Chapter 7

Monitoring of smoking-induced emphysema with multidetector-row computed tomography in a lung cancer screening setting: What is the minimum increase in emphysema scores required to distinguish real increase in extent of emphysema from interscan variability?

Hester Gietema
Arnold Schilham
Bram van Ginneken
Rob van Klaveren
Jan-Willem Lammers
Mathias Prokop

Accepted for publication in Radiology

ABSTRACT

PURPOSE

To retrospectively establish the minimum increase in emphysema scores (ES) required for detection of real increase in extent of emphysema with 95% confidence, using multidetector-row computed tomography (MDCT) in a lung cancer screening setting.

MATERIAL AND METHODS

The trial was approved by the Dutch ministry of health and by the ethics committee of each participating hospital. For our part of the study a waiver was received. Of the 1684 men screened at our hospital with low-dose MDCT (30mAs; 16 x 0.75mm collimation) between April 2004 and March 2005, we included only participants, who underwent repeat MDCT after three months on the same CT-scanner because of an indeterminate pulmonary nodule. Extent of emphysema was considered to remain stable in this short period. Extent of low-attenuated areas representing emphysema was computed for repeat and baseline scans as percentage of lung volume below three attenuation thresholds (-910HU, -930HU and -950HU). Limits of agreement were determined with the Bland-and-Altman approach and upper limits were used to deduce the minimum increase in ES required for detecting increase in extent of emphysema with 95% probability. Factors influencing the limits of agreement were determined.

RESULTS

In total 157 men (52-77y, mean 60y) were included in our study. The limits of agreement for differences between repeat and baseline scans were -13.4% to +12.6% at -910HU, -4.7% to +4.2% at -930HU and -1.3% to +1.1% at -950HU (percentages of total lung volume). Differences in ES showed weak to moderate correlation with variation in level of inspiration ($r=0.20$ to $r=0.49$, $p<0.05$). Scanner calibration could be excluded as factor contributing to variation in ES.

CONCLUSION

Increase in ES required to detect increase in extent of smoking-related emphysema with 95% probability varies between 1.1% at -950HU and 12.6% of total lung volume at -910HU for low-dose MDCT.

INTRODUCTION

To our knowledge, the most frequently used computer-based method to detect emphysema on CT is highlighting and quantifying low-attenuated areas [1-3], first described by Müller et al [4]. Disappearance of lung tissue produces a relative increase of air within a voxel, which results in a lowered attenuation within the voxel. The percentage volume of the highlighted voxels can be calculated relative to total lung volume, resulting in a voxel index or emphysema score (ES) in the range from 0% to 100%.

Presently there are several ongoing lung cancer screening trials [5-8]. Since lung cancer and emphysema share smoking as the main risk factor, CTs performed in these trials may provide suitable data for studying the prevalence and natural course of smoking-related emphysema in relatively healthy participants [9]. These data could be used to select groups of smokers in whom more aggressive risk-modifying treatment is necessary to prevent development of severe lung destruction and airflow limitation. Before an automated method can be used for screening and monitoring purposes, more information about an issue as interscan variation and the effect of factors that have been shown to influence emphysema scores, such as level of inspiration [10] and scanner calibration [11], is required. Data about the interscan variation are useful to distinguish real progression of the extent of emphysema from measurement variation.

Thus, the aim of our study was to retrospectively establish the minimum increase in emphysema scores required for detection of real increase in extent of emphysema with 95% confidence using multidetector-row computed tomography (MDCT) in a lung cancer screening setting.

MATERIALS AND METHODS

PARTICIPANTS

The NELSON-project is a population-based randomized Dutch-Belgian multi-center lung cancer screening trial that studies 16,000 current and former heavy smokers. The trial was approved by the Dutch ministry of health and by the ethics committee of each participating hospital. For our part of the study a waiver was received. Selection of participants was performed by sending a questionnaire about smoking history and other health-related issues to citizens between 50 and 75 years of age who lived in the areas around the participating centers. Among the respondents, subjects meeting the inclusion criteria of a minimum of 16 cigarettes/day for 25 years or 11 cigarettes/day for 30 years were asked to participate in the trial. Since men had a better chance to meet this inclusion criterion having smoked this minimum number of cigarettes during their life, we started to recruit men. After being informed about, among others, the radiation dose that was exposed to the participants, those who gave written informed consent were equally randomized to either the screening arm or the control arm. Participants in the screening arm underwent baseline CT to assess the prevalence of lung cancer in this population and will undergo two further CT scans in years two and four to establish the one year and three year incidence of lung cancer in this population. Participants with a moderate or poor self-reported health status who were unable to climb two flights of stairs were excluded from participation.

Between April 2004 and March 2005, 1684 male participants received baseline screening in our center. From these participants, we included all participants who, according to the trial protocol, received a short-term repeat chest CT after three months because of an indeterminate nodule (50-500mm^3) found on the baseline scan. Extent of emphysematous lung destruction was considered to remain stable in this short period. To test this assumption, results of pulmonary function tests, performed in subgroup of the investigated population on the same days as the baseline and repeat CTs were performed, were compared. No medical intervention was applied. Since CT scans were performed on various 16-detector-row scanners, we selected only participants scanned twice on the same scanner.

CT SCANNING

Scanning was performed using 16-detector-row CT (either one of two Mx8000 IDT scanners or one Brilliance 16P scanner, Philips Medical Systems, Cleveland, OH). All scans were realized in about 12 seconds in helical mode with 16 x 0.75mm collimation and 15mm table feed per rotation (pitch = 1.3), in a caudo-cranial scan direction to minimize breathing artifacts. Participants were asked to take a deep breath and to hold their breath. No spirometric gating was applied because spirometric gating is not standard in a lung cancer screening setting and spirometric gating would therefore make the results less applicable in a standard lung cancer screening setting. No intravenous contrast was injected. Exposure settings were 30mAs at 120kVp for patients weighing ≤80kg, and 30mAs at 140kVp for those weighing more than 80kg without dose modulation. All participants received the same radiation dose during both scans. Axial images of 1.0mm thickness were reconstructed at 0.7mm increment, using the smallest field of view (FOV) that included the outer rib margins at the widest dimension of the thorax. All scans were reconstructed with a 512x512 matrix and a moderately soft "B" kernel.

EMPHYSEMA QUANTIFICATION

Data were transferred from the CT scanner to a digital workstation. The extent of low-attenuated areas was fully automated for quantification with in-house developed software. Total lung volume was calculated using the following steps. Firstly, segmentation of trachea, left and right lung was performed by a region growing program starting in the trachea, which included all connected areas below -500HU. In a second step, trachea and main bronchi were separated from the lungs. The algorithm is similar to the one described by Hu et al [12]. After segmenting the lung, the data were subjected to a median noise-reducing filter [13].
The extent of low-attenuation areas was determined by computing lung volume with CT attenuation below a certain attenuation threshold as percentage of total lung volume. We studied the three attenuation thresholds often mentioned in literature: -910HU, -930HU and -950HU [4;14-16].

Influence of Level of Inspiration

CT numbers of voxels representing the lungs are lowered when a participant reaches a higher level of inspiration due to increasing relative amount of air per voxel as described by Kalender et al. [17]. So, the extent of low-attenuated areas increases not only when the extent of emphysema increases, but also when a participant reaches a deeper level of inspiration during a repeat scanning than in baseline scanning. For this reason, the correlation between natural variation in level of inspiration of baseline and repeat scan of each participant and changes in emphysema scores was evaluated. Total lung volume as calculated from each scan was used as surrogate for level of inspiration.

Quality Control

Since the method of highlighting and quantifying low-attenuated areas starts from a fixed threshold, the method is sensitive to CT number shifts due to, for example, X-ray tube ageing. We performed weekly air calibrations and completed the screening scans within 24 hours after calibration. In addition, we performed scans of a quality control phantom before and after each data acquisition session. This phantom consisted in a foam body (mimicking emphysematous areas) of 320mm in diameter including two cylinders, each 80mm in diameter (Figure 1). One cylinder contained air; the other cylinder was filled with plastic. The phantom was scanned at 120kVp with otherwise identical parameters as applied to the participants.

Average CT numbers for each structure were measured in a circular region of interest (ROI; 100mm^2) manually drawn by one observer (HG, three years of experience in radiology) in the center of both cylinders and in the periphery of the foam body, 2 cm from the outside border. We performed five scans of the phantom in one session at the start of the study and after three months in order to assess the variation in CT numbers within one session. Changes in average CT numbers within the ROI during the period of data collection were determined.

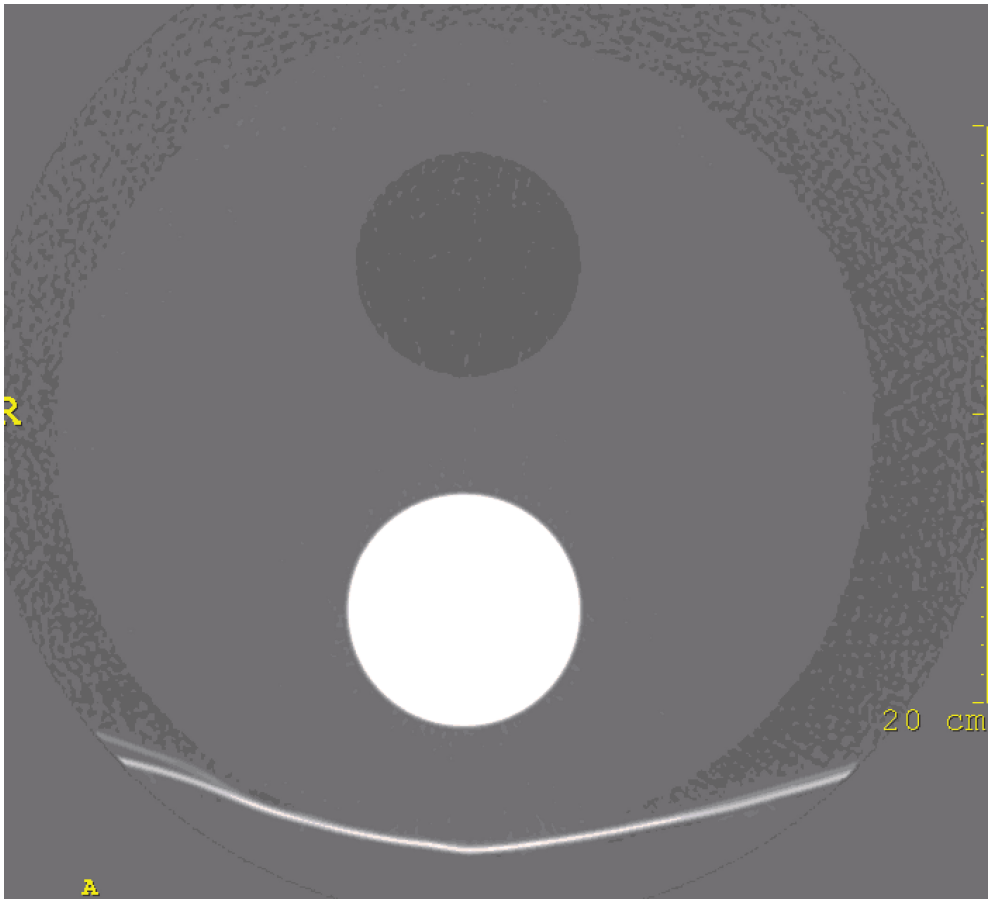


Figure 1

Phantom used to monitor CT-values during the study. The phantom consists in a foam body, 320 mm in diameter, and two free spaces of 80mm in diameter. One of the free spaces is filled with plastic, while the other contains only air.

STATISTICAL ANALYSIS

All statistical calculations were performed using SPSS statistical software release 13.0 (SPSS Inc, Chicago, Ill, USA). We calculated means, standard deviations (SD) and 95% confidence intervals (CI) for normal distributed differences in ES and medians and interquartile ranges for non-normal distributed emphysema scores. Changes in emphysema scores were given as percentages of total lung volume.
Forced expiratory volumes in one second (FEV_1) performed on the day of baseline scanning (FEV_{1A}) and on the day of repeat scanning (FEV_{1B}) were compared after logistic transformation:

$$e^{(\ln FEV1B - \ln FEV1A)} = (FEV_{1B}) / (FEV_{1A})$$

The results of ln (FEV_{1A}) and ln (FEV_{1B}) were compared using paired samples t-testing.
Differences in emphysema scores (ΔES) were calculated by subtracting the ES measured on the baseline scan (ES_1) from the ES measured on the repeat scan (ES_2). These differences were plotted against the mean of both ES, using the approach described by Bland and Altman [18]:

$$\Delta ES = \frac{ES_2 - ES_1}{(ES_2 + ES_1)/2}$$

Limits of agreement were given as 95% confidence intervals (CI). For monitoring purposes, an increase in emphysema score above these upper limits of agreement can, with 95% confidence, be attributed to real increase in extent of emphysema.
To asses the repeatability of the quantification of the extent of low-attenuated areas, we calculated coefficients of variation as ratio of the within subject SD to the mean of both measurements. In order to determine if these coefficients of variation were related to the extent of emphysema, represented by the mean of the two measurements, we calculated Spearman's correlation coefficient for each attenuation threshold.

Correlation coefficients between difference in total lung volumes and difference in emphysema scores for each pair of scans were best after logarithmic transformation of lung volumes as described by Shaker et al. [10]. We determined the corresponding Pearson's correlation coefficients for each attenuation threshold in order to assess if a correction factor for the level of inspiration could be calculated.
P-values <0.05 were considered significant.

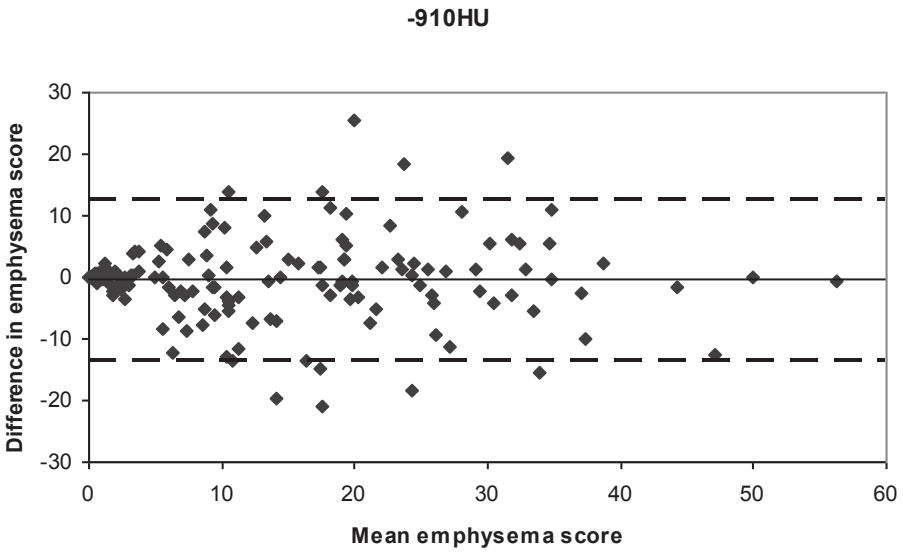
RESULTS

EMPHYSEMA SCORES

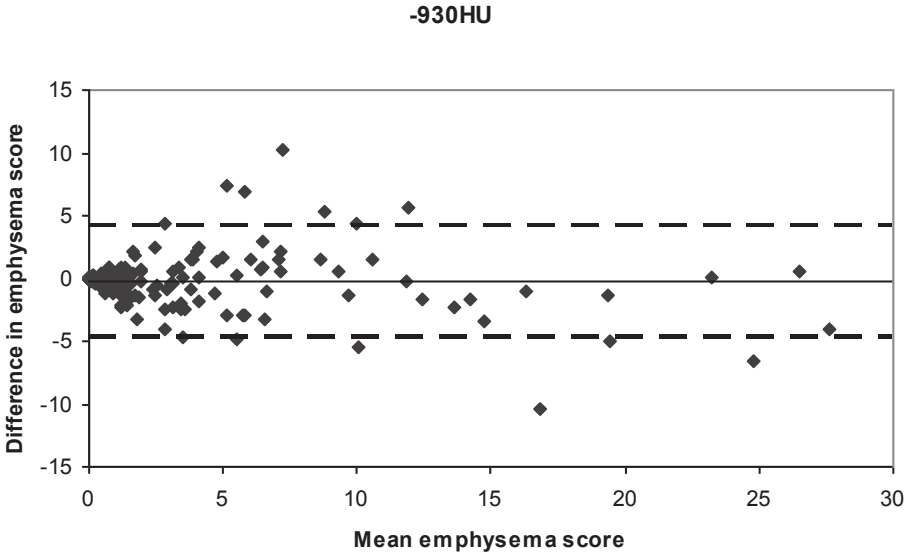
Between April 2004 and March 2005, 249 consecutive male participants underwent a baseline and a 3-month follow-up scan. The group of participants that received both scans on the same scanner included 157 participants (52-77 yrs, mean 60 yrs). These participants were further analyzed (Figure 2).

Sixty subjects underwent pulmonary function testing on the day of baseline scanning and again on the day of repeat scanning. The FEV_1 did not change significantly in the three months interval (p=0.311). The 95% confidence interval of the ratio of the FEV_1 during both tests ranged from 0.99 to 1.03, showing that the variation in FEV_1 was only 4% in this three months interval.

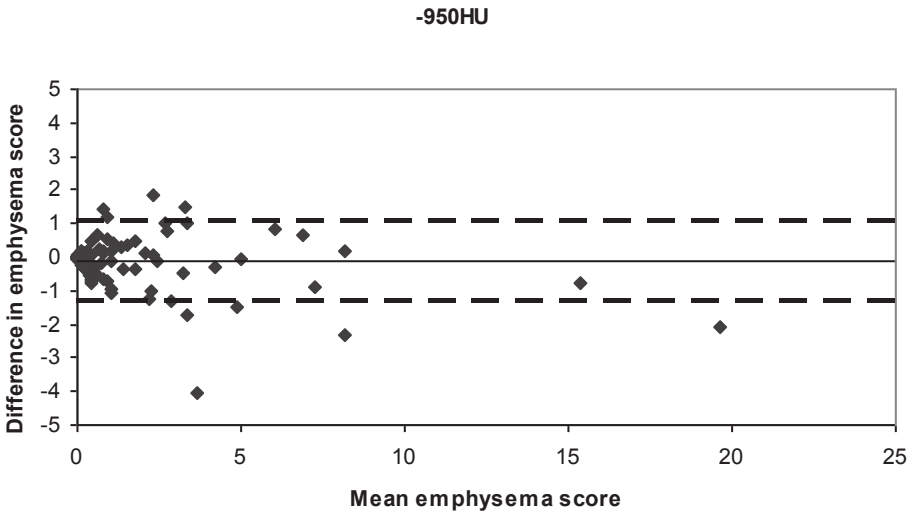
Emphysema scores ranged from 0.0% for volume with an attenuation below -950HU to 56.5% for volume with an attenuation below -910HU for baseline scans (Table 1). Median emphysema scores ranged from 0.08% for volume with an attenuation below -950HU for repeat scans to 11.8% for volume with an attenuation below -910HU for baseline scans (Table 1) . Coefficients of variation ranged from 0.0% to 141% and decreased with increasing extent of emphysema (Table 1). Mean difference in emphysema scores ranged from -0.1% for volume with an attenuation below -950HU to -0.41% for volume with an attenuation below -910HU for baseline scans (Figure 2).


-910HU
Difference in emphysema score
30
20
10
0
-10
-20
-30
0
10
20
30
40
50
60
Mean emphysema score

2A


-930HU
Difference in emphysema score
15
10
5
0
-5
-10
-15
0
5
10
15
20
25
30
Mean emphysema score

2B



2C

Figure 2

Bland-Altman plots for emphysema scores at -910HU (A), -930HU (B) and -950HU (C) The x-axes show the means of emphysema scores on the baseline scan and the repeat scan, the y-axes show emphysema scores on the repeat scan minus emphysema scores on the baseline scan expressed as percentage of total lung volume. The mean differences are shown by the continuous lines, the limits of agreement are shown by the dashed lines. An increase in emphysema score more than the upper limit of agreement or a decrease below the lower limit of agreement has an 95% likelihood to be a real progression or regression of emphysema.

	Threshold		
	-910HU	**-930HU**	**-950HU**
Baseline scan			
Median	11.8%	1.5%	0.17%
Interquartile range	2.7%-21.9%	1.3%-4.9%	0.05%-0.79%
Range	0.0%-56.5%	0.0%-29.7%	0.0%-20.7%
Repeat scan			
Median	8.9%	1.2%	0.08%
Interquartile range	2.3%-22.0%	0.17%-4.8%	0.02%-0.81%
Range	0.0%-55.8%	0.0%-26.8%	0.0%-18.6%
Difference			
Mean (95% confidence interval)	-0.41% (-13.4% to 12.6%)	-0.23% (-4.7% to 4.2%)	-0.1% (-1.3% to 1.1%)
Coefficient of variation			
Median	34%	23%	58%
Interquartile range	8%-55%	8%-35%	19%-98%
Range	0.0%-139%	0.0%-69%	0.0%-141%
Spearman's correlation coefficient	-0.42	-0.42	-0.34

Table 1

Emphysema scores for the study population. The emphysema scores describe the percentage of lung tissue below the designated threshold. Differences represent percentages of total lung. volume. Coefficients of variation represent percentage of the mean score for an individual at a designated threshold. Note that the correlation between coefficient of variation decreases with increasing extent of emphysema as shown by Spearman's correlation coefficients ($p<0.0001$ for all thresholds).

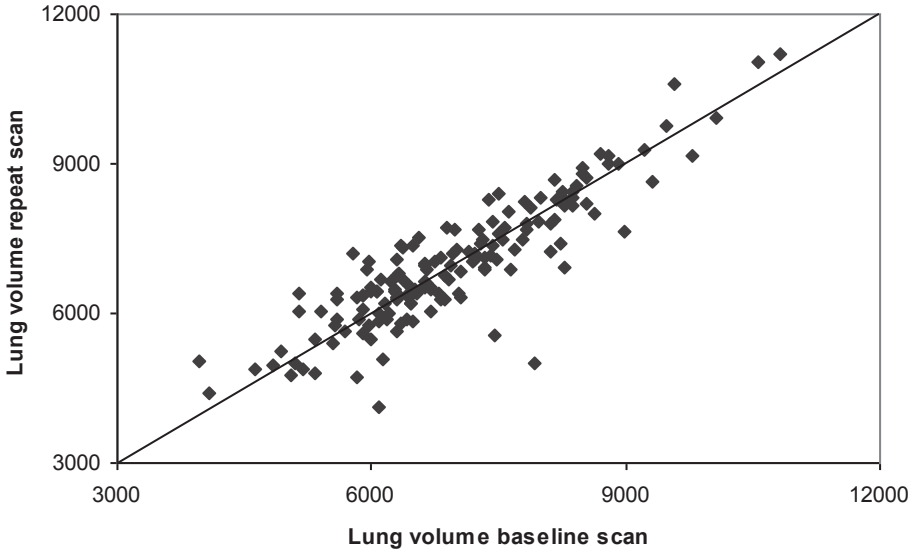
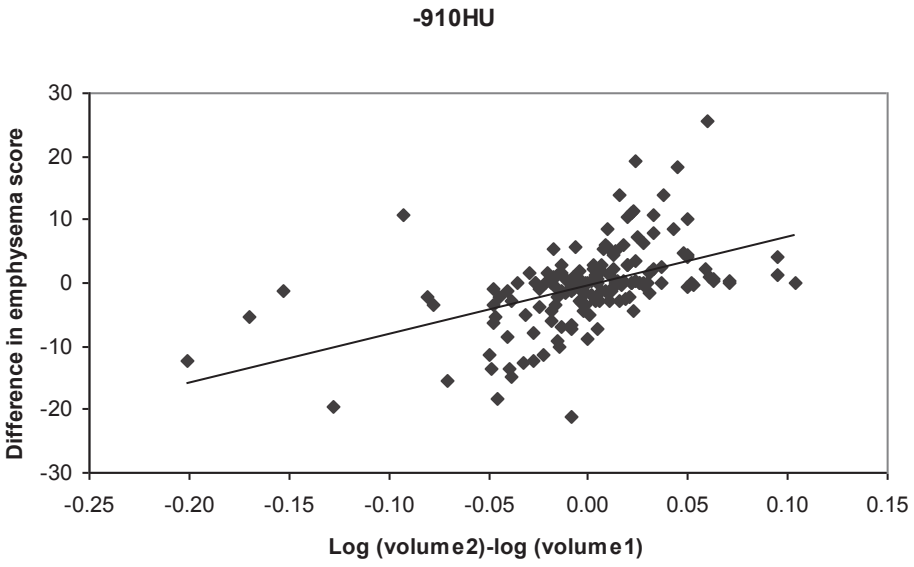


Figure 3

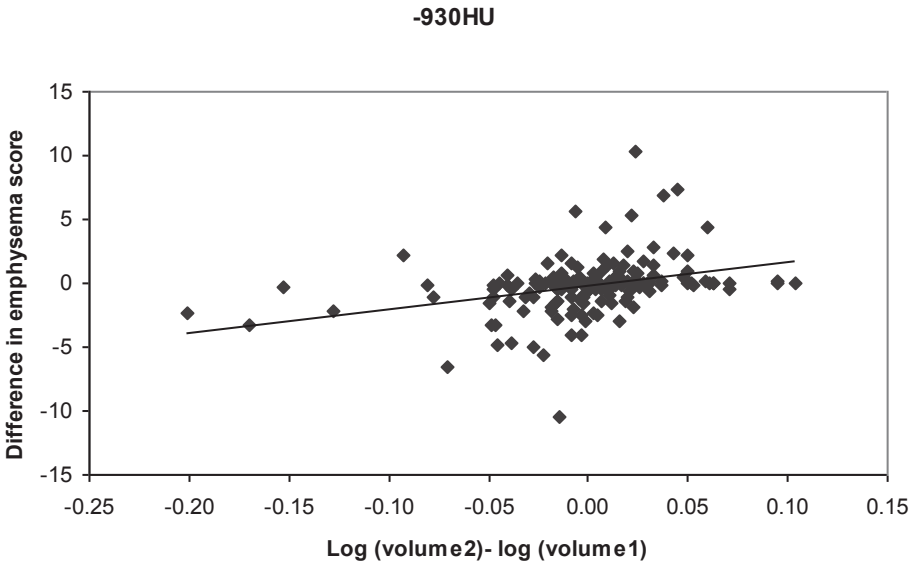
Correlation between lung volumes on the baseline scans and lung volumes on repeat scans. Identical volumes are demonstrated by the continuous line. No systematic difference between lung volume on baseline scan and repeat scan could be demonstrated.

LEVEL OF INSPIRATION

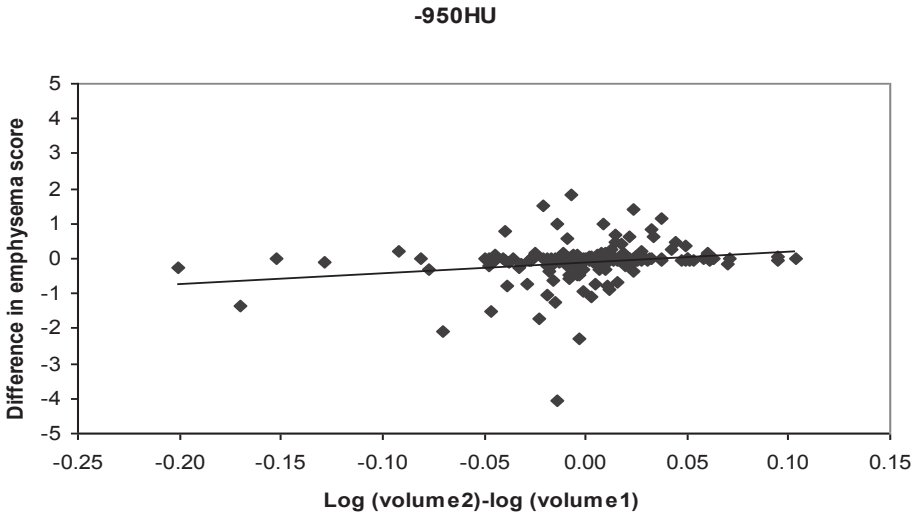
Mean total lung volume was 6935ml (± 1267ml) for the baseline scans and 6945ml (± 1322ml) for the repeat scans. Although many participants were not able to repeat the inspirational volume of the baseline scan during repeat scanning, the level of inspiration was not statistically different for both scans on cohort level (p=0.8, Figure 3). After logarithmic transformation we could demonstrate a significant ($p<0.001$ for -910HU and $p<0.001$ for -930HU, $p<0.01$ for -950HU) but weak to moderate correlation between changes in level of inspiration (lung volume) and emphysema scores for all thresholds ($r = 0.49$ for -910HU, $r = 0.33$ for -930HU and $r = 0.20$ for -950HU; Figure 4).


-910HU
Difference in emphysema score
30
20
10
0
-10
-20
-30
-0.25
-0.20
-0.15
-0.10
-0.05
0.00
0.05
0.10
0.15
Log (volume2)-log (volume1)

4A


-930HU
Difference in emphysema score
15
10
5
0
-5
-10
-15
-0.25
-0.20
-0.15
-0.10
-0.05
0.00
0.05
0.10
0.15
Log (volume2)- log (volume1)

4B



4C

Figure 4

Correlation between difference between inspiration level on repeat scans (volume 2) after logarithmic transformation and inspiration level on baseline scans (volume 1) after logarithmic transformation and difference in emphysema scores between repeat scans (ES2) and baseline scans (ES1). Significant, but low to moderate correlations could be demonstrated.

QUALITY CONTROL

The average CT-value for foam was -967.9HU (±2.0HU) for the 5 scans performed in succession at the beginning of our study and -969.2 HU (±2.2HU) for the 5 scans performed in succession after 3 months, while the average CT-value from April 2004 to March 2005 was 968HU (±2.7HU). Variation in measured CT numbers was independent of the time of the day. The SD of 2.7HU is within the range of tolerance reported by the vendor (0-4 HU).

DISCUSSION

Our results provide information of interscan variation of the quantification of low-attenuated areas, representing emphysema, in a cohort of current and former heavy smokers participating in a lung cancer screening trial. This screening trial aims to detect lung cancer in a curable stage, so participants have to be able to undergo surgery. For this reason, participants with severe airflow limitation were excluded from participation, resulting in a population under investigation with a relatively low extent of emphysema. While in the early nineties the quantification of low-attenuated areas had to be performed slice-by-slice and took hours per scan [19], nowadays, it takes less than 5 minutes for a complete CT and can be applied in large groups of patients. Shaker et al and Gierada et al have demonstrated that determining the extent of emphysema is highly repeatable on a cohort level in patients with large areas of destructed tissue [19;20], but they did not report the limits of agreement, while knowledge about the interscan variability is mandatory to distinguish between real increase in extent of emphysema and measurement variability in a monitor setting. With data reported in our study an increase in emphysema score of more than the corresponding upper limit of agreement can, with 95% likelihood, be subjected to real increase in extent of emphysema.

Since Müller et al introduced the quantification of the extent of emphysema highlighting low-attenuated areas on CT images [4], this method has been used for several scanning techniques. Müller et al. validated the technique to macroscopic histology for a single contrast-enhanced 10mm slice and found that -910HU was the best threshold to detect the extent of macroscopic emphysema. Gevenois et al determined the optimum attenuation threshold for high-resolution CT and recommended -950HU for both microscopicly and macroscopicly detected emphysema [15;21]. The difference in optimum attenuation threshold was subjected to variation in slice thickness and this effect was also investigated by Kemerink et al. [22]. Park et al. reported a high correlation between emphysema quantification on 2D an 3D datasets, making the technique also applicable to volumetric data [23]. Recently Madani et al. compared the extent of both microscopic and macroscopic detected emphysema to the quantification of the extent of low-attenuated areas with multidetector-row CT and reported -960HU to -970HU as optimum attenuation threshold for MDCT [24]. However, they applied less radiation dose than Gevenois et al (140kVp; 80mAs versus 137kVp; 255mAs) and Mishima et al. already showed the impact of applied radiation dose on the extent of low-attenuated areas [25]. Finally Parr et al. investigated several attenuation thresholds for monitoring purposes and recommended -930HU as optimum attenuation threshold to monitor the progression or regression in the extent of emphysema [16]. To our knowledge, there is no consensus about the optimum scanning technique for the quantification of the extent of emphysema by calculating the extent of low-attenuated areas and no consensus on the optimum attenuation threshold [3].

Therefore, we investigated the limits of agreement of the extent of low-attenuated areas on repeated scans for three attenuation thresholds often used in literature so far. Our results do not provide any information about the accuracy of emphysema scores for detecting lung destruction since we studied healthy participants and did not have any histological specimens available.

The effect of level of inspiration on lung attenuation is well described [17;26;27]. Shaker et al reported a large variability of correlation coefficients between the emphysema score and the total lung volume for the lower range of emphysema scores, while for more severe emphysema a more stable correlation could be reported [10]. We demonstrated a low to moderate but significant correlation between natural variation in level of inspiration and changes in emphysema scores, but also a large variation in this effect. Spirometric control could have narrowed the limits of agreement, but would also have limited our results to spirometric controlled CTs. Since spirometric controlled scanning is not available in many hospitals, we have performed the CTs in end-inspiratory volume as usual in clinical routine.

In our study a low-dose protocol was applied, since radiation dose has an intrinsic risk of inducing neoplasm. For a structure of interest with high contrast to its surroundings such as a pulmonary nodule in lung parenchyma, the detection and segmentation of this lesion are not affected by accompanying increase in image noise [28;29]. But for emphysema, especially for low extents of lung destruction, there is a low contrast between the destructed areas and the normal lung parenchyma. In that situation the increased image noise raises emphysema scores, which can be reduced, but not excluded, by the application of a noise reduction filter [30].

Quality control showed that regular scanner calibration for air resulted in stable CT numbers. The small variations in CT numbers were within the range of tolerance of our scanner, but still may contribute to variations in emphysema scores.

Although our results can provide useful information for monitoring high-risk participants in a screening setting, the study has also an important limitation. Our study has been performed in a lung cancer screening setting and the results are therefore useful in a low-dose setting but not necessarily applicable to a clinical setting with standard radiation dose. However, to our knowledge, emphysema quantification in large cohorts is mainly performed for study purposes with low-dose scans [9;20;31].

CONCLUSION

Although emphysema scores in a lung cancer screening setting are highly reproducible on cohort level, individual variation can be substantial. An increase in emphysema score of at least 1.1% for -950HU to 12.6% for -910HU is required for detection of increase of extent of emphysema with 95% confidence when monitoring smoking-induced emphysema with low-dose CT in a lung cancer screening setting.

REFERENCE LIST

(1) Arakawa A, Yamashita Y, Nakayama Y et al. Assessment of lung volumes in pulmonary emphysema using multidetector helical CT: comparison with pulmonary function tests. Comput Med Imaging Graph 2001; 25(5):399-404.

(2) Kinsella M, Muller NL, Abboud RT et al. Quantitation of emphysema by computed tomography using a "density mask" program and correlation with pulmonary function tests. Chest 1990; 97(2):315-321.

(3) Madani A, Keyzer C, Gevenois PA. Quantitative computed tomography assessment of lung structure and function in pulmonary emphysema. Eur Respir J 2001; 18(4):720-730.

(4) Muller NL, Staples CA, Miller RR et al. "Density mask". An objective method to quantitate emphysema using computed tomography. Chest 1988; 94(4):782-787.

(5) Church TR. Chest radiography as the comparison for spiral CT in the National Lung Screening Trial. Acad Radiol 2003; 10(6):713-715.

(6) Henschke CI, McCauley DI, Yankelevitz DF et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999; 354(9173):99-105.

(7) Sone S, Takashima S, Li F et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. Lancet 1998; 351(9111):1242-1245.

(8) van Klaveren RJ, Habbema JD, de Koning HJ et al. [Screening for lung cancer in the Netherlands: the role of spiral CT scan]. Ned Tijdschr Geneeskd 2001; 145(11):521-526.

(9) Omori H, Nakashima R, Otsuka N et al. Emphysema detected by lung cancer screening with low-dose spiral CT: prevalence, and correlation with smoking habits and pulmonary function in Japanese male subjects. Respirology 2006; 11(2):205-210.

(10) Shaker SB, Dirksen A, Laursen LC et al. Volume adjustment of lung density by computed tomography scans in patients with emphysema. Acta Radiol 2004; 45(4):417-423.

(11) Stoel BC, Stolk J. Optimization and standardization of lung densitometry in the assessment of pulmonary emphysema. Invest Radiol 2004; 39(11):681-688.

(12) Hu S, Hoffman EA, Reinhardt JM. Automatic lung segmentation for accurate quantitation of volumetric X-ray CT images. IEEE Trans Med Imaging 2001; 20(6):490-498.

(13) Hilts M, Duzenli C. Image filtering for improved dose resolution in CT polymer gel dosimetry. Med Phys 2004; 31(1):39-49.

(14) Dirksen A, Friis M, Olesen KP et al. Progress of emphysema in severe alpha 1-antitrypsin deficiency as assessed by annual CT. Acta Radiol 1997; 38(5):826-832.

(15) Gevenois PA, De M, V, De VP et al. Comparison of computed density and macroscopic morphometry in pulmonary emphysema. Am J Respir Crit Care Med 1995; 152(2):653-657.

(16) Parr DG, Stoel BC, Stolk J et al. Influence of calibration on densitometric studies of emphysema progression using computed tomography. Am J Respir Crit Care Med 2004; 170(8):883-890.

(17) Kalender WA, Rienmuller R, Seissler W et al. Measurement of pulmonary parenchymal attenuation: use of spirometric gating with quantitative CT. Radiology 1990; 175(1):265-268.

(18) Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1(8476):307-310.

(19) Gierada DS, Yusen RD, Pilgram TK et al. Repeatability of Quantitative CT Indexes of Emphysema in Patients Evaluated for Lung Volume Reduction Surgery. Radiology 2001; 220(2):448-454.

(20) Shaker SB, Dirksen A, Laursen LC et al. Short-term reproducibility of computed tomography-based lung density measurements in alpha-1 antitrypsin deficiency and smokers with emphysema. Acta Radiol 2004; 45(4):424-430.

(21) Gevenois PA, De Vuyst P, De M, V et al. Comparison of computed density and microscopic morphometry in pulmonary emphysema. Am J Respir Crit Care Med 1996; 154(1):187-19

(22) Kemerink GJ, Kruize HH, Lamers RJ et al. CT lung densitometry: dependence of CT number histograms on sample volume and consequences for scan protocol comparability. J Comput Assist Tomogr 1997; 21(6):948-954.
(23) Park KJ, Bergin CJ, Clausen JL. Quantitation of emphysema with three-dimensional CT densitometry: comparison with two-dimensional analysis, visual emphysema scores, and pulmonary function test results. Radiology 1999; 211(2):541-547.
(24) Madani A, Zanen J, de Maertelaer V et al. Pulmonary Emphysema: Objective Quantification at Multi-Detector Row CT--Comparison with Macroscopic and Microscopic Morphometry. Radiology 2006;2382042196.
(25) Mishima M, Itoh H, Sakai H et al. Optimized scanning conditions of high resolution CT in the follow-up of pulmonary emphysema. J Comput Assist Tomogr 1999; 23(3):380-384.
(26) Gotway MB, Lee ES, Reddy GP et al. Low-dose, dynamic, expiratory thin-section CT of the lungs using a spiral CT scanner. J Thorac Imaging 2000; 15(3):168-172.
(27) Lamers RJ, Thelissen GR, Kessels AG et al. Chronic obstructive pulmonary disease: evaluation with spirometrically controlled CT lung densitometry. Radiology 1994; 193 (1):109-113.
(28) Itoh S, Ikeda M, Arahata S et al. Lung cancer screening: minimum tube current required for helical CT. Radiology 2000; 215(1):175-183.
(29) Revel MP, Lefort C, Bissery A et al. Pulmonary nodules: preliminary experience with three-dimensional evaluation. Radiology 2004; 231(2):459-466.
(30) Schilham A, Van Ginneken B, Gietema H et al. Local Noise Weighted Filtering for Emphysema Scoring of Low-dose CT Images. IEEE Transactions on Medical Imaging 2006; 25(4):451-463.
(31) Parr DG, Stoel BC, Stolk J et al. Validation of computed tomographic lung densitometry for monitoring emphysema in {alpha}1-antitrypsin deficiency. Thorax 2006;thx.