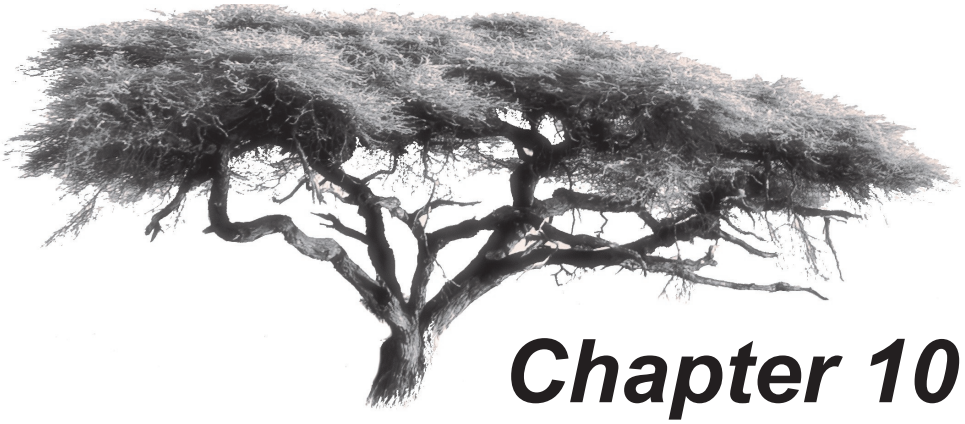

Chapter 10

Distribution of moderate and severe emphysema in heavy smokers joining a population-based lung cancer screening trial: Impact on pulmonary function

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Submitted

ABSTRACT

PURPOSE

To investigate the impact of the distribution pattern of both moderate and severe emphysema, detected on volumetric high-resolution CT, on the severity of airflow limitation and gas exchange impairment in a large population of current and former heavy smokers participating in a lung cancer screening trial.

MATERIALS AND METHODS

Between April 2004 and February 2005, 1386 male current and former heavy smokers underwent low-dose CT (16 x 0.75mm slice collimation) in our center as part of a population-based lung cancer screening trial. In 545 subjects pulmonary function testing was performed on the same day. Severe emphysema was defined as lung volume with an attenuation <-950 Hounsfield units (HU), quantified objectively, while areas with an attenuation between -910HU and -950HU represented moderate emphysema. Impact of distribution on the severity of pulmonary function impairment was investigated.

RESULTS

Corrected for extent of emphysema, for both moderate and severe emphysema an apical distribution was associated with more airflow obstruction and gas exchange impairment than a basal distribution.

CONCLUSION

In an asymptomatic heavy smoking population, an apical distribution is associated with more severe pulmonary function impairment than a basal distribution.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality in the developed countries [1;2], but little is known about its early stages. Since COPD is functionally defined, diagnosis and staging is based on the guidelines provided by the Global initiative on Obstructive Lung Diseases (GOLD) guidelines [3]. These guidelines are based on results of spirometric testing, using forced expiratory volume in one second (FEV_1) and FEV_1/forced vital capacity (FVC) as primary parameters. But COPD is a heterogeneous disease comprising not only mucosal thickening of the bronchioles, resulting in airflow limitation but also emphysema, anatomically defined as a permanent enlargement of the terminal bronchioles and alveoli. Although emphysema can cause airflow obstruction and correlation between pulmonary pathophysiology examined with pulmonary function tests and pathology found with CT has shown moderate to good results [4;5], demonstrating more pulmonary function impairment with increasing amounts of emphysema, emphysema can also exist without impairment of the FEV_1 [6]. 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 [4;7-9]. Therefore, CT can be an attractive alternative to investigate the natural course of emphysema before it reaches the symptomatic stage causing airflow obstruction.

Presently there are several ongoing lung cancer screening trials [10-13]. Since lung cancer and emphysema share smoking as the main risk factor, CT-scans performed in these trials may provide suitable data for studying the natural course of smoking-related emphysema in relatively healthy subjects [14]. 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.

Previous studies have suggested that subjects with similar amounts of parenchymal destruction can show different degrees of severity of airflow limitation and gas exchange impairment according to the distribution of the damage in either the apical or the basal parts of the lungs [15-17].

The impact of these pattern of emphysema distribution has been investigated in patients with α_1-antitrypsine deficiency and severe emphysema[16] and these data can not be extrapolated easily to smoking induced COPD. In a study with unselected smokers [15], only the extent of subjectively quantified lung destruction showed an association between distribution pattern (i.e. apical or basal predominance of emphysema) and pulmonary function, while the extent of objectively quantified emphysema did not. However, subjective scoring has been demonstrated to result in an overestimation of the extent of lung destruction [18]. Moreover, only two slices, one above and one below the carina, were used for analysis. Therefore, the results of this study could have suffered from selection

bias.
The aim the current study was to investigate the impact of the distribution pattern of both moderate and severe emphysema, detected on volumetric high-resolution CT, on the severity of airflow limitation and gas exchange impairment in a large population of current and former heavy smokers participating in a lung cancer screening trial.

MATERIAL AND METHODS

SUBJECTS

The NELSON-project is the population based randomized Dutch-Belgian multi-center lung cancer screening trial, studying current and former heavy smokers. The trial was approved by the Dutch ministry of health and by the ethics committee of each participating hospital. Selection of participants for the trial was performed by sending a questionnaire about smoking history and other health-related issues to people between 50 and 75 years of age, living in the areas around the participating centers. Subjects meeting the inclusion criteria of 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 arm or the control arm. Before inviting eligible subjects, persons with a moderate or poor self-reported health status who were unable to climb two flights of stairs were excluded from participation.
From three thousand participants who underwent baseline screening in our hospital, randomly one in three screened subjects was selected for pulmonary function testing on the same day. For the current study, we included participants who underwent both baseline screening and pulmonary function testing on the same day between April 2004 and February 2005.

CT SCANNING AND CALCULATION EMPHYSEMA SCORES

CT scanning was performed on a 16 detector-row scanner (Mx8000 IDT or Brilliance 16P, Philips Medical Systems, Cleveland, OH, USA). All scans were realized within 12 seconds, in spiral mode with 16 x 0.75mm collimation, 1.0mm reconstruction thickness, without contrast-injection. Exposure settings were 30mAs at 120kVp for subjects weighing ≤80kg or 30mAs at 140kVp for those weighing over 80kg. Scans were performed in end-inspiration after appropriate instruction of the subjects. They were asked to take a deep breath and to hold their breath.
Scans were transferred to a digital workstation with in-house developed software (ImageXplorer (iX) Image Sciences Institute, Utrecht, The Netherlands). Lung volume was calculated after segmenting both lungs using a fully automated region-growing program starting from the trachea and connecting all areas with a

attenuation below -500HU. In a next step, central airways were separated. The algorithm is similar to the one described by Hu et al [19]. Finally, segmented lungs were subjected to a noise reduction filter [20]. Emphysema score (ES) was calculated for volume with an attenuation below two attenuation thresholds (-950HU and -910HU) as percentage of total lung volume. Lung areas with an attenuation between -910 Hounsfield units (HU) and -950HU represented moderate emphysema, while lung volume with an attenuation below -950HU represented severe emphysema as described by the National Emphysema Treatment Trial (NETT) [21]. Emphysema scores were given as percentage of total lung volume in a range from 0% to 100%.

Pulmonary Function Tests

Pulmonary function tests (PFT) included forced expiratory volume in one second (FEV_1) and vital capacity (VC) with a pneumotachograph and assessment of diffusion capacity (Tlco), according to ERS guidelines [22]. Upon arrival, subjects rested for 15 minutes after which non-forced spirometry was performed, immediately followed by recording the FEV_1 by a flow-volume curve. The best of three temptations was selected for analysis. No reversibility testing was performed. Diffusing capacity measurements were performed after spirometry. The inhalation mixture contained 0.3% CO and 10% He with balance air.
Abnormal pulmonary function parameters were defined as values ≤-1.64 standard deviations below reference values [22] and classified according to the updated GOLD guidelines [3]. Results were expressed as percentages of predicted values.

Distribution of Emphysema and Statistics

The lungs were divided in three parts with equal volumes (top, middle and lower part) and the ES for each part was calculated. Since no consensus how to distinguish apical, basal and homogeneous distributions patterns has been established yet, the effects of apical and basal predominance of emphysema on lung function were evaluated via multiple linear regression. However, the extent of emphysema in these three parts of the lungs was highly correlated and therefore multiple linear regression became less reliable. We solved this by using principal component analysis to obtain perfectly uncorrelated predictors based on the principal components scores. These new predictors were incorporated into the multiple regression procedures and the height of the resulting regression coefficients reflect the impact of that predictor for pulmonary function impairment.
In a second step, we added a model-dependent approach forming two groups based on the area with the highest amount of emphysema: a subgroup with mainly apical emphysema and a subgroup with a basal predominance. While mainly subjects with an apical predominance benefit from lung volume reduction surgery, the subjects with the highest emphysema score in the upper third of the

lungs were formed into the apical group, while all other subjects were grouped as subjects with a basal predominance. Analysis of variance (ANOVA) was used to further examine the effects of distribution patterns on lung function parameters.
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. All statistics were calculated with SPSS statistical software package version 13 (SPSS, Chicago, Ill.). P-values <0.05 were considered significant.

RESULTS

SUBJECTS

Between April 2004 and February 2005, 1386 subjects underwent baseline low-dose chest CT and 545 of them (all male) underwent both baseline CT and pulmonary function testing. Descriptive data are shown in Table 1.

The FEV_1 was abnormally low in 60 (11%) subjects, the FEV_1/VC ratio in 143 (26%) subjects, the Tlco in 167 subjects (31%) and the Tlco/$V_{A\ (alveolar\ volume)}$ in 210 (38%) subjects. Since FEV_1/VC and Tlco/V_A ratio detected more subjects with pulmonary function impairments, we used these parameters for further analysis.

MODERATE EMPHYSEMA

In subjects with moderate emphysema, the principal component analysis delivered the following two variables: the total extent of emphysema and the difference between top and basal ES. Multiple regression analysis incorporating these new variables showed that both components significantly reduced the FEV_1/VC ratio. The regression coefficients were respectively -4.88, and -1.65 (both $p<0.001$), showing a strong effect of the total amount of emphysema and a weaker impact of the difference between the ES in top and basal part of the lungs. For the Tlco/V_A ratio a similar effect was detected: the regression coefficients were -5.33 and -4.50 respectively (both $p<0.001$). The model-independent approach so reported a major effect of distribution patterns on pulmonary function and the impact of the patterns on pulmonary function was further investigated, comparing the apical and basal emphysema subgroups.
An apical predominance of moderate emphysema was associated with a lower FEV_1/VC ratio compared to basal distribution ($p<0.001$). Subjects with an apical predominance showed a FEV_1/VC ratio that was 5.84% (95% CI 3.29% - 8.40%) lower than the FEV_1/VC ratio in subjects with a basal predominance. An apical predominance was also associated with a lower Tlco/V_A, compared to a basal predominance ($p<0.001$). Subjects with an apical predominance showed a Tlco/V_A ratio that was 13.04% (95% CI 9.36% - 16.72%) lower than the Tlco/V_A ratio in subjects with a basal predominance.

SEVERE EMPHYSEMA

In subjects with severe emphysema, the principal component analysis also delivered the total extent of emphysema and the difference between top and basal ES as uncorrelated variables influencing the severity of pulmonary function impairment. The resulting regression coefficients for the two components FEV_1/VC ratio were -4.86 and -1.33 ($p<0.001$ and $p=0.005$) for the total extent of emphysema and the difference between top and basal ES respectively, while for the Tlco/V_A ratio the regression coefficients were -7.33 and -2.23 ($p<0.001$ and

p=0.001).

Apical emphysema was associated with a lower FEV_1/VC and $Tlco/V_A$ ratio ($p<0.001$). Subjects with an apical predominance showed a FEV_1/VC ratio, which was 5.85% (95% CI 2.90% - 8.79%) lower than the ratio in subjects with a basal distribution pattern. For the $Tlco/V_A$ ratio the difference was 8.94% (95% CI 4.34%- 13.55%).

	Apical predominance	Basal predominance
Moderate emphysema		
Number of subjects	167	378
Emphysema score Median Interquartile range	 13.5% 3.76%-32.6%	 7.6% 2.65%-20.2%
FEV1 Median Interquartile range	 97.6% 84.3%-110.6%	 98.9% 87.6%-117.7%
Vital capacity Median Interquartile range	 107.3% 99.0%-116.5%	 103.3% 94.7%-112.5%
FEV1/FVC Median Interquartile range	 70.9% 64.4%-76.2%	 73.9% 67.4%-77.5%
Tlco/VA Median Interquartile range	 81.2% 68.9-96.9%	 92.5% 81.7%-102.5%
Severe emphysema		
Number of subjects	209	336
Emphysema score Median Interquartile range	 0.15% 0.037%-0.94%	 0.13% 0.056%-0.31%
FEV1 Median Interquartile range	 97.8% 86.2%-108.3%	 99.0% 86.6%-110.9%
Vital capacity Median Interquartile range	 103.4% 95.8%-112.9%	 105.0% 95.7%-114.4%
FEV1/FVC Median Interquartile range	 96.0% 86.6%-101.4%	 94.8% 87.8%-100.6%
Tlco/VA Median Interquartile range	 86.9% 72.5%-97.6%	 92.2% 80.4%-100.6%

Table 1

Descriptive statistics shown as median values and 25%-75% interquartile ranges. Emphysema scores represent percentages of total lung volume. All lung function parameters are expressed as percentage of the predicted value. Moderate emphysema is detected as lung volume with an attenuation between -950HU and -910HU; severe emphysema is detected as lung volume with an attenuation below -950HU.

DISCUSSION

In this study investigating current and former heavy smokers mainly with a low extent of lung destruction, we demonstrated that for objectively quantified emphysema an apical predominance of lung destruction is accompanied with more severe airflow limitation and gas exchange impairment than a basal predominance. When using the GOLD-guidelines, subjects with an apical distribution have therefore a higher probability to be diagnosed as suffering from functional COPD than subjects with a similar extent of emphysema, but with a basal predominance. A similar argument holds when the diffusion capacity is used as diagnostic parameter.

The literature on the relation between PFT and emphysema distribution shows varying outcomes. Gurney reported a study investigating 59 heavy smokers that the Tlco and TLC showed stronger correlations with basal emphysema than with apical emphysema, but the FEV_1 and FEF_{25-75} showed the highest correlations with apical emphysema [15]. However, these differences were only statistical significant for subjectively quantified emphysema not for objectively quantified emphysema. In a subgroup of 15 patients with both a lowered Tlco and FEV_1, they showed that the Tlco, TLC and FVC correlated significantly better with lower lung zone emphysema, while Saitoh reported in a study in 62 subjects with a prior diagnosis of emphysema, that the FEV_1/VC showed the strongest correlations for with lower lung emphysema and the $Tlco/V_A$ with upper lung emphysema [23]. Haraguchi included 25 subjects with proven emphysema and reported that the Tlco correlated slightly better with middle and basal emphysema, while the FEV_1 showed the best correlation (r=0.64) with basal emphysema only [24]. Nakano concluded in their study of 73 male patients with a prior diagnosis of COPD that the $Tlco/V_A$ was stronger influenced by upper-inner and middle-inner emphysema and the FEV_1/VC by lower-inner and lower-outer emphysema [25]. The major drawback of this study was the use of stepwise backward multiple regression in which multi-collinearity could strongly have influenced the results. Aziz could not demonstrate any significant correlations in a retrospective study in 101 subjects with evidence of emphysema [26]. Finally, the study by Parr in patients with α_1-antitrypsine deficiency showed that the $Tlco/V_A$ ratio was stronger influenced by upper zone emphysema and the FEV_1 with lower zone emphysema [16]. However, these results could not be repeated in a later study [17].

Several reasons for these variations in results can be mentioned. The quantification method of emphysema was not standardized: some authors quantified the extent of emphysema subjectively, while other groups applied objective methods. The inclusion criteria were variable: some investigators included patients with a prior diagnosis of COPD or emphysema on HRCT, while others included subjects at risk to develop COPD. Selection bias can have influenced the outcomes seriously. In studies with a small sample size, outliers

and power can be a problem, while other studies suffered from statistical problems as multi-collinearity and some studies even excluded subjects from analysis.

In the present study we investigated two stages of emphysema (moderate and severe) and we showed similar effects: the stage of emphysema did not influence the impact of the distribution pattern on the extent of pulmonary function impairment. We avoided power problems by investigating a large group of subjects and included all subjects in the analysis. We dealt with multi-collinearity problems via principal component analysis model-independent analysis. Finally, we included smokers without a prior diagnosis of COPD.

The diffusing capacity is influenced by several parameters. In COPD not only the loss of alveolar membrane surface plays a role, but also the change in alveolar capillaries and the magnitude of the ventilation/perfusion (V/Q) mismatch have an impact on the gas exchange capacity. We reported that loss of alveolar tissue was not always accompanied by reduced diffusing capacity. The destruction of lung tissue in the lower lung zones apparently can be more extensive before pulmonary function impairment develops than the amount of apical emphysema. The sensitivity of the diffusing capacity to detect basal lung tissue destruction is lower than the sensitivity to the detect apical emphysema. Even in emphysematous lungs, the lower parts of the lung receive more blood than the upper parts do due to the effects of gravity. An increased capillary blood volume in the lower lung zones reduces the red blood cell resistance in the Roughton-Forster equation. This effect will increase the diffusing capacity and more severe pathologic changes in the alveolar capillary membrane are required to lower the diffusion capacity below normal values. Therefore we hypothesize that the remaining non-emphysematous lower lung tissue can more longer compensate changes in gas exchange due to lung destruction. This compensation mechanism does not occur in the upper lung zones to a similar extent, since the blood supply in this area is lower and lung destruction will result earlier in gas exchange impairment [27].

For the spirometry, the role of small airway disease in limiting airflow is important. Kim et al showed that two types of lung destruction can develop within smokers and that these types behave mechanically differently [28]. They reported that lung function in subjects with centrilobular emphysema (CLE) was more reduced compared to those with panlobular emphysema (PLE) and they reported that this was caused by the degree of small airway disease (SAD). In CLE the FEV_1/FVC ratio was negatively correlated to the severity of SAD, while in PLE SAD did not contribute to airflow reduction. Based on the data reported by Cosio [29], Saetta concluded that “there is also a definite tendency for small airways in the upper lung to be more diseased than those in the lower lung, a topographical distribution that corresponds to centrilobular emphysema”[30]. These observations agree with the results we reported in this study, that a location of lung destruction has a major impact on the extent airflow and gas exchange limitation,

next to the total amount of emphysema. Since small airways disease can lead to airtrapping, this can be an explanation for the reduction of gas exchange in patients with SAD.

In conclusion, subjects with smoking-induced emphysema mainly located in the apical lung zones have a higher risk for developing pulmonary function impairment than those with more basal located emphysema. For this reason, smokers with apical lung destruction should be subjected to a more aggressive risk-modifying approach to prevent them from severe COPD.

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