Respiratory Medicine (2007) **101**, 1924–1930

ELSEVIER

respiratoryMEDICINE

Progression parameters for emphysema: A clinical investigation

Jan Stolk[a,*], Hein Putter[b], Els M. Bakker[c], Saher B. Shaker[d], David G. Parr[e], Eeva Piitulainen[f], Erich W. Russi[g], Elzbieta Grebski[g], Asger Dirksen[d], Robert A. Stockley[e], Johan H.C. Reiber[c], Berend C. Stoel[c]

[a]*Department of Pulmonology, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands*
[b]*Department of Medical Statistics, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands*
[c]*Division of Image Processing, Department of Radiology, P.O. Box 9600, 2300 RC Leiden University Medical Center, Leiden, The Netherlands*
[d]*Department of Respiratory Medicine, Gentofte University Hospital, Niels Andersens vej 65, DK-2900 Hellerup, Denmark*
[e]*Department of Respiratory Medicine, University Hospital, Edgbaston B15 2TH Birmingham, UK*
[f]*Department of Pulmonary Medicine, Malmö University Hospital, 20502 Malmö, Sweden*
[g]*Pulmonary Division, University Hospital Zurich, Ramistrasse 100, 8091 Zurich, Switzerland*

Received 9 February 2007; accepted 22 April 2007

KEYWORDS
Airflow limitation;
Alveolar destruction;
Lung densitometry

Summary
In patients with airflow limitation caused by cigarette smoking, lung density measured by computed tomography is strongly correlated with quantitative pathology scores of emphysema, but the ability of lung densitometry to detect progression of emphysema is disputed. We assessed the sensitivity of lung densitometry as a parameter of disease progression of emphysema in comparison to FEV_1 and gas transfer. At study baseline and after 30 months we measured computed tomography (CT)-derived lung density, spirometry and carbon monoxide diffusion coefficient in 144 patients with chronic obstructive pulmonary disease (COPD) in five different centers. Annual change in lung density was 1.31 g/L/year (CI 95%: −2.12 to −0.50 HU, $p = 0.0015$, 39.5 mL/year (CI 95%: −100.0–21.0 mL, $p = 0.2$) for FEV_1 (−39.5 mL) and 24.3 μmol/min/kPa/L/year for gas transfer (CI 95%: −61.0–12.5 μmol/min/kPa/L/year, $p = 0.2$). Signal-to-noise ratio (mean change divided by standard error of the change) for the detection of annual change was 3.2 for lung densitometry, but 1.3 for both FEV_1 and gas diffusion. We conclude that detection

*Corresponding author. Tel.: +31 71 5262950; fax: +31 71 5266927.
E-mail address: j.stolk.long@lumc.nl (J. Stolk).

0954-6111/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.rmed.2007.04.016

of progression of emphysema was found to be 2.5-fold more sensitive using lung densitometry than by using currently recommended lung function parameters. Our results support CT scan as an efficacious test for novel drugs for emphysema.

Introduction

Pulmonary emphysema is a component of chronic obstructive pulmonary disease (COPD), which has an increasing prevalence worldwide.[1] The forced expiratory volume in 1 s (FEV_1) is traditionally used to quantify disease progression in COPD and emphysema.[2] It is also seen as the most important outcome parameter for the assessment of treatment efficacy of new drugs for this condition.[1] Over the past 10 years, only a few studies have been conducted on the effects of medical treatment of emphysema. However, the cessation of smoking has proved to be the only way to achieve a clinically significant effect on FEV_1.[3–6] A single efficacy measure (such as FEV_1) may not be the optimal outcome parameter for the assessment of treatment effects of the various disease components of COPD (such as chronic bronchitis, small airways disease and emphysema) in therapeutic trials of specific disease modifying drugs and consequently, there is a need for more specific and sensitive parameters.[1]

The introduction of computed tomography (CT) in the field of medical imaging was a major step forward for the diagnosis of emphysema.[7] Cross-sectional studies on quantitative aspects of CT images of the lung, demonstrated the possibility of computerized detection of emphysema and quantitative scoring.[8–10] A common approach is to detect the lung contour in the CT-data and to calculate the frequency distributions of densities, expressed in Hounsfield units, within the identified lung regions.

Based on the strong correlation between quantitative pathological scores and CT-derived quantitative densitometry scores of emphysema in cross-sectional human studies, the assessment of changes in lung density appears to be a promising alternative to lung function parameters.[8–10] The aim of the present study was to assess in a multi-center study, the natural progression of emphysema by measuring change in lung density and changes in FEV_1 and K_{CO} (carbon monoxide gas diffusion coefficient) and determine the sensitivity of these measurements in a patient population with a wide range of emphysema progression.

Methods

Patient population

Five university hospital centers participated in this study and recruited a total of 144 patients through advertisement. Patients were included if they had been diagnosed with emphysema by a high-resolution CT scan and had dyspnea on exertion.[11] Patients with concomitant disease that would prevent the completion of study duration were excluded. All available medication for COPD, including long-acting beta-agonists and tiotropium bromide were allowed. None of the patients diagnosed with homozygous type Z alpha-1-antitrypsin deficiency were receiving alpha-1-antitrypsin augmentation therapy. The study was approved by the institutional review board of each participating center. Patients provided written informed consent.

Study design

The study had a longitudinal design and consisted of two visits, one at baseline and a second after 30 months. At each visit a chest CT scan and post-bronchodilator pulmonary function tests, including spirometry and carbon monoxide gas transfer, were performed (see Characterization of Subjects in online data supplement). Smoking status was confirmed at start and end of the study by cotinine assay of a urine sample.

Computed tomography (CT)

Each of the five participating centers used a different CT scanner. There were four multi-detector scanners (General Electric, Marconi (now Philips), Siemens and Toshiba) and one single detector scanner (Philips AVE). All CT scanners were calibrated for water (with a standard phantom) and for air. In addition, a dedicated phantom was used to check the constancy of the CT scanner during the study period (see CT Quality Control Using Phantom Scans in online data supplement).

During each visit, every patient was scanned twice, at different inspiration levels (one scan after breath hold at full inspiration and one after a voluntary lower level of inspiration). Images were acquired in the supine position with CT settings that allow low radiation dose and high density resolution.[12] A specific acquisition protocol for each scanner has been provided elsewhere.[13] Typically, the acquisition protocol comprised 140 kVp, 40 mAs, pitch factor 1.5, 5 mm collimation, reconstructed with a slice thickness of 5 and 2.5 mm increment and a smooth reconstruction filter for both patients and the phantom.

Densitometry

All CT images were analyzed using densitometry with PulmoCMS (Medis, medical imaging systems, Leiden, the Netherlands).[13] The 15th percentile point (Perc15) was chosen in this study for the assessment of emphysema progression as previously recommended.[12] The Perc15 is defined as the threshold value in Hounsfield units (HU) for which 15 percent of all lung voxels has a lower density value.

Statistical analysis

Analysis of outcome parameters was performed for each participating site, using a mixed-effects regression model with density as outcome and lung volume and time of CT scans as both fixed and random (per patient) variables. Lung volume derived from the CT images was log-transformed to achieve normal distribution, and mean-centered to improve numerical stability. An error distribution with unstructured correlation was used in order to correct for autocorrelation (see Volume Correction in online data supplement).

The progression estimates for each site and their standard errors were then combined using meta-analysis with the software package "R" (the R-project, Statistics Department of the University of Auckland, NZ) with random effects, to account for possible heterogeneity in CT results due to study-site specific differences in either the patient populations or CT equipment.[14]

The meta-analysis approach was also used for progression in FEV_1 and K_{co}, but the site-specific estimates and standard errors were obtained simply by calculating mean and standard errors of the standardized (by the number of years of follow-up) differences between follow-up and baseline for each site.

The signal-to-noise ratio in detecting the annual change of an outcome parameter, was defined as the mean change divided by the standard error of the change, and was calculated for densitometry, FEV_1 and K_{co}.[5]

Data are presented as mean and 95% confidence intervals where appropriate. The correlation between parameters was calculated by Pearson's correlation coefficient. All tests were two-sided, for which an alpha level of 0.05 was considered to indicate statistical significance.

Results

Baseline results

A total of 144 patients were recruited for the study (Table 1a). The correlation between the baseline CO diffusion coefficient and lung density was 0.639 ($p<0.001$) and 0.586 between baseline FEV_1 and lung density ($p<0.001$) (Table 2). The correlation between the CO diffusion coefficient and baseline FEV_1 was 0.413 ($p<0.001$) (Table 2). There was no correlation between age and baseline lung density (-0.069, $p=0.414$). The average time between diagnosis of emphysema and first study visit was 3 ± 1 year.

Progression of emphysema

During the study period a number of patients were lost for follow-up. Ten patients died, four patients had lung transplantation or lung volume reduction surgery and 19 patients refused to attend for follow-up. The data of a single site that contributed 23 patients to the study could not be used (see Figure E1-A and E1-B in online data supplement). Baseline patient characteristics of the remaining 87 patients are shown in Table 1b.

Lung density decreased significantly by 1.31 g/L/year (CI 95%: -2.12 to -0.50 HU, $p=0.0015$, Fig. 1), while FEV_1 decreased by 39.5 mL/year (CI 95%: -100.0–21.0 mL, $p=0.2$, Fig. 2) and the gas diffusion coefficient by 24.3 μmol/min/kPa/L/year (CI 95%: -61.0–12.5 μmol/min/kPa/L/year, $p=0.2$, Fig. 3 and Tables 2 and 3). When the study population was divided into subjects with type ZZ alpha-1-antitrypsin deficiency and non-ZZ deficiency, the decrease in FEV_1 and K_{co} did not differ significantly between groups (Table 4).

The signal-to-noise ratio (defined as the mean change divided by the standard error of the change) in detecting annual change was 3.2 for lung densitometry, but 1.3 for both FEV_1 and the gas diffusion coefficient (Table 3).

Baseline results and progression

There was a weak correlation between FEV_1 and lung density at study baseline and subsequent annual change in gas diffusion ($r=0.213$, $p=0.027$; $r=0.215$, $p=0.025$, respectively). The annual change in lung density or FEV_1 was independent of the severity of emphysema at study baseline when expressed as baseline values for lung density, FEV_1 or CO diffusion coefficient (Table 2). In addition, changes in density and changes in lung function (FEV_1 or diffusion coefficient) were not, or only weakly linked (Table 2). No correlation was found between changes in lung density and age ($r=-0.040$, $p=0.711$).

Discussion

In COPD and emphysema, the rate of FEV_1 decrease is traditionally used to quantify disease progression and the efficacy of new drugs.[2] A single surrogate measure for multiple phenotypic disease components of COPD (such as chronic bronchitis, small airways disease and emphysema) may not be optimal for assessing treatment effects in therapeutic trials with specific disease-modifying drugs. Consequently, there is a challenge to develop emphysema-specific and more sensitive parameters.[15] We report that lung density is 2.5-fold more sensitive than FEV_1 or gas diffusion to detect progression of emphysema.

Few randomized placebo-controlled medicinal intervention strategies for COPD and only one intervention strategy for emphysema showed sensitivity for change in the rate of decline in FEV_1.[3–6] Whereas FEV_1 is a measure of both airway wall thickening and collapse of the small airways due to loss of elastic recoil in the lung lobes, lung density is a more specific reflection of airspace enlargement by alveolar destruction present in emphysema.[8–10,16] This difference in pathological correlation may explain the poor correlation between the rate of decrease in lung density and FEV_1 or K_{co} in our study population (Table 2). Based on the sensitivity (or signal-to-noise ratio) of our progression parameters, this lack of correlation can be explained by significant differences in the signal-to-noise ratios of the three measurements.[17] It has been demonstrated that measurements such as FEV_1 and K_{co} are relatively insensitive to changes in end-stage COPD and emphysema.[2,4] Yet, the histopathology of end-stage disease still contains signs of active inflammation rather than of resolution.[18] In contrast to FEV_1 and K_{co}, lung densitometry is able to detect disease progression in severe emphysema as supported by our finding that decreases in lung density were not associated with the severity of

Table 1a Characteristics of 144 patients at study baseline.

	Absolute[a]	Predicted (%)	Range (% predicted)
Sex male/female	75/69	–	–
Age [yr]	58.5 (11.1)	–	–
Alpha-1-antitrypsin phenotype (ZZ/non-deficient)	79/65	–	–
Smoking status [c/e/n][b]	42/70/32	–	–
FEV_1 [L]	1.59 (0.9)	54.8 (26.9)	20–115
FEV_1/FVC [%]	0.43 (0.12)		24–86
K_{co} [mmol/min/kPa/L]	0.96 (0.4)	63.4 (22.5)	19–109
Urine cotinine assay positive	37/144	–	–
Inhaled corticosteroid use	122/144	–	–
Inhaled LABA use[c]	135/144	–	–
Inhaled tiotropium use	103/144	–	–

[a]Mean values (SD).
[b]c/e/n means current/ex/never smoker.
[c]Long-acting beta agonist.

Table 1b Characteristics of 87 patients at study baseline, included in analysis of progression.

	Absolute[a]	Predicted (%)	Range (% predicted)
Sex male/female	44/43	–	–
Age [yr]	58.6 (10.4)	–	–
Alpha-1-antitrypsin phenotype (ZZ/non-ZZ)	53/34	–	–
Smoking status [c/e/n][b]	24/47/16	–	–
FEV_1 [L]	1.45 (0.6)	50.2 (19.2)	20–115
FEV_1/FVC [%]	0.45 (0.13)		24–86
K_{co} [mmol/min/kPa/L]	0.90 (0.3)	60.8 (19.8)	19–109
Urine cotinine assay positive	24/87	–	–
Inhaled corticosteroid use	79/87	–	–
Inhaled LABA use[c]	85/87	–	–
Inhaled tiotropium use	84/87	–	–

[a]Mean values (SD).
[b]c/e/n means current/ex/never smoker.
[c]Long-acting beta agonist.

emphysema present at study baseline (expressed by FEV_1 or K_{co}). Indeed, the rationale behind the development of CT densitometry was to overcome rather than reflect the deficiencies of FEV_1 and the lack of correlation between these two should not necessarily be interpreted as disadvantageous. On the contrary, it supports the concept that lung densitometry is a more appropriate method for monitoring progression of emphysema.

The calculation of the progression of lung density decrease is subject to various confounders. Firstly, the relationship between lung density and the inhaled volume of air in the lung during the scan must be accounted for.[19] In addition lung density is dependent on lung size. Large lungs have a lower density than small lungs.[19] Therefore, in order to compare individuals, lung densities need to be corrected for lung volume.[20] Secondly, CT scanners from different vendors use different software for image-reconstruction which results in different density distributions.[21] We addressed these issues in a separate study by comparing three different mathematical models to characterize the optimal correction of density for lung volume (submitted for publication). We found that a combined estimate approach was needed to allow pooling of the mean of density values of four study centers.

Our study population had a wide range of values in FEV_1 and CO diffusion capacity indicating a range from mild to severe emphysema. The latter may also explain the relatively low annual decrease in FEV_1 of 45 mL measured over a relatively short period of time.[22] The contribution of emphysema to the rate of increase of airflow limitation remains uncertain, mainly because of the absence of longitudinal studies delineating the alveolar and airway components that contribute to FEV_1 values.

In cross-sectional studies, measurements of CO diffusion capacity correlate well with pathological scores of emphysema and therefore CO diffusion measurements qualify as a progression parameter for emphysema.[9] Few previous studies have followed individuals with regular measurements of gas transfer for sufficiently long periods of time to be able to describe the rate of decrease in patients with

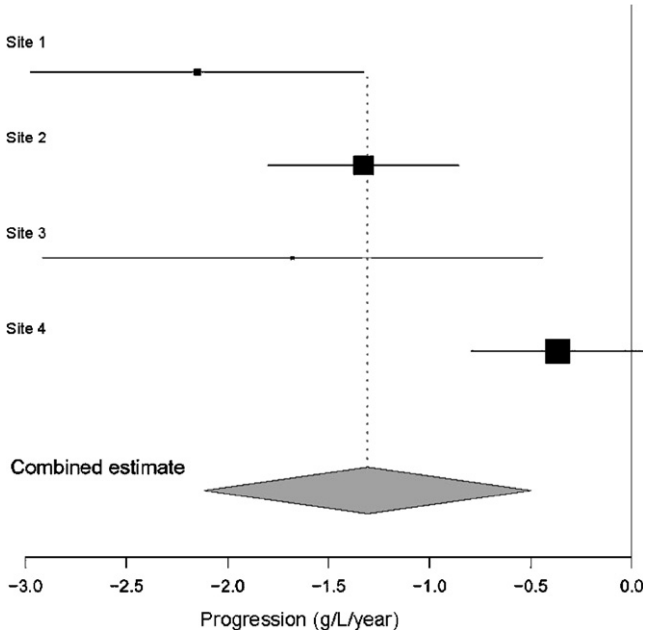

Figure 1 Progression of emphysema measured using densitometry. Annual change in lung density (g/L) of patients with emphysema measured at four different study centers. Values are mean change and 95% confidence interval. The combined estimate represents the mean change of patients of all four sites and its 95% confidence interval. The weight with which the data of each site contribute to the combined estimate is represented by the size of the square markers.

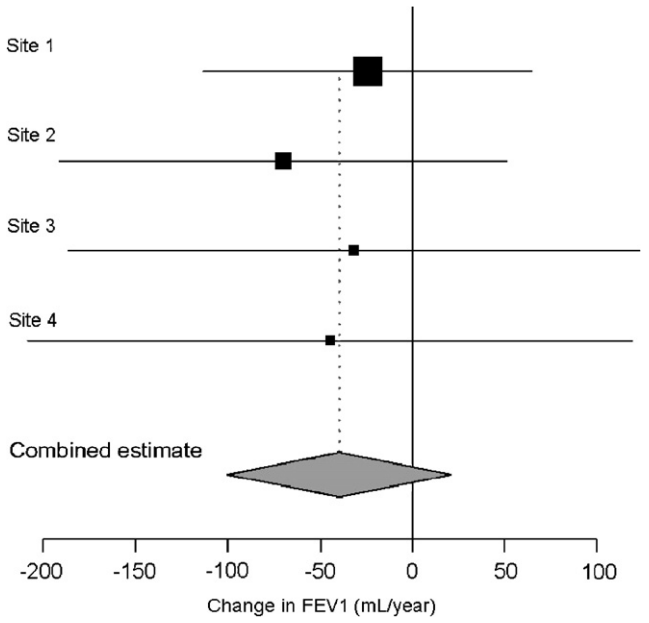

Figure 2 Progression of emphysema measured using FEV_1. Annual change in FEV_1 (mL) of patients with emphysema measured at four different study centers. Values are mean change and 95% confidence interval. The combined estimate represents the mean change of patients of all four sites and its 95% confidence interval. The weight with which the data of each site contribute to the combined estimate is represented by the size of the square markers.

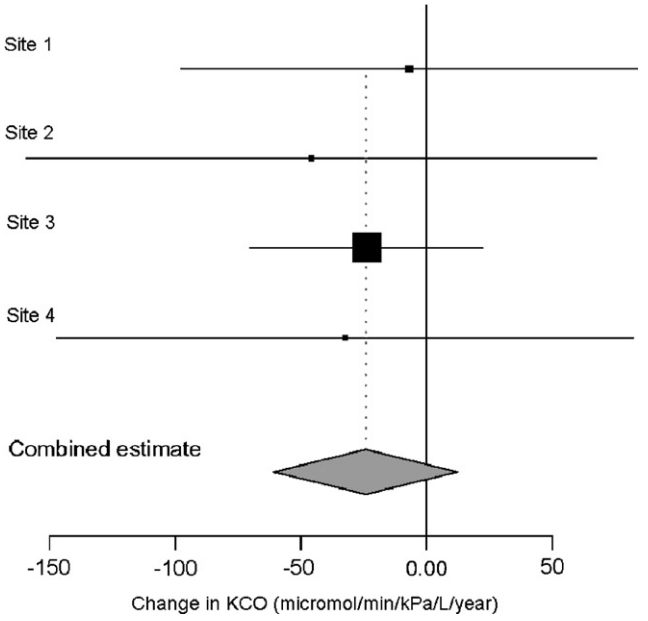

Figure 3 Progression of emphysema measured using CO diffusion capacity. Annual change in K_{co} (μmol/min/kPa/L) of patients with emphysema measured at four different study centers. Values are mean change and 95% confidence interval. The combined estimate represents the mean change of patients of all four sites and its 95% confidence interval. The weight with which the data of each site contribute to the combined estimate is represented by the size of the square markers.

moderate-to-severe emphysema.[5,23,24] We designed our study to last for 30 months, a period of time that is likely to be the maximal duration that is acceptable for both patients and pharmaceutical companies to investigate a beneficial effect of a new investigational drug. In addition, little is known about how the direction of change in CO transfer relates to change in FEV_1. In one small study, carried out over 22 years, men with an initially reduced CO transfer coefficient had significantly faster subsequent decrease in FEV_1.[24] In contrast, analysis of 543 subjects who participated in the Tucson epidemiology study revealed that the slope of DL_{co} was not significantly different between smokers and never smokers.[3] Moreover, higher results for FEV_1 at study baseline were not associated with different DL_{co} slopes.[3] We found that changes in K_{co} (DL_{co} proportional to ventilating lung area) and changes in FEV_1 correlated only very weakly with baseline FEV_1 and baseline K_{co}, respectively (Table 2). In addition, the changes in FEV_1 and the changes in K_{co} correlated weakly with baseline lung density. However, none of the changes with time correlated with each other (Table 2). Taken together, the published results and our own findings indicate that change in gas diffusion capacity, airflow and lung density in patients with emphysema occur independently from the level measured at study baseline.

This study has some limitations: patients were selected based on the presence of emphysema identified using high resolution CT. Because the gold standard for emphysema diagnosis is based on pathological examination of lung tissue, the presence of emphysema seen by a pathologist

Table 2 Pearson correlations (including *p*-value) of density (Perc15) and lung function parameters (FEV_1 and K_{co}).

	Baseline FEV_1	Baseline K_{co}	Change Perc15	Change FEV_1	Change K_{co}
Baseline Perc15	0.586 ($p \ll 0.001$)	0.639 ($p \ll 0.011$)	−0.049 ($p = 0.652$)	0.182 ($p = 0.054$)	0.215 ($p = 0.025$)
Baseline FEV_1		0.413 ($p \ll 0.001$)	0.123 ($p = 0.257$)	−0.043 ($p = 0.655$)	0.213 ($p = 0.027$)
Baseline K_{co}			0.088 ($p = 0.420$)	0.175 ($p = 0.066$)	0.134 ($p = 0.165$)
Change Perc15				0.166 ($p = 0.123$)	−0.083 ($p = 0.451$)
Change FEV_1					0.049 ($p = 0.615$)

Table 3 Progression of emphysema of 87 patients.

Center	Number of patients	Change in density (g/L/year)	Change in FEV_1 (mL/year)	Change in K_{co} (μmol/min/kPa/L/year)
1	19	−2.15 (0.41)	−24.1 (45.4)	−7.0 (46.4)
2	34	−1.33 (0.24)	−70.1 (61.9)	−45.9 (57.9)
3	17	−1.68 (0.62)	−31.7 (78.9)	−23.8 (23.6)
4	17	−0.37 (0.21)	−44.6 (83.7)	−32.5 (58.5)
Combined estimate of centers 1–4	87	−1.31 (0.40)	−45.8 (30.9)	−30.9 (18.7)
95% CI		(−2.12; −0.50)	(−100.0; 21.0)	(−61.0; 12.5)
P-value		0.0015	0.2	0.2
Signal/noise ratio		3.2	1.3	1.3

Values of change are presented as mean and (standard error). FEV_1, forced expiratory volume in 1 s; K_{co}, carbon monoxide gas diffusion coefficient; 95% CI, 95% confidence interval, sensitivity defined as mean divided by standard error of mean.

Tabel 4 Progression of emphysema related to alpha-1-antitrypsin deficiency.

Alpha-1-antitrypsin fenotype	Number of patients	Change in density (g/L/year)	Change in FEV_1 (mL/year)	Change in K_{co} (μmol/min/kPa/L/year)
ZZ	53	NA	−48.2 (70.6)	−29.5 (49.3)
Non-ZZ, non serum deficient	33	NA	−42.1 (63.7)	−32.9 (54.8)

Values of change are presented as mean and standard deviation. NA, not applicable. Similar comparison of analysis for density values could not be performed reliably due to the significant heterogeneity of the density data between study centers.

and the characteristics of emphysema seen on HRCT by a radiologist may not always be the same.[8,9,11] Therefore, it is possible that some of our participants may have been misclassified as emphysema patients. Likewise, the correlation between the pathological score for emphysema and lung density scores of CT images published in the literature is at best 0.77.[9] The latter suggests that not all patients with a low Perc15 value have emphysema to the same extent. Therefore, the estimates of progression of emphysema may be subject to some error although if anything this may underestimate the true sensitivity of the density progression.

Finally, we assumed that progression of our lung density parameter is linear over time. This assumption was based on the results of a previous study, in which annual CT and lung densitometry showed almost linear decrease in lung density in 28 placebo-treated patients.[5] The general applicability of the data and methodology to all patients with emphysema could be debatable. However, subgroup analysis showed that there was no significant difference between emphysema patients with and those without type Z alpha-1-antitrypsin deficiency when analyzed for decrease in FEV_1 or K_{co}. Similar comparison of analysis for density values could not be performed reliably due to a combination of low patient numbers and the significant heterogeneity of the density data between study centers.

In summary, we studied a group of patients with a wide range of lung function impairment and found that assessment of emphysema progression was more sensitive when CT-derived lung densitometry was used compared to FEV_1 and measurements of gas transfer. The rate of lung density decrease was independent of the severity of emphysema at study baseline. The results support this methodology for testing the efficacy of novel drugs for emphysema.

Acknowledgments

The study was supported by Grants from the Fifth Framework Program of the European Commission (Project number QLG1-2000-01752 (JS and BCS) and the Swiss Science Foundation (EWR). The sponsor had no involvement in any part of this study.

Conflict of interest statement

All authors of this manuscript declare to have no conflict of interest concerning the content of this manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.rmed.2007.04.016.

References

1. Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). *Lancet* 2004;**364**: 613–20.
2. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J* 1997;**1**:1645–8.
3. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1. *J Am Med Assoc* 1994;**272**:1497–505.
4. Decramer M, Rutten-van Molken M, Dekhuijzen PN, Troosters T, van Herwaarden C, Pellegrino R, et al. Effects of N-acetylcysteine on outcome in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet* 2005;**365**: 1552–60.
5. Dirksen A, Dijkman JH, Madsen F, Stoel BC, Hutchison DC, Ulrik CS, et al. A randomized clinical trial of alpha-1-antitrypsin augmentation therapy. *Am J Respir Crit Care Med* 1999;**160**: 1468–72.
6. Rabe KF, Bateman ED, O'Donnell D, Witte S, Bredenbroker D, Bethke TD. Roflumilast–an oral anti-inflammatory treatment for chronic obstructive pulmonary disease (COPD). *Lancet* 2005; **366**:563–71.
7. Hayhurst MD, MacNee W, Flenley DC, Wright D, McLean A, Lamb D, et al. Diagnosis of pulmonary emphysema by computerised tomography. *Lancet* 1984;**2**:320–2.
8. Gevenois PA, DeVuyst P, de Maertelaer V, Zanen J, Jacobovits D, Cosio MG, et al. Comparison of computed density and microscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med* 1996;**154**:187–92.
9. Gould GA, MacNee W, McLean A, Warren PM, Redpath A, Lamb D, et al. CT measurements of lung density in life can quantitate distal airspace enlargement—an essential defining feature of human emphysema. *Am Rev Respir Dis* 1988;**137**:380–92.
10. Coxson HO, Mayo JR, Behzad H, Moore BJ, Verburgt LM, Staples CA, et al. Measurement of lung expansion with computed tomography and comparison with quantitative histology. *J Appl Physiol* 1995;**79**:1525–30.
11. Muller NL. Chronic obstructive pulmonary disease-4: imaging the lungs in patients with chronic obstructive pulmonary disease. *Thorax* 2002;**57**:982–5.
12. Newell JD, Hogg JC, Snider GL. Report of a workshop: quantitative computed tomography scanning in longitudinal studies of emphysema. *Eur Respir J* 2004;**23**:769–75.
13. Bakker ME, Stolk J, Putter H, Shaker SB, Parr DG, Piitulainen E, et al. Variability in densitometric assessment of pulmonary emphysema with computed tomography. *Invest Radiol* 2005; **40**:777–83.
14. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**:177–88.
15. Barnes PJ, Stockley RA. COPD: current therapeutic interventions and future approaches. *Eur Respir J* 2005;**25**:1084–106.
16. Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. *N Engl J Med* 1968;**278**:1355–60.
17. Rousson V, Gasser T, Seifert B. Assessing intrarater, interrater and test-retest reliability of continuous measurements. *Statist Med* 2002;**21**:3431–6.
18. Hogg JC, Chu F, Utokaparch S, Woods R, Elliot WM, Buzatu L, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004;**350**: 2645–53.
19. Rosenblum LJ, Mauceri RA, Wellenstein DE, Thomas FD, Bassano DA, Raasch BN, et al. Density patterns in normal lung as determined by computed tomography. *Radiology* 1980;**137**: 409–16.
20. Dirksen A, Friis M, Olesen KP, Skovgaard LT, Sorensen K. Progress of emphysema in severe alpha-1-antitrypsin deficiency as assessed by annual CT. *Acta Radiol* 1997;**38**:826–32.
21. Kemerink GJ, Kruize HH, Lamers RJ, van Engelshoven JM. Density resolution in quantitative computed tomography of foam and lung. *Med Phys* 1996;**23**:1697–708.
22. Tager IB, Segal MR, Speizer FE, Weiss ST. The natural history of forced expiratory volumes effect of cigarette smoking and respiratory symptoms. *Am Rev Respir Dis* 1988;**138**: 837–49.
23. Sherrill DL, Enright PL, Kaltenborn WT, Lebowitz MD. Predictors of longitudinal change in diffusing capacity over 8 years. *Am J Respir Crit Care Med* 1999;**160**:1883–7.
24. Watson A, Joyce H, Pride NB. Changes in carbon monoxide transfer over 22 years in middle-aged men. *Respir Med* 2000;**94**:1103–8.