Volume Correction in CT Densitometry in Follow-up Studies on Pulmonary Emphysema: Results From SPREAD

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Aims

Pulmonary emphysema is characterized by destruction of lung tissue, increased areas of trapped air and decreased blood circulation. As these factors together cause a decrease in lung density, progression of emphysema can be quantified accurately by lung densitometry using Computed Tomography (CT).
To further increase its reproducibility, required for longitudinal studies, confounding factors should be eliminated. The most important physiological confounder is the inspiration level, as lung density decreases with increasing lung volume. In a European study (the SPREAD project), we developed and validated different statistical models to correct for inspiration changes.
With low-dose CT it became feasible to scan patients twice per visit with different inspiration levels. This made it possible to explore methods which correct for inspiration changes for each patient individually.

Materials & Methods

Patient groups and image acquisition

In five different hospitals, 144 subjects with the diagnosis of emphysema were scanned by CT at baseline and after 2.5 years. Images were acquired in supine position during approximately full inspiration, with CT settings that allow low radiation dose and high density-resolution.

Image analysis

All CT images were analyzed with Pulmo-CMS (Medis medical imaging systems, Leiden, the Netherlands). Images were recalibrated for both blood and air. Subsequently, the total lung volume was determined and the density distribution of the lungs was quantified with the 15th percentile point (Perc15).

Statistical analysis

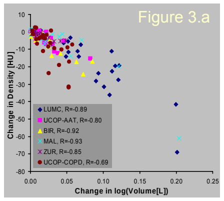
Relation between density and volume

To obtain linearity, the proper transformation of volume and density was determined by considering the individual differences in density as a function of the differences in volume. In this way, the influence of inspiration level could be considered, independently of the relation between lung size and density (see Figure 1).
Whether the volume-density slope is dependent on lung size was determined by the correlation between this slope and the mean volume. In order to determine the influence of disease severity on the volume-density slope, the correlation between slope and mean 15th percentile point was studied. See Figure 2.

Results

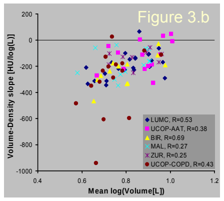
Relation between density and volume

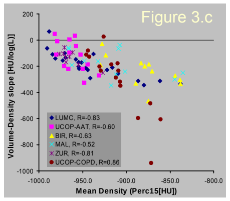
The highest level of linearity was obtained when both volume and density were log-transformed. However, using log-transformed density in the correction model causes density to become a relative measure, whereas lung density changes are known to be linear over time. Therefore, we used the original density values with log-transformed volumes, resulting in an acceptable level of linearity (Figure 3.a).



Dependency on lung size and disease severity

As indicated in Figures 3.b and 3.c, the volume-density slope is dependent on both lung size and disease severity. The latter suggests that indeed volume correction should be performed on an individual level.





Statistical models for volume correction

Four correction methods were developed, using the paired measurements at baseline and follow-up. Data were corrected using a volume-density slope obtained in three different ways:

- Estimated over the entire patient group, assuming that each patient has the same volume-density slope that does not change over time. This can be accomplished with one CT scan per patient per visit (**Method A**) or with repeated scans per visit (**Method B**);
- Estimated for each patient separately, assuming that the volume-density slope does not change over time (**Method C**); or
- Estimated over the entire patient group, allowing the mean volume-density slope to change over time (**Method D**).

Progression estimates (and SE) were calculated for each site and each method. Differences in goodness-of-fit between models were tested.

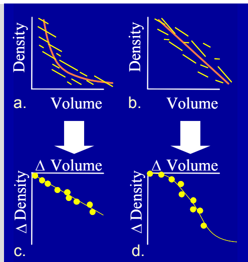


Figure 1. Establishing the influence of respiration on density, by plotting the differences in volume against differences in density: a) fictive non-linear relation between lung size and density with a linear influence of inspiration level; b) fictive linear relation between lung size and density with a non-linear influence of inspiration level; c) and d) scatter graph of differences in volume and differences in density from figures a) and b), respectively, indicating the influence of respiration (Δ Volume) only.

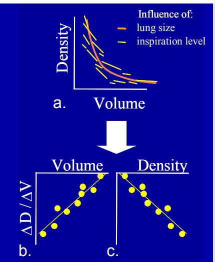


Figure 2. Determining the influence of lung size and disease severity on the volume-density relation: the non-linear relation between lung size and density (a) may reveal a dependency on lung size (b); or a dependency on disease stage (c).

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

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

- d_{ijk} predicted density for patient i at visit j (j=1,2) during scan k;
- α mean density (intercept) over all patients within one center;
- a_i mean deviation from α for patient i; $a_i \sim \mathcal{N}(0, \sigma_a^2)$;
- β_j mean volume-density slope over all patients during visit j;
- b_i mean deviation from β_j for patient i; $b_i \sim \mathcal{N}(0, \sigma_b^2)$;
- v_{ijk} log volume for patient i, visit j, and scan k;
- γ change in density over time;
- t_{ij} time of visit j for patient i;
- ε_{ijk} residual error for patient i, visit j, scan k; $\varepsilon_{ijk} \sim \mathcal{N}(0, \sigma_e^2)$.

Method A: $\sigma_b^2=0$; $\beta_j=\beta$; k=1
Method B: $\sigma_b^2=0$; $\beta_j=\beta$; k=1,2
Method C: $\sigma_b^2>0$; $\beta_j=\beta$; k=1,2
Method D: $\sigma_b^2=0$; $(\beta_j=\beta_j)$; k=1,2

Correction methods

Model D was not suitable because the progression estimation becomes dependent on the normalization for volume. The results of the remaining models are presented below. In all patient groups, except for the Copenhagen's AAT patients, Model C fitted significantly better than Model B (p<<0.001).

Repeated scans per visit considerably decreased the standard error in the progression estimation in all sites (Method A versus Method B, see below).

Site	Model	Mean	SE	p-value	-LogLik	p-value
LUMC	A	-1.62	0.80	0.0566	N/A	
n=24	B	-1.60	0.59	0.0083	326.8	} <0.0001
	C	-1.60	0.49	0.0018	291.8	
UCOP-AAT	A	-1.09	0.36	0.0079	N/A	
n=25	B	-0.90	0.26	0.0015	205.1	} 0.2950
	C	-0.97	0.27	0.0008	203.2	
UCOP-COPD	A	-1.02	0.68	0.1541	N/A	
n=25	B	-1.62	0.38	0.0001	245.0	} 0.0002
	C	-1.78	0.31	<0.0001	235.0	
LUND	A	-1.31	0.99	0.2079	N/A	
n=23	B	-1.57	0.79	0.0530	292.1	} <0.0001
	C	-1.25	0.92	0.1817	262.5	
ZUR	A	-0.89	0.30	0.0105	N/A	
n=23	B	-0.61	0.25	0.0177	191.3	} 0.0002
	C	-0.51	0.24	0.0368	181.3	

Conclusions

- To obtain linearity, lung volume should be log-transformed, with original density values
- Individual volume-density relations depend on severity of emphysema
- Correcting for changes in volume-density slope over time is not feasible
- Repeated scans make it possible to individually correct for volume changes

Acknowledgements

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