Quantitative CT of Obstructive Lung Disease:

Standardized Protocols with Reduced CT Dose

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Quantitative Imaging Biomarkers Alliance RSNA

Quantitative Lung CT Measures

The primary mission of the QIBA development strategy for the COPD/Asthma technical subcommittee is to identify best practices for quantitative CT measures of lung parenchymal density. This includes:

- Development and publication of standard protocols based on current best practices.
- Claims of achievable repeatability and limits for detecting reduction (increase) in parenchymal density (i.e. progression (regression) of emphysema or air trapping) with qCT.
- Research and testing of emerging and future methods to reduce radiation dose and improve quantitative accuracy.

Proposed Image Bio-Markers

The most established measures of lung parenchymal density are "RA950" and "Perc15" (**Figure 1**):

- The RA950 is defined here as the relative lung area (or lung voxels) at total lung capacity (TLC) with CT attenuation below -950 Hounsfield units (HU).
- The Perc15 is defined as the HU value at which 15 percent of all voxels have a lower density.

These measures are the most common, based on studies comparing to tissue histology in resected lung [1] and established in longitudinal studies of emphysema progression [2].

RA950 and Perc15 in COPD

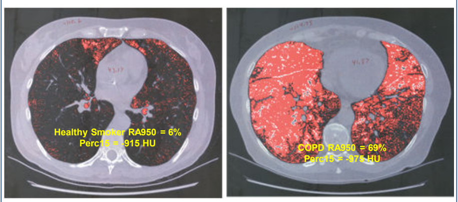

Figure 1: Red voxels have attenuation below -950 HU indicating regions of low parenchymal density. RA950 and Perc15 measures are indicated for a healthy smoker and COPD patient.

References:

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4. D Chong et al, Reproducibility of volume and densitometric measures of emphysema on repeat computed tomography with an interval of 1 week, Eur Radiol (2012) 22:287–294
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12. J.P. Sieren at el, Sinogram Affirmed Iterative Reconstruction (SAFIRE) versus weighted filtered back projection (WFBP) effects on quantitative measure in the COPDGene 2 test object. Medical physics 09/2014; 41(9):091910. DOI: 10.1118/1.4893498
13. Rodriguez et al, CT reconstruction techniques for improved accuracy of lung CT airway measurement Med Phys. 2014 (In Press).

COPDGene 2 "Test Object"

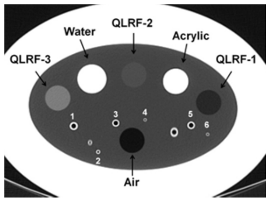


Figure 2: Using the COPDGene test object**, calibration across sites and vendors over time becomes feasible. Foams of different density (QLRF 1-3), acrylic, water and air standards are included.

Table 1: Example of profile specifications

Parameter	Specification	DICOM Tag
Total Collimation Width	CT equipment shall have a total detector collimation width greater than or equal to 20mm.	(0018,9307) Total Collimation Width
Single Slice Collimation	CT equipment shall have a single slice collimation less than or equal to 0.9mm.	(0018,9306) Single Slice Collimation
Table speed	The CT shall acquire the exam with a table speed of greater than 40 mm/sec.	(0018,9309) Table Speed
Spiral Pitch	The CT shall acquire the exam with a spiral pitch between 0.9 and 1.1 for source exams and equivalent for dual source	(0018,9311) Spiral Pitch Factor
Table Feed Per Rotation	Record	(0018,9310) Table Feed Per Rotation
Rotation Time	The CT shall acquire the exam with rotation time of equal to or less than 500 msec.	(0018,9305) Rotation Time
Scan Options	Record	(0018,0022) Scan Option = Helical Mode

Standard Protocols

The COPD/Asthma Biomarker Committee will specify CT protocol requirements to obtain repeatable and robust measures of RA950 or Perc15 through a published Profile.

The strategy is to establish general specifications that are not vendor specific. Acquisition speed and geometry of source, slice collimation and pitch must be sufficient to acquire a 3D volume in a single breath-hold. Minimum noise and spatial resolution thresholds will be identified that must be met using the COPD Gene 2 test object (**Figure 2**).

Specifications require a noise standard deviation(s) of ≤ ±20 HU, an isotropic voxel size of < 0.9 mm, a scan time of 8-10s, and a low dose threshold (**Table 1**).

This approach enables vendors to ***adapt*** their architectures and reconstruction algorithms to meet these general standards thus ***fostering creativity***, better vendor ***involvement*** and ***compliance***, and ***flexibility*** as CT systems continue to evolve.

Determining Bias and Repeatability

A meta-analysis was performed inclusive of recent studies (Table 2) that met three major criteria:

- The study was performed using 16 or 64 slice architectures with 3D volumetric scanning similar to the specifications in Table 1.
- The study performed qCT in subjects for at least two time points in identical CT scanners with ≤ 4 months separating the two time points to mitigate the degree of possible disease progression.
- Perc15 and/or RA950 HU measurement methods were used to assess lung parenchymal density.

Table 2. Summary of parameters for the selected studies used to determine the claims.

Author	Year	N	Disease Severity	Time Interval	Scanner	Density Measures	Recon Kernel	Nc,Nv	Tube mAs	Meets Criteria?
Park [3]	2012	52	GOLD 0	8 mo	Siemens Sensation 16	RA950, Perc1, Perc15	B30f	1, 1	40	N
Chong [4]	2012	44*	COPD mild (>GOLD 0)	7 d	GE, Siemens, Toshiba	RA950, Perc15	Bone, B45f, FC51 (high freq.) ♭	3, 3	80-150	Y
Keller [5]	2011	105⁺	Mild	< 4 mo, 78±27 d	GE Lightspeed Ultra (16 det)	RA910, Perc15	Bone	1, 1	40	Y
Hochhegger [6]	2011	50*⁺	No clinical emphysema	< 3 mo, 78 d	Phillips Brilliance 64	RA950	D (Sharp)	1, 1	200	Y
Diciotte [7]	2011	99*ᵒ	NCE or lung cancer >20 pk/y	3 mo	Siemens Sensation 16	RA950, Perc15	"Sharp"; 3X3 Gaussian♮	1, 1	30	Y♮
Gietema [8]	2007	157	"Heavy" Smokers	3 mo	Phillips MX800IDT or Brilliance 16p	RA950	B (moderately soft)	1, 2	30 **	Y**

*Subset of a multi-center, multi-platform study for which two baseline scans were obtained.
⁺Subset of subjects with < 4 months between scans
*⁺Subset of 475 subjects screened for cancer
*ᵒMILD trial only (16 slice)
** 140 kVp (vs. 120 kVp) for > 80kg weight
♮Smoothing operation in image domain
♭ High frequency instead of smooth kernel used for reconstruction.

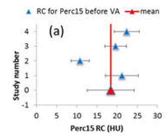
N – number of subjects, Nc – number of centers, Nv – number of vendors.

Note that Park et al was removed from further evaluation because it did not meet all of the inclusion criteria. Park et al is retained in subsequent graphical displays as a reference case where disease progression may also be contributing to the bias and precision measures.

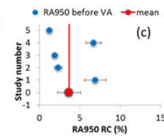
Claims

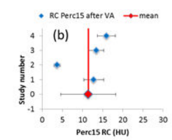
Mean repeatability coefficients were determined from the meta-analysis using the random effects model [9], shown in a summary Forest plot (**Figure 3**), for before and after volume adjustment (VA). Each study reported limits of agreement (LOA), defined as $1.96SD_{bias}$, from which the repeatability coefficient (RC) can be calculated. The RC is deemed the Smallest Real Difference (SRD), to be used in the claims.

Forest plots of the results of meta-analysis: RC for Perc15 and RA950



Forest plots of the RC of the studies (blue) and their pooled RC (red), with the 95% CI (defined as 1.96 √SE_RC) shown as error bars:
(a) Perc15 before VA
(b) Perc15 after VA
(c) RA950 before VA.





For RA950, only two studies performed VA, and the effect of VA on the bias and precision were statistically insignificant.

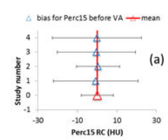
Study number designations:
Perc15: 1 – Park; 2 – Chong; 3 –Keller; 4 – Diciotte.
RA950: 1 – Park; 2 – Chong; 3 –Hochhegger; 4 – Diciotte; 5 – Gietema.

Summary table for meta-analysis of RC	#studies	mean RC	SE	95% CI (2-sided)	Lower bound RC	Upper bound RC
(unit in HU)						
Perc15 without VA	4	18.4	3.0	5.9	12.6	24.3
Perc15 with VA	4	11.4	3.5	6.8	4.6	18.3
(unit in %)						
RA950 without VA	5	3.7	0.7	1.4	2.3	5.1

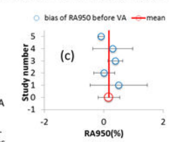
Random effects models used for RC of all metrics

Figure 3: Repeatability was determined with and without lung volume adjustment (VA) for (a) Perc15 before VA, (b) Perc15 after VA, and (c) RA950 before VA. (There was an insufficient number of studies that performed VA using the RA950 measure, therefore no meta-analysis was performed for this case.)

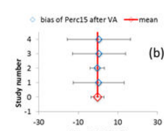
Forest plots of the results of meta-analysis: bias of Perc15 and RA950



Forest plots of the bias of the studies (blue) and the mean bias (red), with the 95% CI (defined as 1.96 √SD_bias) shown as error bars:
(a) Perc15 before VA
(b) Perc15 after VA
(c) RA950 before VA.
For RA950, only two studies performed VA, and the results were statistically insignificant.



Random effects models used for RA950 bias



Fixed effects models used for perc15 bias

Summary table for meta-analysis of bias	#studies	mean bias	SD	95% CI (2-sided)	Lower bound bias	Upper bound bias
(unit in HU)						
Perc15 without VA	4	0.1	4.1	8.1	-8.0	8.2
Perc15 with VA	4	-0.3	1.7	3.3	-3.6	3.0
(unit in %)						
RA950 without VA	5	0.2	0.2	0.4	-0.2	0.5

Figure 4: Meta-analysis of the bias (defined as the mean of the difference between scan 2 and scan 1 for each subject) was also performed for (a) Perc15 before VA, (b) Perc15 after VA, and (c) RA950 before VA.

Technical Improvements: Reducing Radiation Dose

Automatic Exposure Control (AEC): an important limitation of AEC for qCT methods is that different vendors use significantly different approaches to adjust X-ray tube current as a function of patient size. We propose a common phantom setup designed to test AEC protocols across different scanner platforms including GE Healthcare, Toshiba Medical, Philips and Siemens Healthcare systems (**Figure 5**).

Phantoms are COPD Gene with:

- A: 25 X 35 cm urethane attenuation ring that is near water electron density (standard)
- B: 30 X 38 cm urethane attenuation ring (elliptical)
- C: 38 X 38 cm urethane attenuation ring (circular)
- Standard Lung protocol for Severe Asthma Research Program (SARP)
  - Median target dose (~ 100 mAs)

Phantoms used

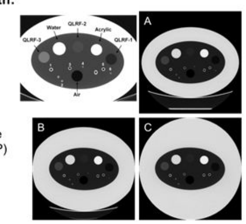


Figure 5: Phantom configuration used for preliminary tests of AEC across GE and Siemens platforms. A modified Alderson phantom [10] is also being considered.

Iterative reconstruction (IR) methods generally impact the standard deviation of lung density measures but not their median values [11]. Model-based IR methods such as ASIR, VEO, SAFIRE and ADMIRE are promising methods to reduce CT dose for qCT measures of both lung parenchymal density [11] and airway dimensions (**Figure 6**) [12].

Airway Wall Line Profiles (2.5 mm diameter)

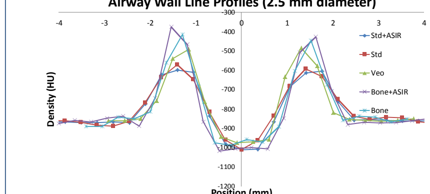


Figure 6: Improvements in airway wall resolution with increased sampling, higher frequency kernel and adaptive statistical IR. These improvements are maintained with a reduction of CT dose by a factor of 2-4.

Conclusions and Next Steps

- Meta-analysis showed negligible bias with upper bound repeatability coefficients of 5.1% for RA950 and 18.3 HU for Perc15 after volume adjustment (**Figures 3 and 4**).
- IR reconstruction methods can preserve median parenchymal density and enhance airway wall thickness measures to help reduce CT dose.
- Studies to standardize AEC and IR approaches across vendors are a main priority for future development.

**** 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 COPDGene Study supported the development, evaluation and uses of the COPDGene Reference Test Object.**