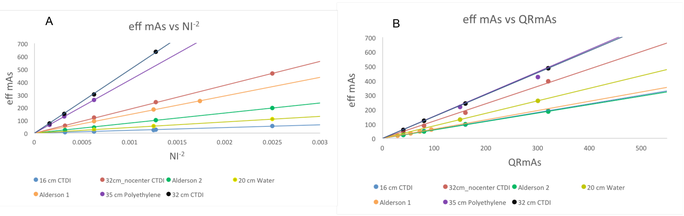

Figure 3: Effective mAs vs (Noise Index)$^{-2}$ on the GE 750 HD (left) and vs. QRmAs on Siemens Edge (right).

Assessment of volume adjustment methods

The two types of VA methods in general fall into physical models, sometimes referred to as the "sponge" model of the lungs, and statistical models.

$\rho = m/V$
$\Delta log\rho = -\Delta log V$ "Sponge model"
"Change" $\Delta\rho \sim \Delta V$
Log or linear

Statistical model*
$\rho_{ij} = \alpha + \alpha_i + (\beta + b_i)V_{ij} + \gamma t_{ij} + \varepsilon_{ij}$
$i = 1, N$ subject index
$j = 1, 2$ measurement index

Data from two sets of studies – NLST and COPDGene – were used to assess the various methods of volume adjustment on the repeatability coefficient (RC) of the lung density metric perc15. Both data sets have 31 paired baseline-repeat scans each, although the NLST data include 2 (as opposed to only 1) follow up scans.

Volume adjustment using the various models shown in in Table 1 were applied to both the NLST and COPDGene data sets. The models assume a different linear or log relationship between perc 15 values and the known corresponding lung volumes at each visit, or between the CHAMGE of these values between visit 1 and visit 2. The results of the LOA values after VA (at inspiration) for both data sets are shown as bar graphs in Fig. 4, matched by color. The top bar represents the raw uncorrected data. The reduction of the repeatability coefficient (RC) between visit 1 and 2 was achieved to various degrees for all models.

Method		Regression model	RC (visit 1,2) NLST	RC (visit 1,2) COPDGene
uncorrected			26.72	47.38
Fixed model		a_i=0, b_i=0	22.71	19.86
Model A		b_i=0	18.60	26.05
Model C		Full model	19.43	-
Model C' LogPerc15		Full model log	18.42	-
Sponge model		ΔlogPerc15~ΔlogV	17.25	44.78
Semi-linear model		ΔPerc15~ΔlogV	16.97	44.70
Linear model		ΔPerc15~ β ΔV+ α	13.35	32.74
Linear model, time 1,2 only			7.60	-

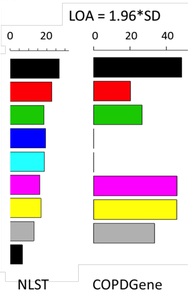

Table 1 and Figure 4. Statistical models and the results of volume adjustment demonstrating improved RC, for both NLST and COPDGene data. Models C and C' did not converge for the latter data set. The bar graphs correspond to the values listed in the table, with color coded for each model.

Standardizing lung density metrics across vendors

Round 1 of vendor scans using the COPDGene 2 lung phantom (Figure 5) was carried out at 4 different scanner models and a total of 22 protocols. Extensive data analysis resulted in the a calibration procedure (manuscript under review in Medical Physics) as follows:

1. Perform air-water calibration using the air and water values from inside the phantom, by setting the CT number to -1000 and 0, respectively.
2. Determine a protocol dependent parameter α, by fitting the CT number from each foam as a function of the electron density ρe* and effective atomic number Z_{eff}*, in this fashion: $H - \rho_e^* Z_{eff}^{*n} = \alpha\rho_e^*(1 - Z_{eff}^{*n})$, where *H* is the shifted CT number, *H* = CT number (HU) / 1000 + 1, ρe* = 0.956 ρm, where ρm is the calibrated mass density of each foam, and Z_{eff}* = 0.871, calculated for the assumed composition based on best available information, and n = 3.21 [3].
3. Use α to obtain a relative electron density for the "lung foam" (large pink foam that filled entire phantom) based on its measured CT number H_{lung}, and map to 80 keV (a monoenergetic value that represents the mean value of the attenuated CT spectrum):

$$H_{80keV} = H_{lung}\frac{\alpha_{80keV}(1 - Z_{eff}^{*n}) + Z_{eff}^{*n}}{\alpha(1 - Z_{eff}^{*n}) + Z_{eff}^{*n}}$$ where α_{80keV} = 0.9459 [3].

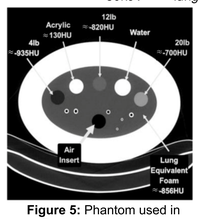

Figure 5: Phantom used in Round 1 vendor scan.

A new version of the phantom (QIBA-SRM) incorporates a suite of 5 reference foam inserts, as well as air, water and PEP. The foam inserts, machined from commercially available sheet stock (General Plastics, FR-7104, 7108, 7112, 7116, and 7120, with the last two digits representing the nominal density in lb/ft^3), have been certified for the physical density value in kg/m^3 (Standard Reference Material SRM-2088, NIST). This phantom has been used in Round 2 vendor scanning with a data set with a total of 66 protocols. Data analysis is underway.

- Standardization procedure performed on the backing lung foam in the phantom (which served as an "unknown").
- Statistical analyses of the data before and after standardization, considering the effects of vendor, tube potential (kVp), and dose (mGy), based on fitting mixed effects models to the two datasets. Results are summarized in Figure 6.
- The same analysis has been performed for all densities to confirm the reduction of variability.
- The heterogeneity across vendor platforms for each density (assessed by the standard deviation) was reduced by 50 % after standardization, and the residual standard deviation was reduced almost 5-fold. The standard uncertainty (1 standard deviation, SD) of the mean CT number was also reduced by about 50 %. The SD of the final CT number was within ± 1 HU for all 3 reference foam densities and for the backing lung foam in the phantom.

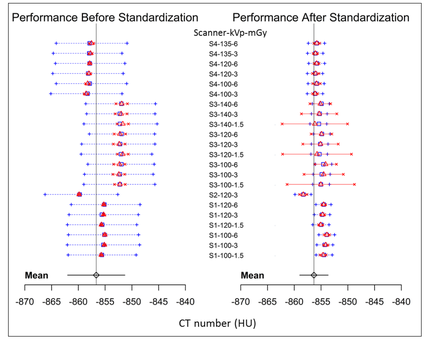

Figure 6: Results of the linear mixed effects model expressed in a forest Plots: Left panel -- CT number as measured, right panel -- CT number (mapped to monoenergetic 80 keV) after the recalibration standardization procedures, for the backing lung foam in the phantom (which served as an "unknown"), showing the reduction in variability and improved accuracy. The red symbols and lines are the measured data points, and the blue ones are the predicted values using the linear mixed effects model. The 95 % confidence intervals of the mean CT number is [-862.0 HU, -851.3 HU] before standardization, and [-859.0 HU, -853.7 HU] after standardization, shown as the error bars for the overall mean at the bottom.

Next steps

- A suite of 5 NIST traceable reference standard lung density foams, covering the nominal range of -950 HU to -695 HU, have been incorporated into a new phantom (QIBA-SRM)
- Preliminary results show utility of a calibrated lung density phantom with calibrated foams in reducing the scanner variation to the 1 HU level
- The Committee plans field testing to translate this phantom-based calibration to COPDGene, a multi-site, multi-vendor longitudinal clinical research trial
- This will also be an important test of the technical feasibility of the draft profile procedures in an ongoing clinical research trial.
- The proposed correction technique derived from phantom studies could potentially reduce or eliminate the variation due to scanner make and model in patient data, which would be a major advance in quantitative CT of the lung.

References:

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