Correcting Non-Pathological Variation in Longitudinal Parametric Response Maps of CT Scans in COPD Subjects: SPIROMICS.

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SUPPLEMENTARY METHODS

Parametric Response Mapping (PRM).

Two thresholds were used to classify individual voxels with paired HU values as: emphysema (red voxels), fSAD (yellow voxels), and normal parenchyma (green voxels). Classifications are defined as voxels having paired HU values at inspiration and expiration: <-950 HU and <-856 HU as emphysema, ≥-950 HU and <-856 HU as fSAD and ≥-950HU and ≥-856 HU as normal. Whole-lung PRM measures were calculated by normalizing the sum of all voxels within a classification by the total lung volume, which include all parenchymal voxels over the range -1000 HU to -500 HU on both inspiration and expiration scans. The nomenclature of these measures for normal lung parenchyma, fSAD, and emphysema are PRM_{Normal}, PRM_{fSAD}, and PRM_{Emph}, respectively. Thresholds of -950 HU and -856 HU on the inspiration and expiration scans, respectively, were defined as specified by the COPDGene study [1, 2].

Assess Functional Distribution of Serial Inspiration and Expiration HU Values

Prior to calculating non-pathological variance in the CT scans, the functionality of the histogram distribution was determined for changes in voxel HU values from CT scans at each breath-hold (ΔIns and ΔExp). This assessment was performed by fitting a broad library of density functions to each histogram of ΔExp and ΔIns for each subject. Optimal distributions were based on minimizing the Bayesian information criterion (BIC).

Calculation of Parameter Values from IMV Function

The estimated value of ±30 HU for δ was determined by calculating the 97.5th percentile from HU values of ambient air dorsal to the thoracic cavity at approximately the first bifurcation on a CT slice. This calculation was determined using both Exp and Ins scans obtained from two subjects. A non-linear optimization was performed to fit the function to IMV with x, defined for the fit as the modes of the HU histograms from interval CT scans ([mode HU @ baseline + mode HU @ follow-up]/2) averaged over each breath-hold. The individual HU modes were determined from a fit of a generalized extreme value distribution to the HU histograms. To improve the accuracy of the fit of the function to the experimental data, values of IMV and average HU mode from both inspiration and expiration scans were pooled. Optimal values of V and r were determined using Levenberg-Marquardt algorithm. Only those subjects with relative change in lung volume below 10% (either ΔExp or ΔIns) were considered for this analysis (N = 57).
RESULTS

Initial PRM distributions

The 95% confidence intervals for changes in $\text{PRM}^{\text{Normal}}$, $\text{PRM}^{\text{ISAD}}$ and $\text{PRM}^{\text{Emph}}$ over the complete cohort of subjects were found to be 20%, 20% and 2%, respectively. These values dropped when considering only those subjects with relative change in lung volume below 10% ($n=57$; 8%, 8%, and 2%; Supplemental Table 1), which were in near agreement with previous results [3].

Analysis of Regression Slope and Y-intercept

Additional analyses were performed on the slope and Y-intercept of the regression line transformed back to the original space. In the absence of noise (i.e. scanner, acquisition and registration), a fit of the HU values for all voxels from serial CT examinations should result in a regression line with slope 1 and Y-intercept 0 (i.e. diagonal line: $x=y$). Deviation of the fits from the diagonal line may indicate discrepancies between serial scans. To test discrepancies between the slope and Y-intercept of regression fits for calculating IMV to serial inspiration and expiration, one-sample Student t-tests were applied to determine significance between the slope and Y-intercept of the fits from their respective ideal values of 1 and 0, respectively.

Over the entire population, the regression lines, with corresponding IMV, were found to generate Y-intercepts that were negligibly different from that of the diagonal line (i.e. 0) (32.27±222.1, $P = .171$ for IMV at expiration; 3.02±103.7 $P = .783$ for IMV at inspiration). As well, negligible differences were observed between the mean slope of the regression lines for all subjects and the slope of the diagonal line (i.e. 1) (1.04±0.24, $P = .150$ for expiration; 1.00±0.11, $P = .790$ for inspiration).

Scanner Types and FOV

We observed negligible differences in the %agreement scores ($P > .48$) between subjects with CT obtained with the same scanner, 85.9 ± 11.3% (N=79), and those with different scanners, 84 ± 9.9% (N=11). Subjects with percent difference of FOV < 5% had slightly less agreement in voxel PRM classification ($P = .05$), 84.4 ± 11.6% (N=68), than subjects with $\Delta$FOV ≥ 5%, 89.5 ± 8.5% (N=22).

Effect of Data Processing on 95% CI for PRM and Optimal IMV Parameters

Additional analyses were performed for calculating the 95% confidence interval for PRM metrics and optimal IMV parameters using data processed using the sponge and a median filter. Although techniques exist for correcting for density changes in serial CT scans due to inconsistent breath-holds, such as those proposed by Gorbunova and colleagues [4, 5] and the sponge model proposed by Starring and Bakker [6], we elected to not use these methods during the analysis of our correction technique. To further acknowledge varying approaches that address system noise and insufficient ventilation, we have determined the 95% CI for PRM metrics and the set of optimal parameters for IMV(<HU>) (Supplemental Table 1 and 2, respectively) from serial CT data processed using combinations of median filter and global sponge model methodology prior to PRM analysis. Although application of the sponge model had a negligible effect on the calculated values of $V$ and $r$ in IMV(<HU>), $V$ was found to increase when determined using unfiltered data, which is expected.
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## SUPPLEMENTARY TABLE 1. Effect of Data Processing on 95% CI for ΔPRM (N=57)

| Data Processing | Normal | fSAD | Emph |
|-----------------|--------|------|------|
| None            |        |      |      |
| Median Filter   | 8.26   | 8.49 | 2.42 |
| No Filter       | 7.95   | 7.63 | 2.28 |
| Global          |        |      |      |
| Median Filter   | 6.12   | 5.74 | 1.81 |
| No Filter       | 5.68   | 4.80 | 1.76 |

Values are in percent lung volume (%).
**SUPPLEMENTARY TABLE 2. Effect of Data Processing on Optimal IMV Parameters.**

| Data Processing | V   | r    |
|-----------------|-----|------|
| None            |     |      |
| Median Filter   | 66.5| -0.014|
| No Filter       | 119.9| -0.016|
| Global          |     |      |
| Median Filter   | 66.7| -0.014|
| No Filter       | 120.0| -0.016|

Optimal parameters $V$ and $r$ for the IMV function under different data processing. First division assumes the consideration of the sponge model (Global) or not (none) in data. Second division stands for the application of a median filter on CT scans.