Radiology: Cardiothoracic Imaging

ORIGINAL RESEARCH

Comparison of CT Lung Density Measurements between Standard Full-Dose and Reduced-Dose Protocols

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Conflicts of interest are listed at the end of this article.

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Purpose: To evaluate the reproducibility and predicted clinical outcomes of CT-based quantitative lung density measurements using standard fixed-dose (FD) and reduced-dose (RD) scans.

Materials and Methods: In this retrospective analysis of prospectively acquired data, 1205 participants (mean age, 65 years ± 9 [standard deviation]; 618 men) enrolled in the COPDGene study who underwent FD and RD CT image acquisition protocols between November 2014 and July 2017 were included. Of these, the RD scans of 640 participants were also reconstructed using iterative reconstruction (IR). Median filtering was applied to the RD scans (RD-MF) to investigate an alternative noise reduction strategy. CT attenuation at the 15th percentile of the lung CT histogram (Perc15) was computed for all image types (FD, RD, RD-MF, and RD-IR). Reproducibility coefficients were calculated to quantify the measurement differences between FD and RD scans. The ability of Perc15 to predict chronic obstructive pulmonary disease (COPD) diagnosis and exacerbation frequency was investigated using receiver operating characteristic analysis.

Results: The Perc15 reproducibility coefficients with and without volume adjustment were as follows: RD, 29.43 HU ± 0.62 versus 32.81 HU ± 1.70; RD-MF, 7.42 HU ± 0.42 versus 19.40 HU ± 2.65; and RD-IR, 7.10 HU ± 0.52 versus 22.46 HU ± 3.91. Receiver operating characteristic curve analysis indicated that Perc15 on volume-adjusted FD and RD scans were both predictive for COPD diagnosis (area under the receiver operating characteristic curve [AUC]: FD, 0.724 ± 0.045; RD, 0.739 ± 0.045) and for having one or more exacerbation per year (AUCs: FD, 0.593 ± 0.068; RD, 0.589 ± 0.066). Similar trends were observed when volume adjustment was not applied.

Conclusion: A combination of volume adjustment and noise reduction filtering improved the reproducibility of lung density measurements computed using serial FD and RD CT scans.

Supplemental material is available for this article.

Emphysema is one of the most clinically important features of smoking-related lung injury. The presence and severity of emphysema, measured by CT lung densitometry (CTD), is associated with severity of physiologic impairment, risk of exacerbation of chronic obstructive pulmonary disease (COPD), and mortality. CTD is increasingly used to monitor temporal progression of emphysema (1,2), and it has also been used to evaluate the efficacy of treatment for emphysema related to α-1 antitrypsin deficiency (3). CTD is also used to identify clinically relevant subphenotypes of COPD (4), which may require differing treatment strategies.

Measurement reproducibility is critical for assessing change in CTD measurements during longitudinal imaging studies. Differences in radiation dose (5–8) and breath-hold volume (9–11) between scans reduce CTD reproducibility. The effort to appropriately minimize and individualize radiation dose in accordance with the "as low as reasonably achievable" principle poses a challenge for standardization of CTD, at a time when reduced-dose (RD) CT is increasingly used to screen for lung cancer in individuals who smoke cigarettes, and there is increasing interest in detecting emphysema as an important comorbidity and prognostic determinant at lung cancer screening CT (12–14).

The purpose of this study was to *(a)* evaluate the reproducibility of CTD measurements between standard fixed-dose (FD) and RD (ie, lung cancer screening) protocols with and without breath-hold volume adjustment and *(b)* investigate the differences in the ability of lung densitometry to predict clinical outcomes (COPD diagnosis and exacerbation frequency) in COPD using CT acquisitions with FD, RD, and RD with noise filtering applied.

Abbreviations

AUC = area under the receiver operating characteristic curve, COPD = chronic obstructive pulmonary disease, Perc15 = CT attenuation at the 15th percentile of the lung CT histogram, CTD = CT lung densitometry, FD = fixed dose, GOLD = Global Initiative for Chronic Obstructive Lung Disease, IR = iterative reconstruction, LAA_{-950} = percentage of lung voxels with CT attenuation less than −950 HU, MF = median filtering, RD = reduced dose

Summary

Noise reduction filtering applied to CT scans performed with reduced-dose lung cancer screening protocols, in combination with volume adjustment, significantly improves the reproducibility of lung density measurements for longitudinal analysis.

Key Points

- Variations in dose and breath-hold volumes between serial CT scans resulted in an attenuation at the 15th percentile of the lung histogram (Perc15) reproducibility coefficient of 32.81 HU ± 1.70 (1.96 times standard deviation).
- Median filtering and volume adjustment improved reproducibility, reducing the Perc15 reproducibility coefficient to 7.42 HU ± 0.42.
- Receiver operating characteristic curve analysis indicated that volume-adjusted Perc15 using a standard fixed-dose (FD) protocol and a reduced-dose (RD) protocol were both predictive of chronic obstructive pulmonary disease diagnosis (areas under the receiver operating characteristic curve [AUCs]: FD, 0.724 ± 0.045; RD, 0.739 ± 0.045) and one or more annual exacerbation (AUCs: FD, 0.593 ± 0.068; RD, 0.589 ± 0.066).

Materials and Methods

Study Overview

The Genetic Epidemiology of COPD (COPDGene) study (COPDGene; ClinicalTrials.gov: NCT00608764) (15), a prospective multicenter observational cohort study of more than 10 000 individuals who had been current and former smokers at the time of inclusion, was conducted with the aim of understanding the etiology, progression, and heterogeneity of COPD (16). The COPDGene study was approved by the institutional review boards at each of the 21 participating clinical sites. For this current study, we obtained written informed consent from all participants, and the study was compliant with the Health Insurance Portability and Accountability Act. C.R.H. and J.P.C. were employed by Imbio and Thirona, respectively, at the time this study was conducted. Statistical analysis was performed by C.R.H., and image processing was partially supervised by J.P.C. Neither C.R.H. nor J.P.C. had influence over participant inclusion.

Participant Overview

This was a retrospective analysis of prospectively acquired data. Scanning occurred between November 2014 and July 2017. To investigate the effects of radiation dose on lung density measurements, a subset of 1358 participants enrolled in the COPDGene study were scanned at full inspiration using both the study's original CT protocol (15) with an FD of 200 mAs and an updated RD protocol with average dose between 40 and 80 mAs that varied owing to dose modulation. A subset of participants also had RD scans reconstructed using iterative reconstruction (IR). Only patients who had FD and RD in the same scan field of view were included in the study, resulting in a total of 1205 subjects, 640 of which also had RD-IR scans. A study consort diagram is shown in Figure 1. Study population demographics are listed in Table 1.

CT Imaging

A total of 12 scanners were used in this study, with different convolution kernels (Tables E1 and E2 [supplement]). Manufacturer-specific RD protocols with dose modulation were designed to have a fixed-reference tube current–time product (Siemens, Philips) or noise index (GE Healthcare). Detailed CT protocols are provided in Appendix E1 (supplement).

The FD and RD scans were performed during consecutive inspiratory breath-holds without the patient leaving the table. In an effort to reduce breath-hold volume variability and to ensure that scans were recorded as close as possible to total lung capacity, a standardized list of breathing instructions was used by site imaging technologists during scanning. Specific instructions can be found in the Quantitative Imaging Biomarkers Alliance lung density profile (17).

Image Processing

The lungs and airways were automatically segmented from each CT image using LungQ software (Thirona) and visually verified for accuracy by trained imaging analysts at the National Jewish Health Quantitative Imaging Laboratory. If a segmentation error was identified, it was manually corrected by an analyst using LungQ software. The 15th percentile point (Perc15) was computed by generating the attenuation histogram for the combined left and right lungs and finding the attenuation value corresponding to the 15th percentile of the histogram. Percentage of lung voxels with CT attenuation less than −950 HU (LAA_{-950}) was computed by dividing the number of voxels less than −950 HU by the total number of voxels in the lungs.

The inspiratory FD and RD scans were performed serially and therefore did not always have the same breath-hold volume, which is known to produce variations in lung density measurements (11). For this reason, the FD and RD scans were adjusted to a predicted volume level based on an equation developed in the Multi-Ethnic Study of Atherosclerosis Lung Study (18). See Appendix E2 (supplement) for equations describing volume adjustment.

In addition to the RD-IR scans, the effect of applying a simple open-source noise reduction filter to the RD scans was investigated. A 3 × 3 median filter (MF) (19), which replaces every pixel in the image with the median of itself and neighboring pixels, was applied to each section in the RD scans prior to computing lung density measurements using SciPy software (version 1.4.1; scipy.ndimage.median_filter). This is referred to as "RD-MF" herein. Figure 2 presents a visual example of differences in LAA_{-950} and the effects on attenuation histograms owing to the use of different dose and noise reduction methods.

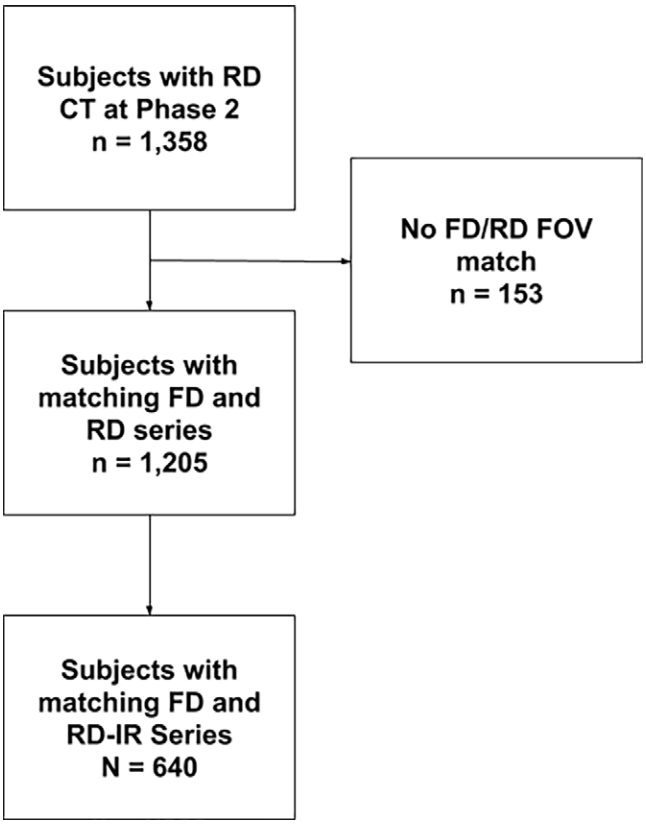

Figure 1: Consort diagram. FD = fixed dose, FOV = field of view, IR = iterative reconstruction, RD = reduced dose.

Table 1: Study Population

Parameter	Value
No. of participants	1205
Demographic information	
Age (y)	64.7 ± 8.8
No. of men	618 (51%)
BMI (kg/m^2)	29.0 ± 6.3
GOLD stage	
PRISm	169
0	494
1	111
2	190
3	74
4	33
Never smokers	120
Unknown	14
Annual exacerbation frequency	
0	1028
1	107
2	43
3	10
4	8
5	3
6	6
Functional parameters	
FEV_1 percentage predicted	83.1 ± 22.8
FEV_1/FVC	0.71 ± 0.13
Lung volume (L)*	5.3 ± 1.4
$\%LAA_{-950}$*	3.95 ± 6.68
Perc15 (HU)*	−912.2 ± 29.3
Volume adjusted lung density*	87.4 ± 22.3

Note.—Continuous variables are mean ± standard deviation. Other data are counts. BMI = body mass index, FEV_1 = forced expiratory volume in 1 second, FVC = functional vital capacity, GOLD = Global Initiative for Chronic Obstructive Lung Disease, $\%LAA_{-950}$ = percentage of lung voxels with CT attenuation less than −950 HU, Perc15 = CT attenuation at the 15th percentile of the lung CT histogram, PRISm = preserved ratio impaired spirometry.
* Calculated from standard-dose CT scan.

Statistical Analysis

Bland-Altman plots (20) were generated showing the bias (mean of differences) and limits of agreement (1.96 times standard deviation of differences) between FD and RD CTD measurements and between breath-hold volumes. The reproducibility coefficient between FD and RD CTD measurements was also computed; this is the value under which the difference between repeated measurements on the same participant performed under different conditions (ie, different dose levels) should fall within 95% probability (21,22). See Appendix E2 (supplement) for details.

The reproducibility 95% CIs were generated using bootstrapping with 5000 resamples. A paired *t* test was performed using scipy.stats.ttest_rel (version 1.4.1) to test the null hypothesis that the CTD measurements between FD and RD, FD and RD-MF, and FD and RD-IR scans were equal.

To illustrate the importance of reproducibility with regard to measuring longitudinal changes in lung density, the average change over time between CTD measurements was computed from FD scans at baseline of the COPDGene study and FD, RD, RD-MF, and RD-IR scans at 5-year follow-up. For these comparisons, volume adjustment was applied to all scans. A paired *t* test was used to test for differences in average change in Perc15 over all participants. Differences in longitudinal changes in CTD values (ie, "differences of differences") for each dose and noise reduction method were compared with the standard method.

Finally, we also compared associations between CTD measures, COPD diagnosis, and exacerbation frequency. COPD diagnosis was defined as a forced expiratory volume in 1 second–to–forced vital capacity ratio of less than 0.70 as measured by spirometry. Exacerbation frequency was determined using a questionnaire. Area under the receiver operating characteristic curve (AUC) and Youden *J* statistic (sensitivity + specificity – 1) (23) values were calculated for detection of spirometrically defined COPD and the occurrence of one or more annual exacerbations. Spearman correlations between CTD measurements and Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage were computed. The 95% CIs were generated using bootstrapping with 5000 resamples. Statistical differences between AUC values derived from FD and RD scans were assessed using the DeLong test. All statistical analyses were performed using scipy.stats (version 1.4.1). Because the purpose of this analysis was to

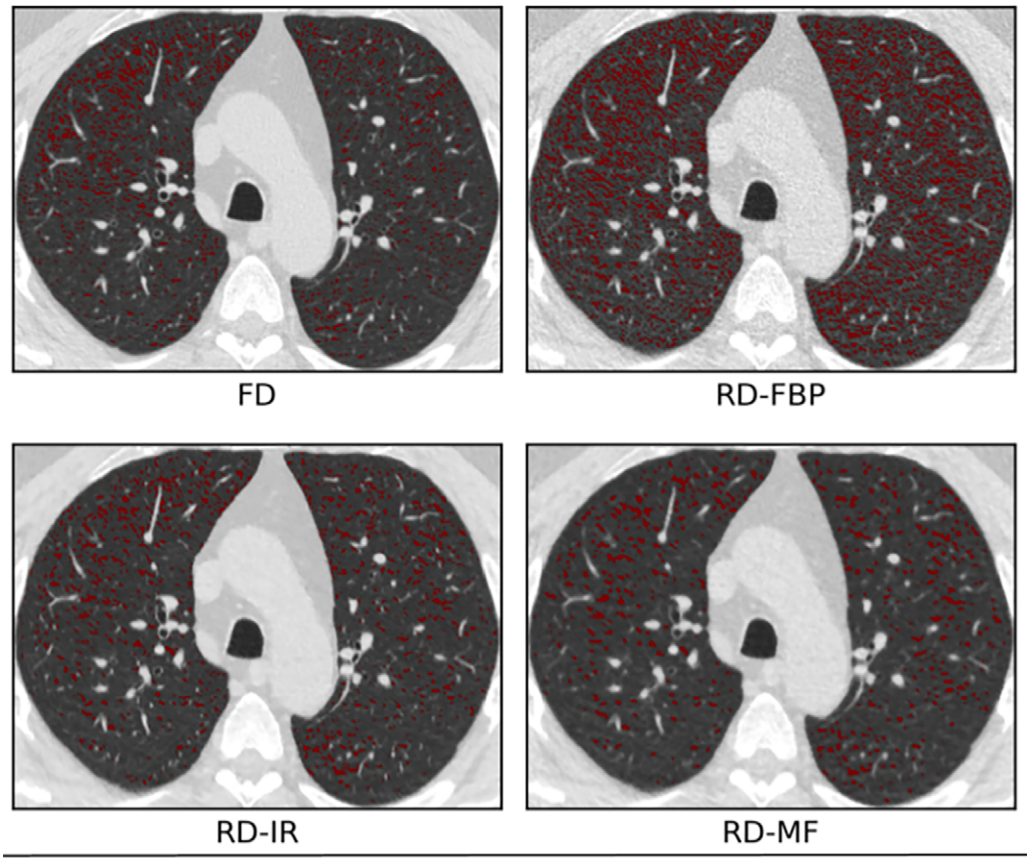

Figure 2: Effects of varying dose and noise reduction filtering. In this example, the difference in lung volumes between reduced-dose (RD) and standard fixed-dose (FD) scans were negligible and volume adjustment was not applied. (Top) Low-attenuating area less than −950 (LAA_{-950}) differences between the FD, RD, RD-iterative reconstruction (RD-IR), and RD-median filter (RD-MF) scans presented in this study. (Bottom) Lung attenuation histograms for FD, RD, RD-MF, and RD-IR. FBP = filtered back projection.

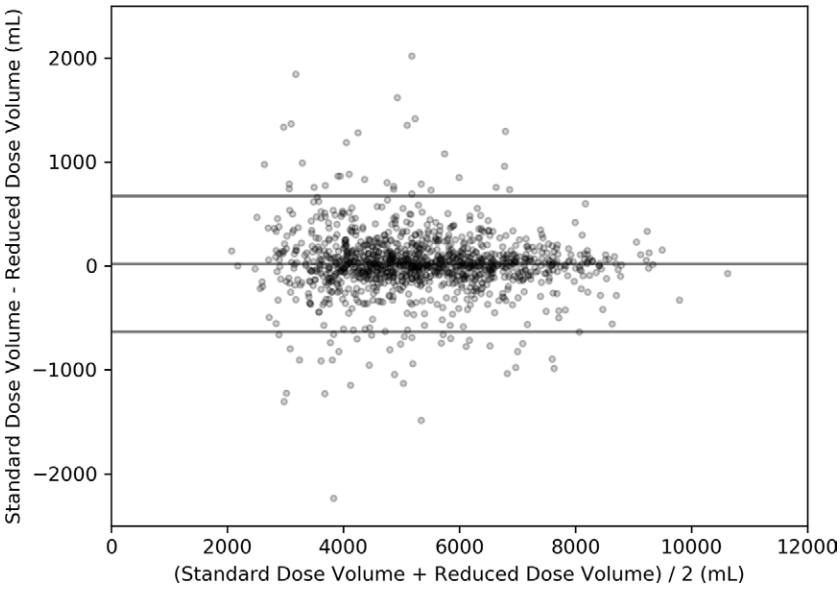

Figure 3: Bland-Altman plot for total lung capacity breath-hold repeatability. The bias ± limits of agreement (19.6 mL ± 645) are represented as horizontal lines on the plot.

conduct a head-to-head comparison of the ability of CTD measurements from FD, RD, RD-MF, and RD-IR scans to predict clinical outcomes, only participants for whom RD-IRs in addition to filtered back-projection reconstructions were available were considered.

Results

Breath-hold Volume Reproducibility

A Bland-Altman plot comparing the total lung capacity breath-hold lung volumes between FD and RD scans is shown in Figure 3. The FD volume was not different from the RD volume (FD, 5339.3 mL vs RD, 5319.7 mL; P = .73). The bias ± limits of agreement were 19.6 mL ± 654, which corresponds to −14.4% and +16.6%.

CTD Reproducibility

Bland-Altman plots showing differences in whole-lung in Perc15 and LAA_{-950} between FD and RD scans are shown in Figures 4 and E1 (supplement). Reproducibility coefficients, limits of agreement, bias, and t test results are summarized in Tables 2 and E3 (supplement). The same statistics are summarized in Tables E4 and E5 (supplement) for the subset of the cohort for whom IRs were available. When volume adjustment and noise reduction filtering were not used, variations in dose and breath-hold volumes between serial CT scans resulted in a Perc15 reproducibility coefficient of 32.81 HU ± 1.70 (95% CI). MF and IR, combined with volume adjustment improved reproducibility, reduced the Perc15 reproducibility coefficient to 7.42 HU ± 0.42 for RD-MF and 7.10 HU ± 0.42 for RD-IR scans. MF and IR appeared to remove most of the Perc15 measurement bias regardless of whether or not volume adjustment was applied, whereas application of volume adjustment contributed mainly to reducing measurement variability (ie, smaller limits of agreement). Significant differences in the mean measurements between FD scans and RD scans were demonstrated in all cases, indicating that lung density measurements are on average different for RD scans compared with FD scans, even when noise reduction filtering and volume adjustment were applied.

Changes in mean ± standard deviation Perc15 (volume adjustment applied) between baseline and 5-year follow-up are shown in Table 3. Differences in longitudinal change between different doses and standard dose are shown in Table E6 (supplement). While the mean change over time computed using all FD and RD scanning methods was significantly different from the mean change computed using FD scans at both phases (−2.46 HU ± 14.1), the magnitude of the difference was smaller when the RD-MF (−4.67 HU ± 14.0) and RD-IR (−0.97 HU ± 14.4) methods were used for 5-year follow-up CTD measurements, as opposed to RD scans with no noise reduction (−17.48 HU ± 14.2).

Association with Clinical Outcomes

Receiver operating characteristic curve analysis results are shown in Table 4 for Perc15 and Table E7 (supplement) for LAA_{-950}. When volume adjustment was used, the ability of Perc15 to predict clinical outcomes was the same for FD and RD-MF scans (FD, 0.724 ± 0.045; RD-MF, 0.726 ± 0.046; P = .73 for COPD diagnosis, and FD, 0.593 ± 0.068; RD, 0.585 ± 0.068; P = .45 for one or more annual exacerbation). However, the ability to predict COPD diagnosis was higher when using RD scans (RD, 0.739 ± 0.045; P = .012) and lower when using RD-IR scans (RD-IR, 0.707 ± 0.046; $P <$ .001). Spearman correlations (Table E8 [supplement]) revealed significant relationships between CTD measurements and GOLD stage for FD, RD, RD-MF, and RD-IR scans. AUC values tended to be higher when volume adjustment was not applied. For LAA_{-950}, AUC values for RD, RD-MF, and RD-IR were typically lower than for FD scans.

Discussion

We demonstrated that the use of noise reduction filtering and volume adjustment on RD scans improves the reproducibility of CTD measurements when compared with FD scans, allowing for more accurate detection of true smoking-related changes in lung density. Emphysema has been found to occur in 29% of smokers undergoing lung cancer screening with low-dose CT, and its presence has been shown to be strongly associated with increased risk of lung cancer diagnosis (24,25) and respiratory and lung cancer mortality (14,26). Additionally, quantitatively detected emphysema at CT can progress before any changes are evident at pulmonary function testing (1). When performing longitudinal analysis to assess changes

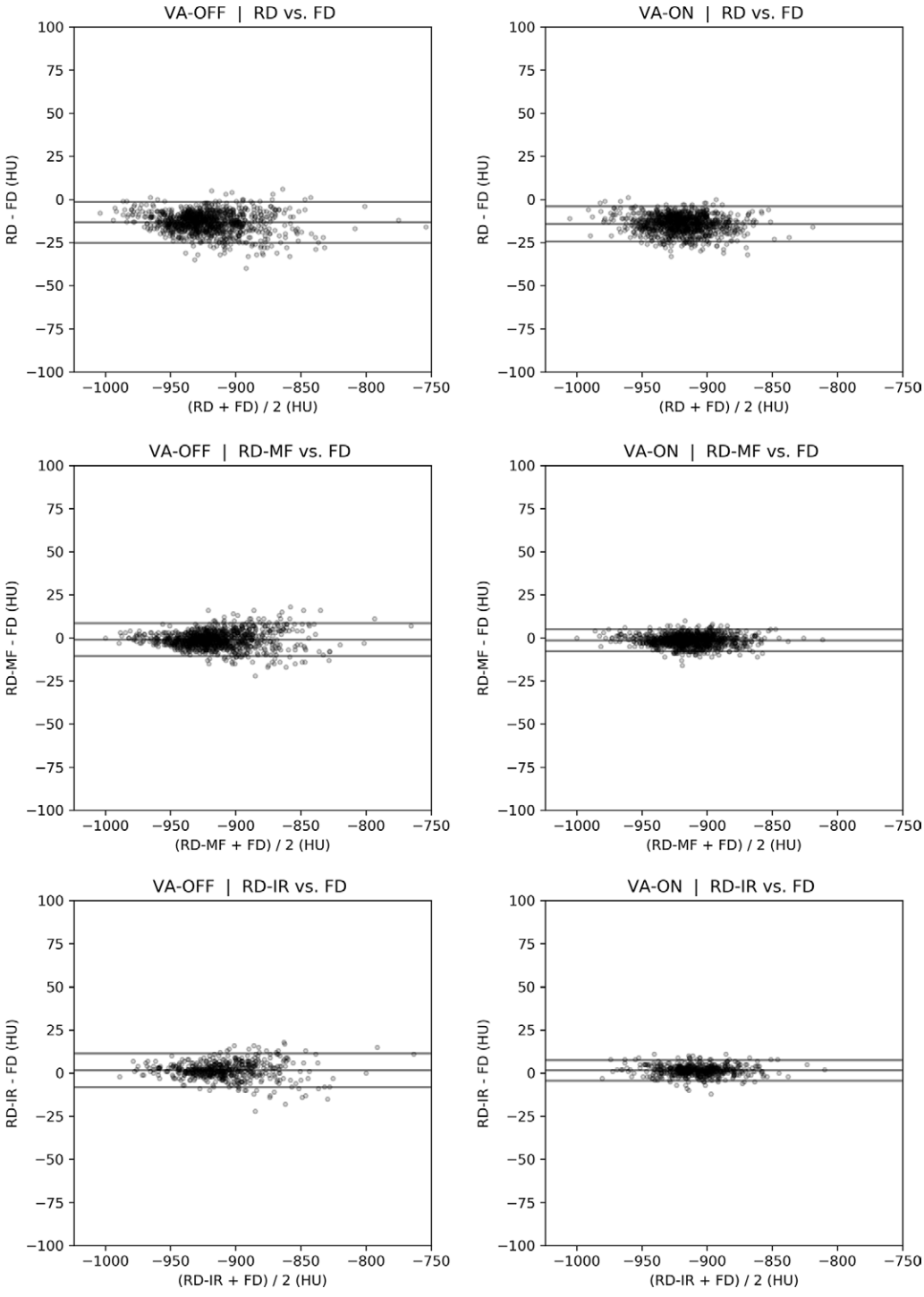

Figure 4: Bland-Altman plots for CT attenuation at the 15th percentile of the lung CT histogram between standard fixed-dose (FD) and reduced-dose (RD) scans. IR = iterative reconstruction, MF = median filtered, VA = volume adjustment.

in lung density between a baseline FD scan and a follow-up RD scan, the threshold for clinically significant change if no volume adjustment or noise filtering is applied is a difference of 32.8 HU for Perc15; however, if both volume adjustment and MF are applied, the threshold for significant change drops to 7.4 HU. Pompe et al (1) recently showed that patients with GOLD stages 1–4 had an average Perc15 decrease of 5.07 HU over 5 years in the COPDGene study. Because lung density does not change quickly for a typical patient with COPD, reducing the reproducibility coefficient to a value as low as possible will be important for detecting patients with clinically significant radiologic progression of emphysema.

It should be noted that although there was a very short time interval between the FD and RD scans, the variability in breath-hold lung volumes was relatively high compared with other studies. For example, lung volume differences (mean ± 1.96 times

Table 2: Perc15 Reproducibility Coefficients, Limits of Agreement, and Biases for Each Comparison between FD and RD Scans

Dose Comparison	Perc15 Reproducibility Coefficient (HU)	Perc15 Limits of Agreement	Perc15 Bias	*P* Value
No volume adjustment				
FD vs RD	32.81 ± 1.70	20.30 ± 2.53	13.15 ± 0.58	<.001
FD vs RD-MF	19.40 ± 2.65	19.36 ± 2.67	0.65 ± 0.56	.022
FD vs RD-IR	22.46 ± 3.91	21.86 ± 3.83	−2.63 ± 0.87	<.001
Volume adjustment applied				
FD vs RD	29.43 ± 0.62	10.53 ± 0.46	14.03 ± 0.31	<.001
FD vs RD-MF	7.42 ± 0.42	6.94 ± 0.42	1.35 ± 0.20	<.001
FD vs RD-IR	7.10 ± 0.52	6.49 ± 0.56	−1.47 ± 0.26	<.001

Note.—Data are mean ± 95% CI. Standard fixed-dose (FD) versus reduced-dose (RD) comparisons were between 1205 participants, while FD versus RD-iterative reconstruction (RD-IR) were between 640 participants. MF = median filtered, Perc15 = CT attenuation at the 15th percentile of the lung CT histogram.

Table 3: Mean Changes in Perc15 from COPDGene Baseline to 5-year Follow-up

ΔPerc15	Mean Change ± SD (HU)	*P* Value
$FD_{follow\text{-}up} - FD_{baseline}$	−2.46 ± 14.1	NA
$RD_{follow\text{-}up} - FD_{baseline}$	−17.48 ± 14.2	<.001
$RD\text{-}MF_{follow\text{-}up} - FD_{baseline}$	−4.67 ± 14.0	<.001
$RD\text{-}IR_{follow\text{-}up} - FD_{baseline}$	−0.97 ± 14.4	<.001

Note.—A paired *t* test was conducted between change values computed with follow-up standard fixed-dose (FD) scans only and with all possible FD follow-up/reduced-dose (RD) baseline combinations. COPDGene = Genetic Epidemiology of COPD, IR = iterative reconstruction, MF = median filtering, NA = not applicable, Perc15 = CT attenuation at the 15th percentile of the lung CT histogram, SD = standard deviation, Δ = change.

standard deviation) of 50.0 mL ± 80.0 with 9 months between scans (27) and 40.0 mL ± 80.0 with 15 minutes between scans (28) have previously been reported, compared with 19.6 mL ± 654 in our study. It is unclear why these differences in lung volume reproducibility exist, but one possible explanation is that the CT scans from our study were performed at 17 different sites and thus posed more of a challenge from the standpoint of imaging quality control. One advantage is that our study may more accurately reflect the breath-hold volume variability that would be encountered in a typical clinical scenario.

Associations between lung density and clinical outcomes were demonstrated for all FD and RD scan types. AUC values typically were higher with FD scans than with RD scans, but the difference was not always significant. Interestingly, the AUC and Youden *J* statistic values associated with prediction of COPD tended to increase when volume adjustment was not applied. This suggests that, although volume adjustment is important for achieving measurement reproducibility in longitudinal studies, there is some information loss associated with applying volume adjustment. This may be because increases in breath-hold volume may not be purely due to poor inspiratory effort but may also represent real change in disease, which application of volume adjustment removes.

A measurement of percentage of low-attenuation area greater than 5% is considered to be a clinically significant finding owing to differences observed in symptoms, annual exacerbations, and mortality for participants above and below that threshold (29). Based on data from the cohort described in this study, clinically significant thresholds for detection of COPD using Perc15 are −915 HU and −934 HU for FD and RD, respectively, and using LAA_{-950} are 1.8% and 8.6% for FD and RD, respectively. Similar values are useful for prediction of one or more annual exacerbations, although the predictive ability is weaker. This shows that, although CTD applied to FD and RD scans for prediction of clinical outcomes is not significantly different, the optimal thresholds used to determine clinically significant findings change depending on the dose and noise filtering techniques.

In terms of improving reproducibility between lung density metrics for FD and RD scans, there was no strong evidence that MF was superior to IR or vice versa. Both greatly improved reproducibility and had similar results in terms of predicting clinical outcomes. One advantage of MF is that it is simple to implement in commercial software and will always exhibit the same performance, whereas IRs vary between manufacturers and their performance is subject to change over time.

This study had a few limitations. The study population included sequential COPDGene participants scanned during the latter part of the second phase of the study. IR was not available at all sites, depending on equipment. We also did not evaluate the effect of RD on visual assessments of emphysema or lung texture. Finally, we did not investigate the effect of so-called partial iterative algorithms on lung density measurements.

Overall, the results of this study suggest that lung density measurements obtained from low-dose scans can be used for identification of clinical outcomes in COPD just as effectively as

Table 4: ROC AUC Results for Perc15-based Prediction of Spirometrically Defined COPD Diagnosis and at Least One Annual Exacerbation using Different Dose and Noise Filtering Methods

	Volume Adjustment Applied			No Volume Adjustment		
Dose Comparison	ROC AUC	Youden *J* Statistic	Optimal Threshold (HU)	ROC AUC	Youden *J* Statistic	Optimal Threshold (HU)
COPD diagnosis						
FD	0.724 ± 0.045 (*P* = NA)*	0.379 ± 0.077	−914.20 ± 5.17	0.780 ± 0.043 (*P* = NA)*	0.468 ± 0.074	−919.53 ± 6.00
RD	0.739 ± 0.045 (*P* = .012)*	0.404 ± 0.076	−932.93 ± 4.79	0.770 ± 0.043 (*P* = .108)*	0.471 ± 0.075	−935.15 ± 3.43
RD-MF	0.726 ± 0.046 (*P* = .729)*	0.366 ± 0.076	−917.31 ± 7.27	0.768 ± 0.044 (*P* = .048)*	0.449 ± 0.073	−921.97 ± 10.35
RD-IR	0.707 ± 0.046 (*P* < .001)*	0.339 ± 0.074	−912.95 ± 10.65	0.763 ± 0.044 (*P* < .001)*	0.441 ± 0.075	−920.95 ± 7.19
At least one annual exacerbation						
FD	0.593 ± 0.068 (*P* = NA)*	0.226 ± 0.098	−918.76 ± 8.57	0.596 ± 0.068 (*P* = NA)*	0.233 ± 0.097	−924.09 ± 12.09
RD	0.589 ± 0.066 (*P* = .965)*	0.232 ± 0.100	−933.00 ± 6.79	0.588 ± 0.066 (*P* = .429)*	0.200 ± 0.091	−939.96 ± 18.42
RD-MF	0.585 ± 0.068 (*P* = .445)*	0.234 ± 0.100	−919.94 ± 7.66	0.583 ± 0.067 (*P* = .183)*	0.201 ± 0.092	−929.03 ± 17.90
RD-IR	0.585 ± 0.068 (*P* = .10)*	0.211 ± 0.095	−917.29 ± 10.89	0.582 ± 0.067 (*P* = .147)*	0.197 ± 0.091	−924.46 ± 18.80

Note.—Values are means ± 1.96 times standard deviation. Because this is a direct comparison between reduced-dose (RD) scan noise reduction techniques, only scans that had iterative reconstruction (IR) were included in the analysis. AUC = area under the ROC curve, COPD = chronic obstructive pulmonary disease, FD = fixed dose, MF = median filtering, NA = not applicable, Perc15 = CT attenuation at the 15th percentile of the lung CT histogram, ROC = receiver operating characteristic, SD = standard deviation.
* *P* value calculated by comparing value with that of the FD scan.

measurements obtained from FD scans, and that thresholds for detection of real changes in disease between FD and RD scans are comparable to what was previously reported in the literature for scans that had the same dose level if volume adjustment and noise reduction are applied to the RD scan. With the recent coverage of low-dose CT lung cancer screening by the Centers for Medicare & Medicaid Services (30), early detection and phenotyping of emphysema becomes important in identifying individuals at increased risk of mortality, lung cancer diagnosis, progressive airflow obstruction, and progressive emphysema (24,25,31). Considering that individuals who smoke are the main population at risk, detection of real changes may be useful in risk-modifying interventions such as smoking cessation in this screening population (32).

Author contributions: Guarantors of integrity of entire study, C.R.H., S.M.H.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, C.R.H., A.S.O., D.A.L., S.M.H.; clinical studies, D.A.L., S.M.H.; experimental studies, C.R.H., J.P.C., S.M.H.; statistical analysis, C.R.H., N.A.O., S.M.H.; and manuscript editing, C.R.H., A.S.O., D.A.L., S.M.H.

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