Chapter 8

Early detection of emphysema: Computed tomography versus pulmonary function testing

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ABSTRACT

OBJECTIVE

To establish the extent of moderate and severe emphysema detected on high-resolution computed tomography (HRCT) in a lung cancer screening setting for participants with and without pulmonary function impairment or gas exchange impairment.

METHODS

Between April 2004 and March 2005, we included 545 male current and former heavy smokers (51-74y, mean 62y) participating in a lung cancer screening trial (NELSON) with baseline low-dose HRCT (16x0.75mm slice collimation) in who also flow-volume curves and diffusion capacity testing were assessed. Moderate emphysema was determined as areas with an attenuation between -910 Hounsfield units (HU) and -950HU, where as areas with an attenuation below -950HU represented severe emphysema. Both were expressed as emphysema score (ES), representing percentage of total lung volume. The extent of moderate and severe emphysema was assessed for participants with and without pulmonary function impairment or gas exchange impairment.

RESULTS

Twelve percent lung volume with moderate emphysema appears to be the optimal cut-off to result in a lowered FEV_1/VC, while 9% of total lung volume with moderate emphysema appears to be the optimal cut-off to result in a lowered $Tlco/V_A$ ratio. The optimal cut-off for severe emphysema is 0.15% for both a lowered FEV_1/VC ratio and a lowered $Tlco/V_A$ ratio.

CONCLUSION

The probability of moderate emphysema to result in a pulmonary function impairment or gas exchange impairment is low, while small amounts of severe emphysema already resulted in pulmonary function impairment and gas exchange impairment.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the most frequent chronic disease in developed countries and is predicted to be the third cause of death in 2020 [1]. COPD is functionally defined on the extent of airflow obstruction, which can be detected by pulmonary function testing (PFT): impairment of the forced expiratory volume in 1 second (FEV_1) is fundamental for the diagnosis according to the guidelines of the Global initiative on Obstructive Lung Diseases (GOLD) [2]. Emphysema is anatomically defined as an abnormal permanent enlargement of the airspace distal to the terminal bronchioles without fibrosis [3]. Several investigators correlated the extent of emphysema determined via CT with pulmonary function parameters and reported that the FEV_1/VC and $Tlco/V_A$ ratios were the best correlating parameters [4;5], but relations were not very strong. However, the detection of early changes can enable more aggressive risk-modifying interventions in this group of patients [6]. Moreover, emphysema can cause airflow obstruction, but emphysema can also exist without impairment of the FEV_1 [7].

Because of the anatomical definition, histology is required for the diagnosis of emphysema, but computed tomography (CT) can non-invasive provide anatomical information and the extent of emphysema detected with CT has been shown to correlate well with histology [8-11]. Therefore, CT can be an attractive alternative to detect emphysema before it reaches the symptomatic stage causing airflow obstruction. To our knowledge, the most frequently used technique is the one firstly described by Müller et al [12] highlighting low-attenuated areas, representing emphysema. The extent of emphysema is expressed as percentage of total lung volume in a range from 0% to 100%. This method has been validated for high-resolution CT against pathology for both microscopic and macroscopic techniques by Gevenois and co-workers [10;13].

Since pulmonary function testing (PFT) is more easily performed and to lower costs in a large population at-risk than CT-scanning, the aim of our study was to assess the extent of moderate (loss of lung tissue) and severe emphysema (complete destruction of lung tissue) in participants of a lung cancer screening trial that elicits pulmonary function impairment or gas exchange impairment.

MATERIAL AND METHODS

PARTICIPANTS

The NELSON-project is the Dutch-Belgian multi-center lung cancer screening trial, studying current and former heavy smokers [14]. The trial was approved by the Dutch ministry of health and by the ethics committee of each participating hospital. Selection of participants was performed by sending a questionnaire about smoking history and other health related questions to people between 50 and 75 years of age, living in the areas around the participating centers. Current and former male smokers meeting the inclusion criteria of having smoked a minimum of 16 cigarettes/day for 25 years or 11 cigarettes/day for 30 years, who gave written informed consent, were equally randomized to either the screening or the control arm. Persons with a self-reported moderate or bad health status, who were unable to climb two flights of stairs were excluded. Persons with current or past renal cancer, melanoma, breast cancer or with lung cancer diagnosed less than 5 years before recruitment were also excluded. From the participants who underwent baseline screening in our hospital, randomly one out of three participants was selected for pulmonary function testing on the same day. For the present study, we included participants who underwent baseline screening between April 2004 and February 2005.

CT SCANNING AND CALCULATION OF EMPHYSEMA SCORES

CT scanning was performed by a 16 detector-row scanner (Mx8000 IDT or Brilliance 16P, Philips Medical Systems, Cleveland, OH) with 16 x 0.75mm collimation. A caudo-cranial scan direction was applied and the entire chest was scanned in approximately 10 seconds. No intravenous contrast injection was used. Exposure settings were 30mAs at 120kVp for patients weighing £80 kg and 30mAs at 140kVp for those weighing >80 kg. We reconstructed axial images of 1.0 mm thickness at 0.7 mm increment, using the smallest field of view (FOV) to include the outer rib margins at the widest dimension of the thorax. All scans were reconstructed with a soft kernel (Philips "B") at 512x512 matrix.

EMPHYSEMA QUANTIFICATION

Extent of low-attenuation areas was determined, using in-house developed software (imageXplorer (iX), Image Sciences Institute, Utrecht, The Netherlands). Segmentation of trachea, left and right lung was performed by a fully automated 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 and co-workers [15]. The number of voxels within the segmented area was multiplied by the size of a voxel to calculate total lung volume. Finally, segmented lungs were subjected to a noise reduction filter [16].

Emphysema scores (ES) were calculated as volume with an attenuation below a fixed attenuation threshold as percentage of total lung volume. For the definitions of moderate and severe emphysema, we used the criteria described by the National Emphysema Treatment Trial (NETT) 17: areas with an attenuation below -950HU represented severe emphysema, areas with an attenuation below -910HU represented moderate emphysema.

PULMONARY FUNCTION TESTS

Pulmonary function tests (PFT) included forced expiratory volume in one second (FEV1) and vital capacity (VC) with a pneumotachograph followed by assessment of diffusion capacity (Tlco), according to ERS guidelines [18]. Upon arrival, participants rested for 15 minutes after which non-forced spirometry was performed, immediately followed by recording the FEV1 by a flow-volume curve. The best of three temptations was selected for analysis. No reversibility testing was applied.

Diffusing capacity measurements were performed after spirometry. The inhalation mixture contained 0.3% CO and 10% He with balanced air. A breath-holding period of 10 seconds was used. Participants were asked to refrain from smoking, but the Tlco was not corrected for Hb, because in a normal population such correction is not useful [19]. For analysis Tlco was corrected for alveolar volume (Tlco/VA). Abnormal pulmonary function parameters were defined as values below the lower limit of normality (LLN), i.e. ≤-1.64 standard deviations below reference values [18]. Participants were staged according to updated GOLD guidelines [20].

STATISTICS

We calculated means, standard deviations and 95% confidence intervals (CI) for normal distributed parameters and medians and 25%/75% quartiles for non-normal distributed ones. Spearman's correlation coefficients were used to assess a relationship between lung function parameters and ES for all participants and for a subgroup of participants fulfilling the criteria of GOLD stage II and more. Kruskal-Wallis tests were performed to detect differences between GOLD-stages in both pack years smoked (one pack of cigarettes a day during one year) and ES.

Using the presence or absence of a lowered PFT as outcome variable, the area under the receiver-operator characteristic (ROC) curve of moderate and severe ES was estimated: this area denotes the probability to correctly diagnose the presence or absence of a lowered PFT. From that ROC analysis an optimal cut-off value for moderate and severe ES can be derived, which is that value showing the combined highest sensitivity and specificity. We also used logistic regression with the presence or absence of a lowered PFT as independent and moderate and severe ES as continuous dependent variable to further chart the relation between ES and the probability of a lowered PFT. This analysis was performed for both

lowered FEV1 and lowered Tlco/VA.

All statistics were calculated with SPSS statistical software package version 13 (SPSS, Chicago, Ill.). P-values <0.05 were considered significant.

RESULTS

Five hundred forty-five participants (50-74y, mean 62y), 185 smokers and 360 former smokers, underwent CT scanning and pulmonary function testing on the same day. Characteristics of the study participants are shown in Table X. None of the participants fulfilled the criteria for GOLD stage IV.

GOLD stage	age (years) (SD)	VC (SD)	FEV1 (SD)	FEV1/ VC (SD)	Tlco (SD)	Tlco/ VA (SD)	Pack years (25th-75th percentile)
All	59.8 (5.5)	105.1 (13.6)	97.3 (17.9)	90.6 (12.1)	83.7 (17.8)	90.0 (24.5)	37.8 (27.3 - 48.3)
0 (At risk) (n=339)	59.3 (5.4)	106.2 (13.1)	104.9 (13.9)	97.8 (6.0)	87.1 (14.6)	94.2 (15.7)	37.8 (27.3 – 48.3)
I (Mild) (n=135)	60.5 (5.4)	112.4 (11.3)	94.3 (9.1)	83.3 (5.9)	80.4 (17.3)	81.3 (16.1)	42.6 (33.3 – 48.3)
II (Moderate) (n=62)	61.2 (6.4)	94.7 (11.5)	69.5 (7.2)	73.1 (8.3)	75.0 (18.6)	83.3 (19.7)	44.8 (33.3 – 58.8)
III (Severe) (n=9)	60.7 (2.4)	90.5 (10.8)	44.1 (2.2)	49.0 (6.8)	47.4 (14.3)	50.8 (13.8)	37.8 (37.8 – 57.0)

Table 1
Descriptive statistics shown as mean values (±SD) according to GOLD stage. All pulmonary function parameters are expressed as percentage of the predicted value.

Correlation between emphysema and PFT parameters were low but significant, as shown in Table 1. The coefficients calculated in subsample of participant fulfilling the criteria for GOLD stage II and III were considerably higher for FEV_1 and Tlco, while for FEV_1/VC ratio and Tlco/V_A ratio only moderate changes were found (Table 2). This indicates that selection bias can and will influence the correlation coefficients: in more severe disease stronger relations will be found. The FEV_1/VC and Tlco/V_A ratio correlated best with the ES scores and so these two parameters were selected for further analysis. Hundred forty-three participants (26.2%) showed a FEV_1/VC ratio below the LLN, 210 participants (38.5%) showed a lowered TL_{co}/V_A.

GOLD stage	VC	FEV$_1$	FEV$_1$/VC	TI$_{co}$	TI$_{co}$/V$_A$
All	0.23[*]	-0.16[*]	-0.48[*]	-0.28[*]	-0.47[*]
II & III	0.08	-0.35[*]	-0.44[*]	-0.48[*]	-0.49[*]

Table 2

Non-parametric correlation coefficients between emphysema scores and pulmonary function parameters, expressed as percentage of predicted results, calculated for the total study sample and for a subgroup of subjects with GOLD II and III.

	Median ES (25th-75th percentile)	
GOLD stage	**-910HU to -950HU (moderate emphysema)**	**-950HU (severe emphysema)**
All	8.6% (2.8-21.7%)	0.1% (0.04-0.45%)
0 (At risk)	5.8% (1.6-13.5%)	0.08% (0.04-0.19%)
I (Mild)	17.8% (7.3-30.1%)	0.3% (0.11-0.96%)
II (Moderate)	15.0% (4.6-26.4%)	0.4% (0.17-1.5%)
III (Severe)	18.9% (15.5-29.3%)	4.2% (0.5-16.7%)

Table 3

Median tissue destruction (percentage of total lung volume) and 25th-75th percentile for mild and severe emphysema, according to GOLD stage.

In Figure 1 the extent of emphysema is illustrated in a frequency plot. The median ES for severe emphysema was 2.7% (inter-quartile range: 1.4% to 6.9%), the median ES for moderate emphysema was 22.9% (inter-quartile range: 15.2% to 31.1%). Median emphysema scores according to GOLD stage are shown in Table 3. Figure 2 shows the scatterplots of the FEV$_1$/VC and Tlco/V$_A$ values (as percentage of the predicted value) versus the extent of moderate and severe ES.
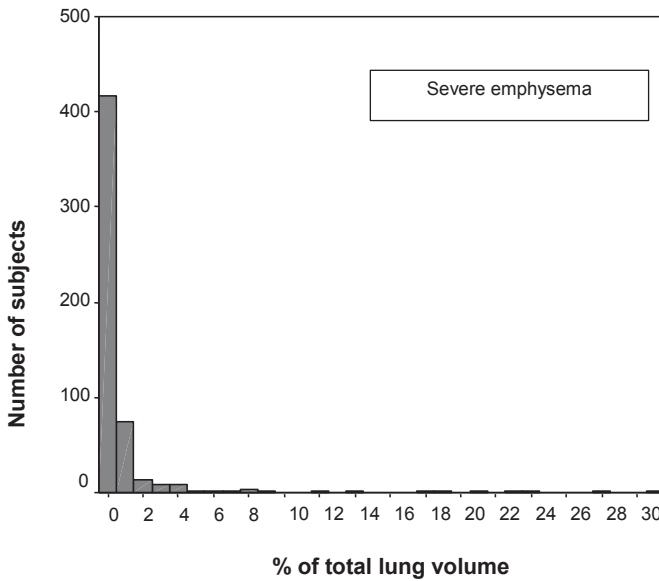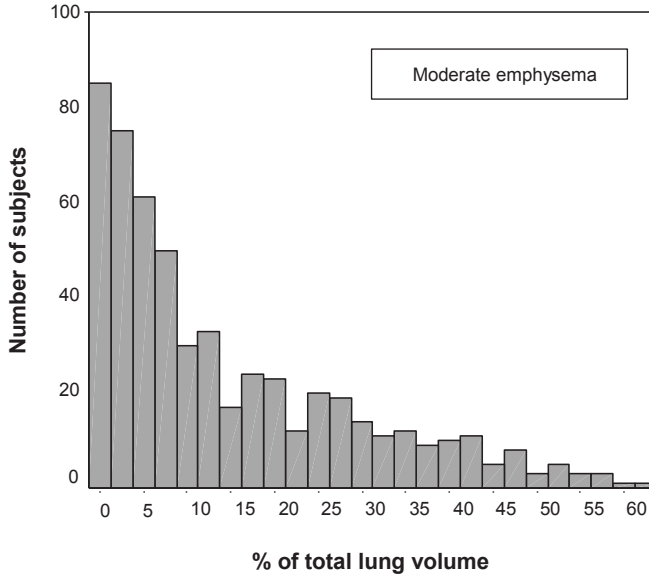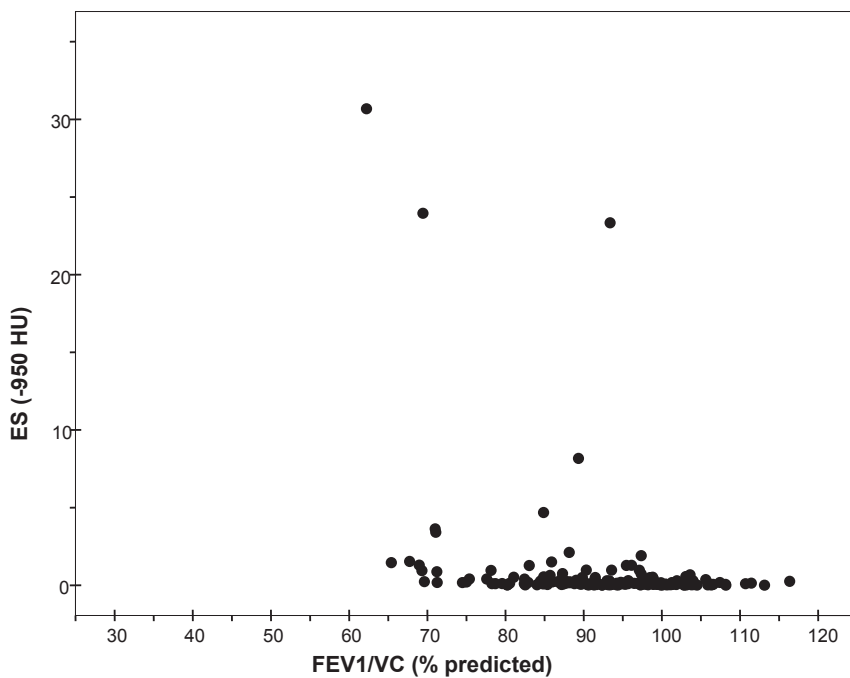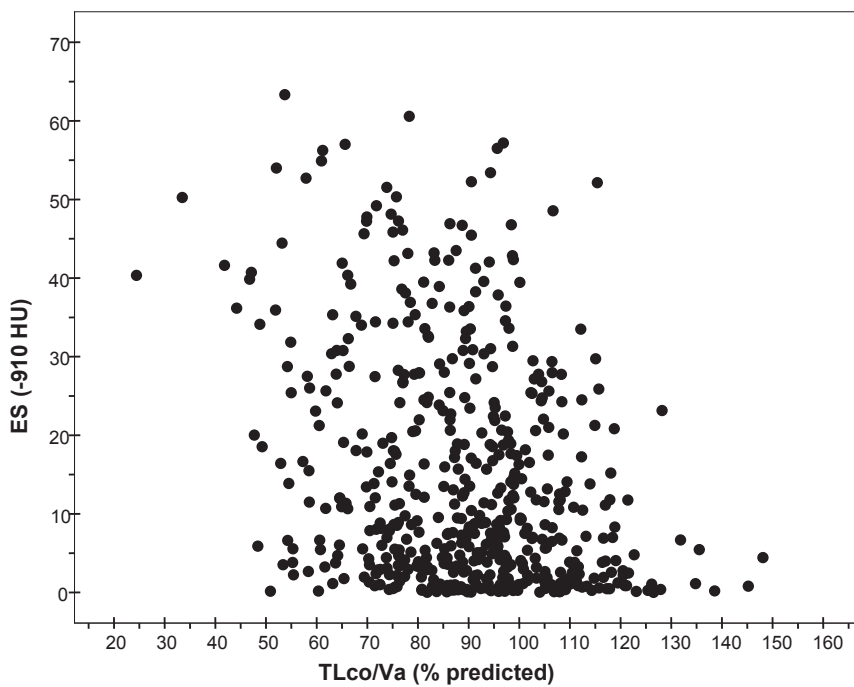
1A

1B

Figure 1
Extent of moderate (A) and severe (B) emphysema plotted against the number of participants
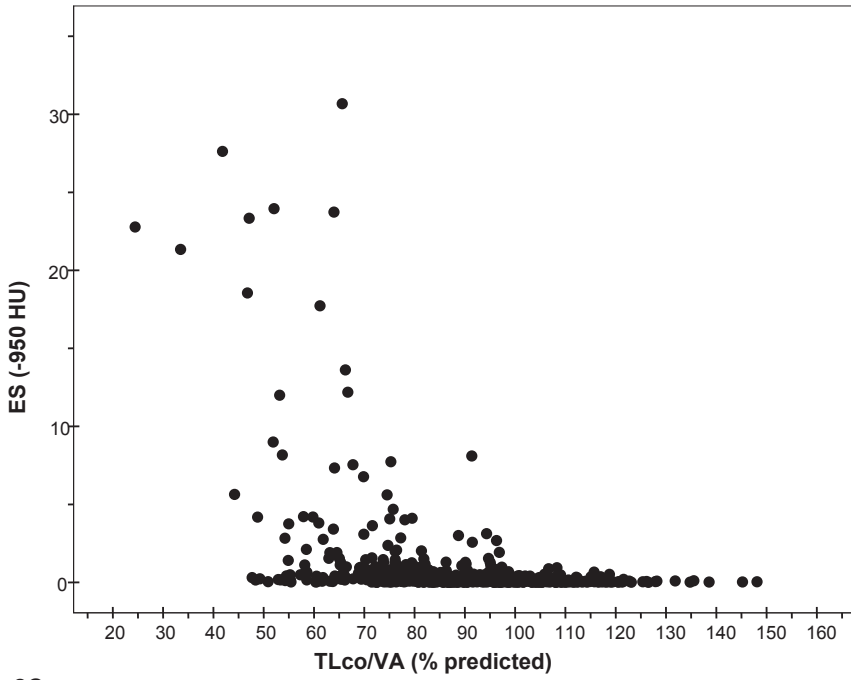
2A

2B

2C

Figure 2

Scatterplots depicting the relation between moderate or severe emphysema scores and FEV_1/VC or TL_{co}/V_A (as percent of the predicted value)

The area under ROC curve for moderate emphysema, predicting the presence or absence of a lowered FEV_1/VC or $Tlco/V_A$ ratio is 0.698 (95% CI 0.650 -0.749) and 0.623 (95% CI 0.575 – 0.672) respectively. Twelve percent of total lung volume with moderate emphysema appears to be the optimal cut-off to result in a lowered FEV_1/VC, while 9% of total lung volume with moderate emphysema appears to be the optimal cut-off to result in a lowered $Tlco/V_A$ ratio. For severe emphysema, the area ROC curve, predicting the presence or absence of a lowered FEV_1/VC and $Tlco/V_A$ ratio is 0.723 (95% CI 0.673 – 0.773) and 0.742 (95% CI 0.698 – 0.786) respectively. For severe emphysema, 0.15% of the total lung volume appears to be the optimal cut-off to result in FEV_1/VC both a lowered FEV_1/VC ratio and a lowered $Tlco/V_A$ ratio.

When we use the GOLD cut-off value of a FEV_1/FVC ratio <0.7, the area under the ROC curve for moderate emphysema, predicting the presence or absence of a FEV_1/FVC <0.70 is 0.732 (95% CI 0.689 -0.775). Moderate emphysema covering ≥11% of the total lung volume appears to be the optimal cut-off in case of both FEV_1/FVC. The area under the ROC curve for severe emphysema, predicting the presence or absence of a FEV_1/FVC <0.70 is 0.765 (95% CI 0.724 - 0.806). Severe emphysema covering 0.15% of total lung volume appears to be the optimal cut-off in case of both FEV_1/FVC.

In Figure 3 we demonstrate the relationship between moderate and severe emphysema and the probability of a lowered FEV_1/VC and $Tlco/V_A$ ratio below the lower limit as established by GOLD.
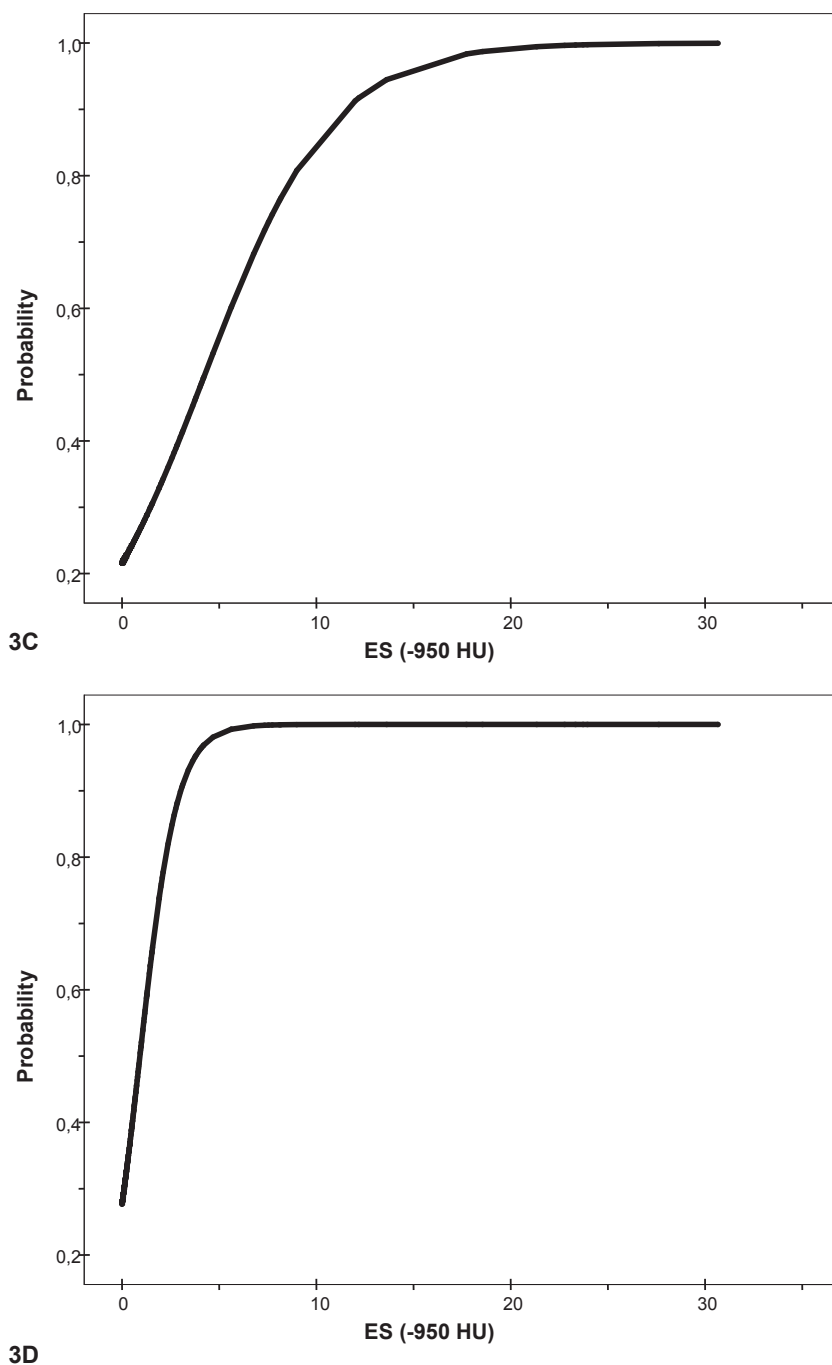
3A

3B

3C

3D
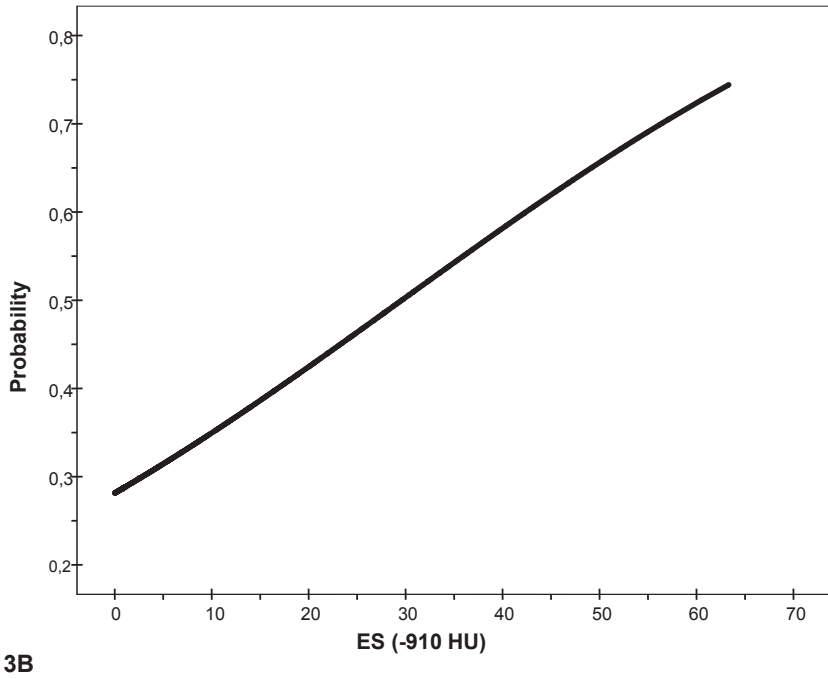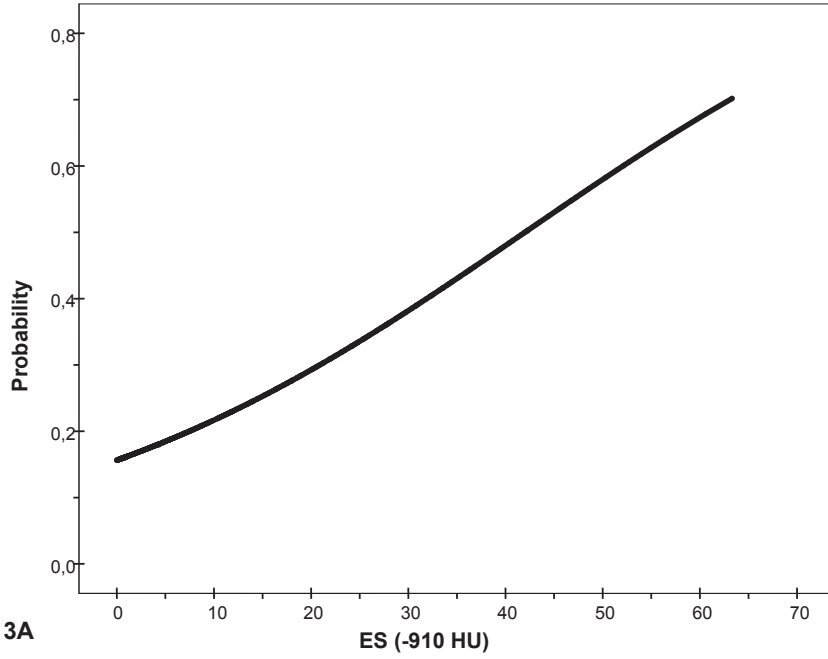
Figure 3

Graphs relating the probability to detect a FEV_1/VC ratio <LLN to the degree of moderate/ severe emphysema (upper left and right) or a TL_{co}/V_A ratio to the same (lower left and right).

DISCUSSION

We demonstrated that the presence of significant amounts of moderate emphysema detected on HRCT does not necessarily result in pulmonary function impairment, while small amounts of severe emphysema already resulted in pulmonary function impairment and gas exchange impairment. Especially for moderate emphysema large areas of destructed lung tissue are required to elicit a high probability of a pulmonary function impairment or gas exchange impairment.

The fact that PFT can still be normal even when CT shows moderate tissue destruction over large areas of the lungs, indicates that pulmonary obstruction is prevented via the non-emphysematous lung parts, which apparently retained their functional characteristics till massive lung destruction is present. In any case, these participants form a substantial subgroup in the spectrum of smoking related lung diseases, which we like to define as 'emphysema with normal pulmonary function' or 'emphysema without obstruction'. Longitudinal studies are required to answer the question whether these participants with smoking related emphysema will also develop obstructive disease or not. If so, screening high-risk participants with low-dose HRCT can be very useful to detect lung destruction before it progresses to a stage with pulmonary function impairment.

The finding that pulmonary function tests are frequently abnormal when tissue destruction is absent or minimal, points at a significant role of apparently ill-functioning, but 'non-destroyed' lung parenchyma, which can not be detected by highlighting low attenuated areas. In line with above, we can define these participants as 'abnormal pulmonary function without emphysema' or as 'obstruction without emphysema'. The Tlco/VA can for example be jeopardized through pathology present at the level of the pulmonary vascular bed [21]. When this damage now precedes gross alveolar destruction, a dissociation between CT and pulmonary function findings is to be expected: small airway disease and respiratory bronchiolitis can lower Tlco/VA ratios in a smoking population [22]. These abnormalities have been demonstrated also to be present in asymptomatic smokers [23;24]. FEV1 and (F)VC are sensitive to mucosal thickening or loss of elasticity resulting from airway inflammation and remodeling. These phenomena can elicit airway obstruction without lung destruction, while not resulting in low-attenuated areas and therefore not being detected by that technique. However, techniques measuring wall thickness of bronchi and bronchioli could provide more insight in this mechanism. Orlandi et al showed significant correlation between both air wall thickness with FEV_1/VC ratio and with D_{CO} in patients with a previous diagnosis of COPD [25] with and without chronic bronchitis (CB). Since patients with COPD and without CB showed a significant higher extent of emphysema, the mechanisms resulting in COPD were supposed to be different. In subjects with CB, the airflow limitation was due to intrinsic bronchial changes resulting in thicker bronchial walls, while in patients without CB the extrinsic

changes such as loss of elastic recoil due to lung tissue destruction result in airflow limitation.

The GOLD-criteria to diagnose COPD are based on an absolute value, not corrected for age, height and sex (FEV_1/FVC <0.7) while others start their diagnostic scheme from the notion that a FEV_1/VC should be lower than the lower than the lower limit of 90% confidence interval for normal results. The data from this study show that both strategies are similar in their relation to moderate or severe emphysema in smokers. More important than choosing between the two is the fact that both approaches are not well suited to detect all aspects of COPD.

This problem might be the result of for example not optimally defined FEV_1/FVC cut off values. Lowering the ratio to values further below 0.70 is rather contra productive because more participants will be depicted as 'healthy', which is not realistic. Moreover we already showed that the correlations between pulmonary function and emphysema will improve with increasing severity of disease: the outcome in terms of ROC areas is a predictable increase. So, for the discussion, we investigated the effects of increasing the FEV_1/FVC cut off values to either 0.75 or 0.80, defining less severe obstruction as already diseased. The area under the ROC curve for moderate and severe emphysema using <0.7 as cut-off value was respectively was 0.732 and 0.765 and increasing the cut off to either 0.75 made the areas decrease by respectively 0.021 and 0.018. Using a FEV-1/FVC cut off values of 0.8 has moderate effects: an increase of moderate emphysema ROC area of 0.002 and a decrease by 0.008 for severe emphysema . These changes are not warranting change of cut off values.

For the diagnosis of emphysema, actually histology is required [3]. No histology was available in the present study, but CT has shown to be able to detect lung tissue destruction on two dimensional images, based on a good correlation with histology, rendering CT-scanning a reliable surrogate marker for pathology [9;10;26-29]. The density mask technique has been reported to be also reliable on three dimensional CTs [4;5]. The main disadvantages of CT are the costs and radiation burden [30;31], but introduction of low-dose protocols as used in our study has reduced the radiation risk substantially [31;32]. The increase of image noise on low-dose scans can influence results of the density mask as shown by Schilham et a [33], but they also showed that emphysema scores performed on low-dose scans filtered with a noise reduction filter revealed results that were similar to ES performed on standard-dose scans realized in the same session. Therefore, our scans were subjected to a noise reduction filter before emphysema scores were calculated.

We here examined the relationship between emphysema and lowered pulmonary function, which is possible because there is consensus on the definition of a impaired pulmonary function. The presence or absence of a lowered function hence easily can act as gold standard. It might be interesting to examine the capability of pulmonary function testing to detect emphysema by reversing the

gold standard, i.e. use the presence of absence of emphysema, too. That definition is pivotal, but unfortunately no consensus exist of the threshold for pathological amounts of emphysema. Ageing in non-smokers could elicit already small amounts of emphysema-like alterations and these have to be separated from smoking induced emphysema. Up to now only small samples of non-smokers were scanned and from those studies no clear cut threshold values could be defined. For the detection of severe emphysema, Kinsella et al proposed a threshold of >1% [34]. The obvious approach is to scan the lungs from a large healthy population, but the question arises whether the radiation risk of CT makes it ethical to obtain these data.

In conclusion, we demonstrated the probability of especially moderate emphysema to result in a pulmonary function impairment or gas exchange impairment is low, while small amounts of severe emphysema already resulted in pulmonary function impairment and gas exchange impairment. Moreover, many current and former smokers suffer from moderate emphysema without clinical diagnosis of COPD.

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