Volume Correction in Computed Tomography Densitometry for Follow-up Studies on Pulmonary Emphysema

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Lung densitometry in drug evaluation trials can be confounded by changes in inspiration levels between computed tomography (CT) scans, limiting its sensitivity to detect changes over time. Therefore our aim was to explore whether the sensitivity of lung densitometry could be improved by correcting the measurements for changes in lung volume, based on the estimated relation between density (as measured with the 15th percentile point) and lung volume. We compared four correction methods, using CT data of 143 patients from five European countries. Patients were scanned, generally twice per visit, at baseline and after 2.5 years. The methods included one physiological model and three linear mixed-effects models using a volume–density relation: (*1*) estimated over the entire population with one scan per visit (model A) and two scans per visit (model B); and (*2*) estimated for each patient individually (model C). Both log-transformed and original volume and density values were evaluated and the differences in goodness-of-fit between methods were tested. Model C fitted best ($P < 0.0001$, $P < 0.0001$, and $P = 0.064$), when two scans were available. The most consistent progression estimation was obtained between sites, when both volume and density were log-transformed. Sensitivity was improved using repeated CT scans by applying volume correction to individual patient data. Volume correction reduces the variability in progression estimation by a factor of two, and is therefore recommended.

Keywords: densitometry; computed tomography; statistical models; clinical trials

Pulmonary emphysema is characterized by a destruction of lung tissue, hyperinflation, increased areas of trapped air, and a reduction in the pulmonary capillary vasculature. These factors together cause a decrease in lung density, which can be quantified by densitometry using computed tomography (CT) (1). By applying image analysis software, the lungs can be detected automatically (2) and the density distribution within the lungs can be quantified in a highly reproducible manner, as demonstrated in cross-sectional studies (3–6).

Consequently, lung densitometry has been introduced as a surrogate marker for the evaluation of drug efficacy in the treatment of emphysema. However, application of the technology to longitudinal studies requires a higher level of reproducibility than in cross-sectional studies, because (long-term) pathophysiological changes or changes in the CT equipment can affect the density measurements. Therefore, these confounding factors should be eliminated to further increase the reproducibility and consequently improve the sensitivity of the assessment to detect changes over time.

Whether differences in inspiration level can be considered an important physiological confounder in determining lung density is subject to debate. If CT scans could be acquired reproducibly at the patient's total lung capacity, volume correction would not be needed, because both tissue loss and volume increase would produce a decrease in density, reflecting progression of emphysema. Therefore, the goal of this study was to determine whether volume correction is required to obtain high sensitivity and, if so, which method would be the most accurate.

Early attempts to standardize for lung volume have been focused on maintaining a constant inspiration level during the course of the study, through spirometric control. However, this proved difficult to accomplish, because a high level of patient compliance is required to limit the inherent variability in lung volume measurement (3).

In a European research project (SPREAD [Software Performance and Reproducibility in Emphysema Assessment: Demonstration], QLG1-2000-01752), we focused on the standardization of acquisition protocols for CT scanners from the four major CT manufacturers and on the standardization of analysis procedures, applied to patient groups from five European countries. As part of this prospective study, we developed and validated different statistical models to correct for inspiration differences, as presented in this article.

With the introduction of low-dose CT in lung densitometry (4, 5), it became feasible to employ a dual-scan protocol at two inspiratory levels, while still decreasing the total X-ray dose compared with previous image acquisition protocols. This made it possible to explore the relation between density and volume for each individual patient and to correct for inspiration differences individually. In this study, we also evaluated the effect of this repeated measurement on the accuracy of the density progression estimation.

METHODS

A group of 143 subjects (six groups of 23–25 patients) with a diagnosis of emphysema participated in this study; 79 patients were homozygous for phenotype PiZZ, and 65 had a non-PiZZ phenotype. Overall patient characteristics are shown in Table 1. After ethics board approval, all patients gave written informed consent.

Patients were scanned in one of five European hospitals at baseline and after an interval of approximately 2.5 years. Each patient was scanned twice without leaving the scanner at baseline and follow-up visits, except for site 2, where patients were scanned at baseline during 3 visits within 1 month and a single scan was made at follow-up (because of the already applied radiation dose at baseline). Images were acquired

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TABLE 1. PATIENT CHARACTERISTICS AT BASELINE: TOTAL GROUP

Characteristic	Value
Male/female	75/69
Age, yr: mean (range)	58 (30–78)
Height, m: mean (range)	1.71 (1.49–1.92)
Body weight, kg: mean (range)	71.8 (46–125)
AAT/COPD	119/25
AAT phenotype, PiZZ/non-PiZZ	79/40
Smoking status, c/e/n*	45/68/31
FEV_1, L: mean (range)	1.59 (0.51–5.08)
Kco, mmol/min/kPa/L: mean (range)	0.96 (0.18–2.05)

Definition of abbreviations: AAT = α_1-antitrypsin deficiency; COPD = chronic obstructive pulmonary disease; Kco = transfer coefficient for carbon monoxide.
* c = current smoker; e = ex-smoker; n = nonsmoker.

in the supine position, after three deep inhalation maneuvers, during breath hold at full inspiration, with a low radiation dose (approximately 1 millisievert [mSv]). The standardized acquisition protocol for each scanner has been optimized to achieve high-density resolution (7) and is described elsewhere (8). All patients were scanned while in stable clinical condition 4 weeks before the CT scan and each CT scan was routinely checked by a radiologist at each site for the presence of concurrent lung diseases.

We analyzed all images with a software package called Pulmo-CMS (Medis Specials, Leiden, The Netherlands) (9). Subsequently, the density of the lungs was quantified with the 15th percentile point (Perc15), which is defined as the threshold density value for which 15% of all voxels has a lower density (10). Throughout this article, the term "density" is used for the quantification by the 15th percentile point, and for the purpose of log-transformation the 15th percentile density is expressed as grams per liter by adding 1,000 to the Hounsfield unit (HU) value.

Relation between Density and Volume

To standardize for lung volume, the influence of inspiration on lung density needs to be determined. However, lung density is not only influenced by inspiration level, but also by the anatomic size of the lungs. In particular, it has been found that individuals with larger but healthy lungs have a lower lung density (11). As the influence of anatomic size is not relevant in longitudinal studies, we focused on establishing the influence of inspiration level independently of anatomic characteristics, by plotting the individual differences in volume against the consequential differences in density, both obtained from the repeated scans. Subsequently, this can be used to determine the transformations that are needed to obtain a linear relation. To do this, we selected paired measurements from either baseline or follow-up data that had the largest volume difference, to estimate the volume–density relation most reliably. For site 2, two samples with the largest volume difference were selected from the three baseline measurements.

From a theoretical point of view, the lungs could be considered a spongelike structure, in which a proportional decrease in lung volume would yield an equally proportional increase in density, as compression would be mass-preserving. Therefore, when considering the Perc15 parameter representative for the global density of the lungs, a log-transform of both volume and density is expected to yield a perfect linear relationship with a slope of -1 (12).

To examine whether the respiration influence itself is dependent on lung size (i.e., whether large lungs have different volume–density relations than small lungs), the correlation was considered between the volume–density slope of each individual ($\Delta D/\Delta V$) and mean lung volume from the two CT scans. The volume–density slope cannot be estimated accurately for small volume differences. Therefore, data with volume differences smaller than 0.2 L were excluded from this specific analysis.

In a similar manner, the influence of disease severity on the volume–density slope was considered by examining the relation between slope and lung density. In other words, we examined whether patients with severe emphysema would be characterized by a different inspiration effect on lung density, compared with moderate emphysema.

TABLE 2. PEARSON CORRELATION COEFFICIENTS BETWEEN DIFFERENCES IN (LOG-TRANSFORMED) VOLUME AND DIFFERENCES IN (LOG-TRANSFORMED) DENSITY

Site	Volume vs. Density	Volume vs. Log(Density)	Log(Volume) vs. Density	Log(Volume) vs. Log(Density)	n
1	−0.66	−0.88	−0.89	−0.96	24
2 (AAT)*	−0.70	−0.71	−0.78	−0.76	25
2 (COPD)*	−0.61	−0.73	−0.68	−0.77	25
3	−0.87	−0.87	−0.90	−0.89	24
4	−0.84	−0.90	−0.93	−0.91	22
5	−0.84	−0.83	−0.83	−0.81	23
Total	−0.76	−0.80	−0.88	−0.83	143

Definition of abbreviations: AAT = α_1-antitrypsin deficiency; COPD = chronic obstructive pulmonary disease.
All correlations were statistically significant ($P \leq 0.001$).
* AAT: group of α_1-antitrypsin–deficient patients; COPD: group of patients with general COPD.

Statistical Models for Volume Correction

We applied three different methods, in which the paired density measurements at baseline and follow-up were corrected, using a slope between density and volume obtained in two different ways:

1. Estimated over the entire patient group, assuming that each patient has the same volume–density slope. For this, we used one CT scan per patient per visit (model A) or both scans per visit (model B); or
2. Estimated with random patient-specific volume–density slopes (model C)

In these models it is assumed that the volume–density relation does not change over time, because the difference in slope over time would make the progression estimation dependent again on the choice of volume for which the data are to be standardized, because the regression lines may not run parallel in that case.

The following linear mixed-effects model was fitted by maximum likelihood to the data of each site separately, with density as outcome, and lung volume and time of CT scan as fixed effects, with random intercept:

$$d_{ijk} = \alpha + a_i + (\beta + b_i)v_{ijk} + \gamma t_{ij} + \varepsilon_{ijk}$$

where d_{ijk} is the predicted density for patient i at visit j (j = 1, 2) during scan k; α is the mean density (intercept) over all patients within one site; a_i is the mean deviation from α for patient i [$a_i \sim N(0, \sigma_a^2)$]; β is the mean volume–density slope over all patients; b_i is the mean deviation from β for patient i [$b_i \sim N(0, \sigma_b^2)$]; v_{ijk} is the log volume for patient i, visit j and scan k; γ is the change in density over time (progression rate), t_{ij} is the time of visit j for patient i; and ε_{ijk} is the residual error for patient i at visit j and scan k.

For models A and B, the volume–density slope is fixed, that is, $\sigma_b^2 = 0$. For model A, k equals 1, and k = 1, 2 for models B and C. For model C, the volume–density slope is patient specific ($\sigma_b^2 > 0$). In all methods, an error distribution with unstructured correlation was used to model the dependence among the within-individual errors. The residual error ε_i was assumed to follow a multivariate normal distribution, with identical diagonal elements and freely estimated correlations. For these models, volume was log-transformed, and in addition, model C was applied with density and volume both log-transformed, indicated by model C′.

The progression estimates and their standard errors were calculated for each site and each method. To compare the goodness-of-fit between models B and C, the log-likelihood ratio was tested. For all analyses we used the software package R (version 2.0.0, the R Project; Statistics Department of the University of Auckland, Auckland, New Zealand).

RESULTS

Relation between Lung Density and Volume

The correlation coefficients for the various transformations are given for each site in Table 2. The highest level of linearity was

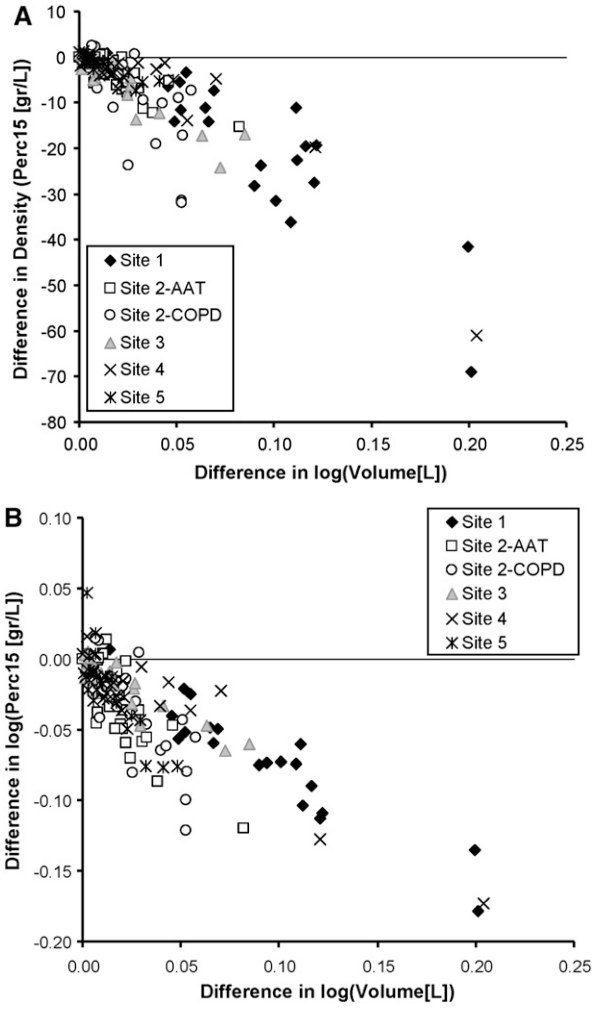

Figure 1. Relation between difference in log(volume) and (*A*) difference in density and (*B*) difference in log(density) for each site. This illustrates the linearity of the relation between volume and density, originating from respiration. AAT = α_1-antitrypsin deficiency; COPD = chronic obstructive pulmonary disease; Perc15 = 15th percentile point, which is defined as the threshold density value for which 15% of all voxels has a lower density.

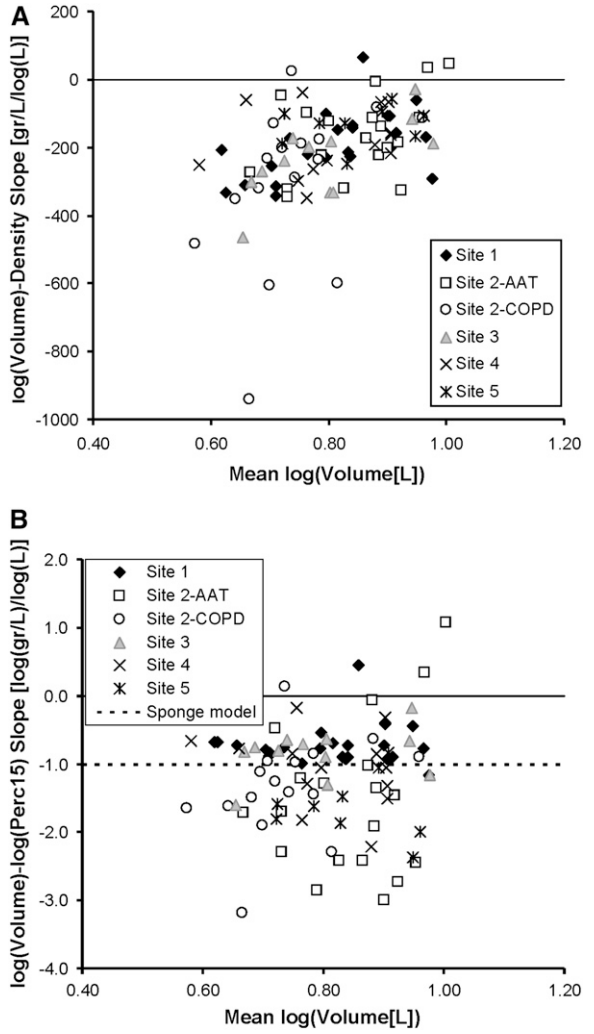

Figure 2. The influence of lung size on the (*A*) log(volume)–density relation and (*B*) log(volume)–log(density) relation is assessed by plotting the slope against the mean lung volume of each patient. The *dotted line* gives this relation according to the sponge model. AAT = α_1-antitrypsin deficiency; COPD = chronic obstructive pulmonary disease; Perc15 = 15th percentile point, which is defined as the threshold density value for which 15% of all voxels has a lower density.

obtained when both volume and density were log-transformed in site 1, whereas other sites obtained comparable results for original and log-transformed density in combination with log-transformed volume (Figure 1). In former studies (13–15), however, density was not log-transformed. For comparison purposes, we present therefore the results of both log-transformed and original density values for model C.

Dependency of Volume–Density Slope on Lung Size and Disease Severity

The relation between slope and mean log volume is shown in Figure 2A and the corresponding correlation coefficients are given in Table 3 for each site. When both density and volume are log-transformed, as illustrated in Figure 2B, no association between slope and mean log volume was observed. The individual slopes deviated considerably from -1, indicating that the sponge model does not fit to the data exactly.

Figure 3A presents the relation between slope and mean density, as an indication of disease severity. Individual correlation coefficients are given in Table 3. In general, a significant correlation was found. A similar association was found when disease severity was assessed with CO diffusion (data not shown). When both density and volume are log-transformed (Figure 3B), no general relation was found between the slope and disease severity. However, with more severe emphysema (lower Perc15 values), the variation in the slopes increased. The sponge model fitted the group with moderate emphysema better than the group with more severe emphysema, except for a small number of patients with chronic obstructive pulmonary disease. The variation in slope between patients was remarkably lower in site 1, compared with the other sites.

Correction Methods

For site 3, the progression estimation was found to be unreliable because of technical problems with the CT scanner between baseline and follow-up, and was therefore omitted from the statistical analysis. The results for the remaining sites are presented in Table 4, where the mean and standard error of the estimated progression are presented. With most applied models a statistically significant decrease in density over time was observed. For comparison of the goodness of fit between models B and C, the log likelihood

TABLE 3. PEARSON CORRELATION COEFFICIENTS BETWEEN LUNG SIZE AND VOLUME–DENSITY SLOPE, AND BETWEEN MEAN PERC15 AND VOLUME–DENSITY SLOPE

		Lung Size vs. Slope*		Mean Perc15 vs. Slope*	
Site	n	Corr. Coeff.	*P* Value	Corr. Coeff.	*P* Value
1	23	0.53/0.04	0.010/0.871	−0.83/−0.24	≪0.001/0.131
2 (AAT)†	19	0.47/0.25	0.043/0.296	−0.61/−0.12	0.005/0.632
2 (COPD)†	16	0.43/0.36	0.097/0.173	−0.86/−0.72	≪0.001/0.002
3	12	0.69/0.32	0.013/0.315	−0.63/−0.16	0.028/0.627
4	13	0.23/−0.30	0.458/0.325	−0.49/0.37	0.087/0.207
5	9	0.25/−0.07	0.522/0.856	−0.81/0.17	0.008/0.664
Total	93	0.48/0.08	≪0.001/0.465	−0.61/0.04	≪0.001/0.680

Definition of abbreviations: AAT = α_1-antitrypsin deficiency; COPD = chronic obstructive pulmonary disease; Corr. Coeff. = correlation coefficient; Perc15 = 15th percentile point, which is defined as the threshold density value for which 15% of all voxels has a lower density.

* Correlation coefficients and *P* values are given for the density–log(volume) relation and log(density)–log(volume) relation, respectively.

† AAT: group of α_1-antitrypsin–deficient patients; COPD: group of patients with general COPD.

values are given for these models. Model C fitted significantly better than model B in sites 1 and 4 and in the chronic obstructive pulmonary disease group in site 2, and almost significantly in site 5. In all patient groups, smaller standard errors were observed in model B, as compared with model A. This indicates that repeated scans considerably increased the sensitivity in measuring progression, as compared with single scans.

If volume correction was applied, the standard errors of the progression estimate decreased on average by a factor of two.

If both volume and density are log-transformed, the progression is by definition estimated relative to the baseline density. These results, indicated by model C′, are expressed as ln(density)/year. These values are calculated as percentage change, indicated in parentheses in Table 4. When a double-log transformation is applied, the estimated progression was most consistent between the different sites, considering the similar statistical significance levels.

DISCUSSION

As for any outcome parameter, the reproducibility of densitometry is the most determining factor to adequately power a clinical trial. We found that variability can be reduced considerably, if densities are corrected for differences in inspiration levels. This is especially true if the correction is performed for each patient individually, using repeated CT scans, and taking into account the introduction of autocorrelation by repeated scans. Because low-dose CT scanning was applied, radiation dose was still well within the range for biomedical studies with an intermediate risk (16). The method does, however, complicate statistical analysis and image acquisition protocols, as scans should then be undertaken at different inspiration levels.

A number of studies have been published in which lung densitometry has been studied longitudinally (13–15, 17–22). Volume correction has been applied in only three of these studies (13–15). By omitting volume correction, not only is the reproducibility suboptimal, but it could also introduce confounding factors. Because total lung capacity may change over time, a measured change in lung density could reflect this functional change alone. Whereas this may also reflect the pathological processes involved, it would enhance lung density changes due to any loss of tissue. Comparison with highly standardized lung function may clarify this point. Nevertheless, volume correction remains mandatory, because of the variation reduction (12). It

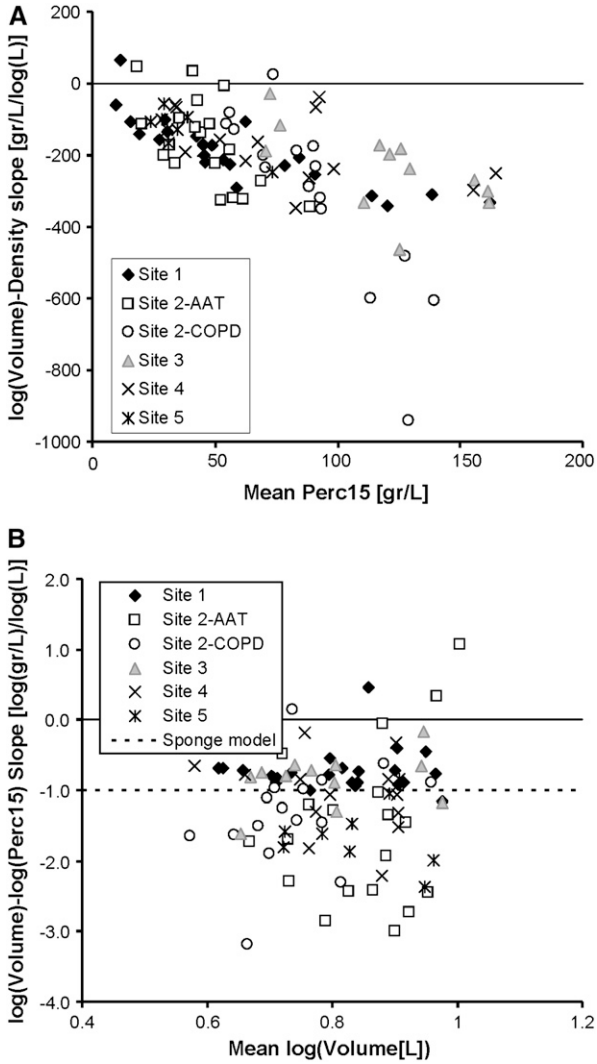

Figure 3. The influence of disease severity on the (*A*) log(volume)–density relation and (*B*) log(volume)–log(density) relation is analyzed by plotting the slope of this relation against the mean density value (Perc15) of each patient. AAT = α_1-antitrypsin deficiency; COPD = chronic obstructive pulmonary disease; Perc15 = 15th percentile point, which is defined as the threshold density value for which 15% of all voxels has a lower density.

may also improve the results of other measurements such as texture-based parameters (23), and even of visual scoring systems, because these measures may also depend on inspiration level. It was found that the volume correction of the percentile point method was more stable over a wide range of thresholds than the alternative density measure, the relative area (12). Therefore, we considered only the 15th percentile as the ultimate density parameter for this study.

Some limitations still remain for the current study. To successfully correct for volume differences, two CT scans with sufficiently different volumes are needed for each patient. As subjects cannot normally reproduce their inspiration level perfectly, it was decided initially to perform two inspiratory scans. From our data it became clear, however, that the patients with more severe emphysema could reproduce the inspiration level better than patients with moderate emphysema. As a result, the success of the volume correction may be dependent on disease severity. An alternative acquisition protocol would therefore be to perform one CT scan at full inspiration and one at approxi-

TABLE 4. RESULTS FROM SITES 1, 2, 4, AND 5, USING THREE MODELS TO ESTIMATE THE PROGRESSION PER YEAR OF EMPHYSEMA WITH THREE DIFFERENT METHODS TO CORRECT FOR VOLUME DIFFERENCES

Site	Model*	Mean Progression†	SE	*P* Value	LogLik	*P* Value
Site 1	—	−0.05	1.12	0.96	—	
(n = 19)	S	−1.31	0.57	0.03	—	
	A	−1.71	0.85	0.06	—	
	B	−1.65	0.58	0.006	269.4	<0.0001
	C	−2.15	0.43	<0.0001	239.4	
	C′	−0.066 (−6.4%)	0.015	0.0001	—	
Site 2 (AAT)‡	—	−1.40	0.44	0.006	—	
(n = 17)	S	−1.25	0.27	0.0003	—	
	A	−1.12	0.36	0.007	—	
	B	−0.87	0.27	0.003	148.5	0.76
	C	−0.96	0.26	<0.0001	147.9	
	C′	−0.023 (−2.3%)	0.007	0.003	—	
Site 2 (COPD)‡	—	−0.27	0.75	0.72	—	
(n = 17)	S	−1.29	0.40	0.01	—	
	A	−1.09	0.69	0.13	—	
	B	−1.74	0.38	<0.0001	180.3	0.0018
	C	−1.79	0.34	<0.0001	172.7	
	C′	−0.026 (−2.6%)	0.005	<0.0001	—	
Site 4	—	0.27	0.78	0.74	—	
(n = 17)	S	−0.64	0.67	0.36	—	
	A	−0.45	0.89	0.62	—	
	B	−0.80	0.64	0.22	217.1	<0.0001
	C	−1.68	0.65	0.01	201.4	
	C′	−0.032 (−3.1%)	0.013	0.02	—	
Site 5	—	−0.90	0.30	0.01	—	
(n = 17)	S	−0.75	0.25	0.01	—	
	A	−0.80	0.30	0.019	—	
	B	−0.61	0.25	0.019	148.7	0.064
	C	−0.37	0.22	0.103	141.3	
	C′	−0.023 (−2.3%)	0.009	0.016	—	

Definition of abbreviations: AAT = α_1-antitrypsin deficiency; COPD = chronic obstructive pulmonary disease; LogLik = log-likelihood ratio.

* Models: — = no volume correction; S = sponge model; A = one scan per visit, fixed slope; B = two scans per visit, fixed slope; C = two scans, random slope. Models A, B, and C are applied using log-transformed volume and original densities. In model C′, volume and density are log-transformed, using model C.

† Mean progression is expressed as g/L per year, except for model C′, for which mean progression is given as ln(g/L) per year. For this model, the relative progression is given as percentage per year in parentheses.

‡ AAT: group of α_1-antitrypsin–deficient patients; COPD: group of patients with general COPD.

mately functional residual capacity, as was decided during the follow-up period at site 1, reflecting a higher reproducibility (*see* Figure 3). If greater differences in inspiration level between the repeated scans could be obtained, the volume–density relation may not be linear over the entire range of volumes. Therefore, scans at a full inspiration and full expiration may not give an optimal estimation of the volume–density relation over small changes seen here and may result in a less accurate volume correction.

Despite standardization of image acquisition protocols, as one of the objectives of this European study, differences in sensitivity to detect density changes still remained between the different sites, as demonstrated in a phantom study (8). These remaining protocol differences may account for the differences in standard error in the progression estimations. In particular, the higher variability of the single–detector row scanner from site 4, found in this study, had already been predicted by the phantom study. Furthermore, the differences between sites can also be due to differences in architecture between CT scanners, patient characteristics, and instructions given by the technician to perform the inhalation maneuvers before breath hold. This was one of the reasons why we estimated progression for each site, separately. The data suggest that site should be included as a covariate in multicenter drug evaluation trials.

At site 2, the repeated CT scans were performed within 1 month. Variability may have been increased because of minor pathophysiological changes occurring during this period and short-term changes in image acquisition, such as differences in patient positioning or the "warming up" of the CT scanner.

As an increase in total lung capacity is one of the characteristics of emphysema, it could be argued that the correction for volume differences would eliminate this potential marker of progression. However, the progression of total lung capacity occurs over a long period of time and has not been detected reliably during clinical trials lasting only a few years. Furthermore, the results of the current study showed that the increase in the reproducibility may outweigh any drawback of failing to capture an increase in total lung capacity. Alternatively, the correction method provides a clean density measure without any influence of changes in volume, which would not relate directly to a decrease in tissue mass, blood perfusion, or increased areas of trapped air.

We have demonstrated that the relation between log(volume) and density [log(volume)–density slope] is influenced by both lung size (mean volume) and disease severity (mean Perc15). This systematic influence was not seen when density is also log-transformed, and therefore a double log-transform would be advantageous as it holds a physiological background comparable

to the sponge model. However, if density is log-transformed and entered in the statistical model, the progression estimate becomes a relative measurement. Therefore, the development of a two-step analysis approach would be needed, in which the density values are first corrected for volume, using log-transforms of both volume and density, followed by an inverse log-transform of the corrected density values, and finally calculation of mean progression rates. As indicated in Figure 3B, volume correction for patients individually would probably still be needed, because of the large deviation in slopes between patients.

For most sites, model C was the best method by which to represent the density data. The sponge model produced surprisingly good results, whereas it assumes an identical volume–density relation between patients. It can therefore be used as a correction method to quickly obtain an indication of progression rates in a patient group. For clinical trials, however, more sophisticated statistical methods, such as those described here, are recommended as they are more sensitive to change.

In summary, volume correction improves considerably the sensitivity to measure changes in density over time, especially if correction is applied for patients individually, using two scans per visit.

Conflict of Interest Statement: The institution at which B.C.S. works, Leiden University Medical Center, received, in 2008, €10,000 from Bio-Imaging, €12,500 from Roche Pharmaceuticals, €59,000 from Talecris Biotherapeutics, and €14,000 from Medis Medical Imaging Systems for a research project. B.C.S. is a consultant for Roche Pharmaceuticals, Talecris Biotherapeutics, CSL Behring, and Bioimaging Technologies, Inc. H.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.E.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.D. has participated as a speaker in scientific meetings organized and financed by Bayer, and Talecris. He received $200,000 in 2005 and 2006 from Bayer as research grants for participating as principal investigator in the current multicenter clinical trial. R.A.S. has received funding to attend international conferences from Boehringer Ingelheim and Talecris, and for speaking at conferences organized by GlaxoSmithKline (GSK), and AstraZeneca (AZ). He served on advisory panels for Roche, GSK, and Merck, Sharpe & Dohme ($5,000 in 2006). He is in receipt of an unrestricted non-commercial grant from AZ (£100,000 in 2006–2007), and Talecris (£634,000 in 2006–2007). E.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. E.W.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. D.P. has received payment for consultancy work, including reimbursement for expenses incurred as a result of attending committee meetings and professional conferences, from Talecris, and Roche as indicated earlier. S.B.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.H.C.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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