Quantitative CT of Obstructive Lung Disease:

Towards More Robust and Accurate Measures

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Quantitative Imaging Biomarkers Alliance RSNA

Quantitative Lung CT Measures

Quantitative lung CT measures in obstructive lung disease emphasize measures of low density lung parenchyma and central airway structures. These measures, especially their regional extent and distribution, are potential surrogate measurements of *emphysema, air trapping, and airway remodeling* in chronic obstructive pulmonary disease (COPD) and asthma.

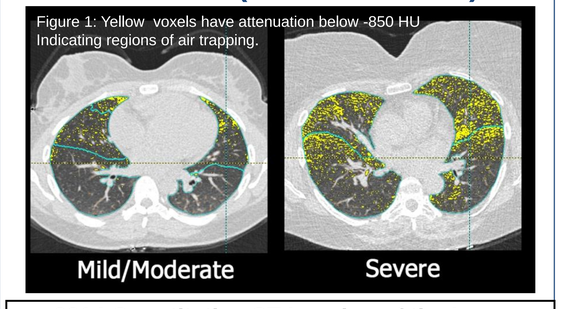
Density Threshold Measures

One of the more established measures is the "low attenuation area" or "emphysema index" defined as the percentage of lung voxels at total lung capacity (TLC) with CT attenuation below a given threshold. The standard thresholds used for severity of emphysema include -950 Hounsfield units (HU) and -910 HU. The -950 HU threshold has been validated with histology, while the -910 HU threshold is thought to be less sensitive to image noise for detecting mild to moderate disease.

Air trapping is also evaluated using a density threshold, but the CT exam is obtained at a lung inflation volume corresponding to functional residual capacity (FRC) and the threshold for the mask is -850 HU. The rationale for this choice is based on empirical measures of air vs. tissue density that have been translated to quantitative studies in asthma (Figure 1).

Density Threshold for Air Trapping in Asthma (-850 HU at FRC)

Figure 1: Yellow voxels have attenuation below -850 HU Indicating regions of air trapping.



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Sponsored by Quantitative Imaging Biomarkers Alliance (QIBA)
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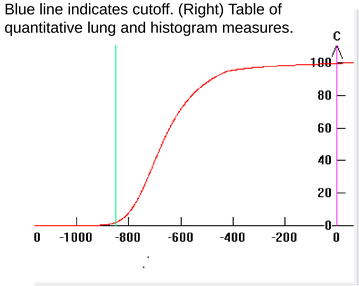
Online registration for the conference at:
http://thoracicrad.org/meetings/index.htm#

A third alternative method, the 15th percentile method (sometimes termed "Perc 15"), is defined as the threshold at which 15 percent of all voxels have a lower density. Longitudinal studies of emphysema have emphasized the 15th percentile.

Cumulative Histogram of Attenuation Values for Expiratory Lung (-850 HU at FRC)

Figure 2: (Left) Red line is cumulative histogram; Blue line indicates cutoff. (Right) Table of quantitative lung and histogram measures.



Whole Lung	
Air Volume	1227.135 (cm^3)
"Tissue" Volume	609.208 (cm^3)
Total Volume	1836.343 (cm^3)
Below & Including -850	111106 (1.95%)
	35.8141 (mL)
(gas/tissue =	5.728 ml/g)
Above & Including 0	23378 (0.41%)
	7.5357 (mL)
(gas/tissue =	0.061 ml/g)
Mean	-646.7
Median	-672
Variance	19592.9
Standard Deviation	140.0
Average Deviation	102.3
Skewness	1.577
Kurtosis	4.356
FWHM	223

Each of these methods is evaluated using a single-point cutoff value of the cumulative histogram (Figure 2) and thus are closely correlated. There is measurement bias due to scanner calibration, reconstruction kernel, radiation dose, and slice thickness. At present multi-center studies must carefully control CT scan protocol to achieve reliable measures of emphysema and air trapping using CT.

Density Correction Using Improved Test Object Design

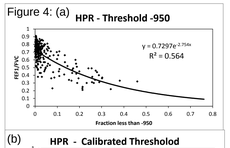
The current design of the COPDGene Reference Test object contains foams with CT numbers similar to lung CT numbers (Figure 3). The Test Object consists of an outer ring and insert. The size and shape is similar to the adult human chest. So it will have beam hardening, x-ray scatter and dose equivalent to the adult human:

- **Outer ring (35cm×25cm 5cm thick, CT number 15HU at 120kV)**
- **Insert (foam with a CT number of -850HU to -860HU)**
- **Acrylic rod (113 HU), water tube, and hole (air) are large 3 cm details.**
- **8 polycarbonate tubes simulate airways**
- **3 additional foams bracketing different ranges of lung parenchymal densities (Table 1).**

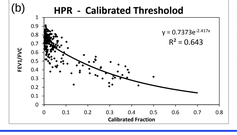
Table 1: Specific Attributes of NIST Foams

Foam Number (see Fig. 3)	Foam Type	Density (g/cc)	Mean Attenuation (HU)
NIST 1 (QLRF-1)	FR-7104	0.0652	-938
NIST 2 (QLRF-2)	FR-7112	0.1800	-831
NIST 3 (QLRF-3)	FR-7120	0.3095	-706

Figure 4: (a)



(b)

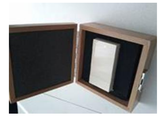


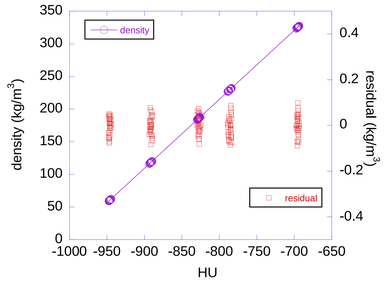
Using the COPDGene test object, calibration across sites or time (e.g. during longitudinal studies) becomes feasible. The consequences of shifts in CT number on the severity of emphysema and degree of air trapping metrics is under investigation. However one potential approach is to use attenuation of air in the trachea to linearly correct the scale of measures (Figure 4).

Figure 4. Improved correlation with whole lung function (FEV1/FVC) measures before (a) and after (b) correcting for differences in air density within the trachea.

NIST SRM 2088: Lung CT reference standard

- Development of lung density reference standard (SRM 2088)
- 5-denisty foam suite corresponding to the range of lung densities calibrated with SI traceable density certification

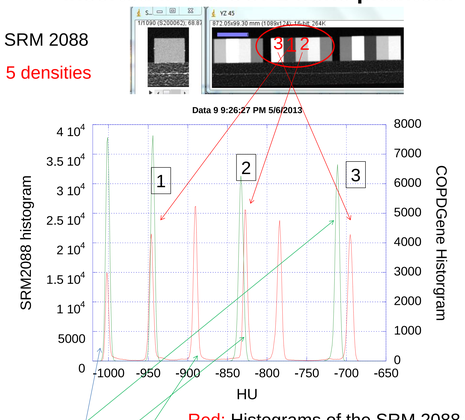


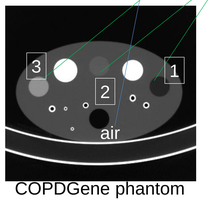


Density of the 200 foam blocks as a function of the HU values measured in a medical CT machine (purple circle, left vertical axis); and the residuals from the mean lot density (red square, right vertical axis).

NIST standard reference foams vs the reference foams inserted in the COPDGene phantom

SRM 2088
5 densities





COPDGene phantom

Red: Histograms of the SRM 2088 for all 5 densities
Green: Histograms of the 3 foam inserts in the COPDGene phantom (chest wall ring removed for closer conditions).
The foams are from the same vendor, but not from the same batch; therefore there could be real density variations. The SRM 2088 has SI-traceable physical density.

***Any mention of commercial products is for information only; it does not imply recommendation or endorsement by NIST.**

Quantitative CT for Airway Morphology Assessment

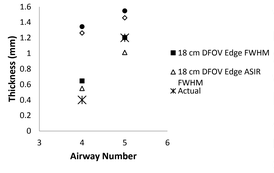
Airway morphology is the measurement of the airway lumen areas and airway wall thicknesses. Typically more distal airways (3rd to 6th airway generations) correlate better with pulmonary lung function measures suggesting that distal segments are most relevant for depicting regional disease.

The COPDGene test object was scanned at 6.6 mGy CTDIvol. The wall thickness and lumen diameter of the 6 axially oriented tubes using 0.5 mm slice images of the Test Object (labeled 1-6 in Fig. 3) were measured over 30 mm axially using the FWHM method. The significant over-estimation of wall thickness and underestimation of smaller airway lumen diameters (2, 4 and 6) suggests spatial resolution is limiting (Table 2).

Table 2: Quantitative measures of axial oriented simulated airways (tubes 1-6 in Figure 3). Measures with greater than 30% error are highlighted in bold font.

Tube	True Value	Wall Thickness		True Value	Lumen Diameter	
	Wall Thickness	Mean	Standard Deviation	Lumen Diameter	Mean	Standard Deviation
1	**1.5**	**1.70**	**0.04**	6.0	5.73	0.08
2	**0.6**	**1.44**	**0.06**	**3.0**	**1.98**	**0.06**
3	**0.9**	**1.40**	**0.05**	6.0	5.45	0.14
4	**0.4**	**1.34**	**0.06**	**2.5**	**1.42**	**0.30**
5	**1.2**	**1.55**	**0.04**	6.0	5.59	0.17
6	**0.4**	**1.39**	**0.07**	**2.5**	**1.40**	**0.18**

FWHM of Wall at 200 mA for Airway 4 and 5:



Reducing the display field of view with a higher resolution modulation transfer function (MTF) improves accuracy of wall thickness (Figure X) and lumen measures (not shown). Adaptive statistical iterative reconstruction (ASIR) yields comparable results.

Next steps for the COPD/Asthma Technical Committee

•Develop methods to obtain consistent CT measurements across CT platforms of the severity of emphysema, degree of air trapping metrics of COPD cases .

• Improve the accuracy of quantitative CT while reducing radiation dose.

Technical Committee is committed to developing a lower-dose emphysema reference method and profile – less than 50mAs.

Committee is evaluating the utility of current modulation protocols and statistical reconstructions.

•Work with manufacturers to standardize CT attenuation measurements at lower end of the Hounsfield scale using the COPDGene Test Object as a standard.

**** The Genetic Epidemiology of COPD Study (www.COPDGene.org) is a study to identify genes that increase an individual's risk of developing COPD. The Study evaluated 10,000 subjects using 44 CT scanners. The COPDGene Study supported the development, evaluation and uses of the COPDGene Reference Test**