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# Emphysematous lesions and lung function in healthy smokers 60 years of age

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We aimed to study the occurrence of emphysematous lesions in symptom free smoking men of about 60 years of age and in a matching group of never-smoking men and the relationship between pulmonary changes at high resolution computed tomography (HRCT) and lung function tests.

Our investigation included 57 smoking and 32 never-smoking healthy men from a randomized epidemiological study. HRCT was performed at full inspiration with a 1·5 mm slice thickness and a 3 cm inter-slice distance. Evaluation was made by two radiologists unaware of smoking history. Emphysematous lesions were scored visually. Pulmonary function tests were performed including spirometry and diffusion capacity test ($D_L$CO).

Emphysematous changes were demonstrated in 25 of 57 smokers but in only one never-smoker. $D_L$CO/$V$A was the most sensitive test for early emphysematous lesions. It also correlated with radiographical scoring.

Emphysematous lesions were evident in 44% of the healthy symptom free smokers. HRCT may reveal early emphysematous lesions in smokers before clinical symptoms have developed.

**Key words:** computed tomography; pulmonary emphysema; respiratory function test; smoking.

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## Introduction

Chronic obstructive pulmonary disease (COPD) with emphysema induced by smoking is a common disease in the industrialized part of the world and causes high morbidity with an increasing mortality rate (1). Earlier studies (2) have stated that about 50% of all smokers will develop chronic sputum production and chronic bronchitis. These symptoms, however, do not predict further deterioration of pulmonary function or development of obstructive disease and emphysema (3,4). Nevertheless in at least 15% of the smokers the condition progresses to a degree that impairs lung function. The early symptoms and signs linked to the development of COPD are not known. No single inflammatory marker in the blood or locally in the bronchial tree, and no single pulmonary function test, has yet been identified which would make early diagnosis possible. Often patients will deny symptoms and will seek medical advice too late and any intervention at that time will have a limited effect. At present much research is going on to understand the pathology and to find early signs of COPD with the aim of making early intervention possible.

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Chest radiography is widely used to detect pulmonary lesions. This method, however, is neither sensitive nor specific for detection of early COPD and emphysema (5). Computed tomography (CT), and in particular high resolution CT (HRCT), is a much more sensitive method for detection of pulmonary disease and also provides a much better basis for specific diagnosis (6). In a study with HRCT on healthy volunteers Remy-Jardin *et al.* (7) found significant differences between current smokers, ex-smokers and never-smokers with more parenchymal micronodules, areas of ground-glass attenuation and emphysema in the smoking group. Presence of emphysema and bronchial wall thickening on HRCT was also associated with deterioration of lung function. In another study HRCT detected emphysema in patients with dyspnoea despite normal chest radiography and normal lung function tests (8). This suggests that HRCT may be used as a method for detection of early COPD, in particular emphysema.

We have investigated smoking and never-smoking men, all born in 1933, with HRCT. The men were recruited from an epidemiological study designed for the investigation of risk factors for cardiovascular disease (9). The aims of the present study were 1. to investigate the incidence of emphysematous lesions on HRCT in a group of non-symptomatic male smokers of about 60 years of age who had no history of lung disease in com-parison with a matching group of men who had never smoked and 2. to find out to what extent the changes demonstrated by HRCT correlated to results of lung function tests.

## Material and methods

Our study was cross-sectional with one group of never-smokers and one group of smokers. The purpose was to investigate the early development of COPD induced by smoking, in particular its effect on inflammatory and immunological parameters. The subjects were recruited from the randomized epidemiological study 'Men born in 1933 in Göteborg'. For this study 879 men were invited 532 of whom accepted (9). This cohort included 112 smokers, 222 ex-smokers and 198 men who had never smoked. The group of ex-smokers was not investigated further. All the smokers were invited, as was a random sample of 60 of the 198 never-smokers.

Men having sought medical attention for any cardiopulmonary problem including asthma ($n$=11) or congestive heart failure ($n$=2) were excluded. Another 11 persons were excluded because of various other diseases (rheumatoid, kidney disease etc). The rest of the drop-outs were for various reasons unavailable for the study. In all 58 smoking and 34 never-smoking men were examined by HRCT. Images from three subjects, one smoker and two never-smokers were of insufficient technical quality and were therefore excluded from further analysis. The final material therefore comprized for 89 men, 57 smokers and 32 never-smokers. The subjects were examined in the period from February 1994 to July 1995. Since all the men were born in 1933, they all were 61 or 62 years of age.

At the visit to our clinic the subjects first answered a questionnaire about their health. They then had lung function tests including spirometry and test of the diffusion capacity. These tests were followed by HRCT and a conventional X-ray examination of the chest. The study was approved by the Ethics Committee of Göteborg University, Göteborg, Sweden.

### HIGH RESOLUTION COMPUTED TOMOGRAPHY

The examination was performed with a Picker PQ2000 (Picker International, Cleveland, U.S.A.). The subjects were examined in a supine position and at full inspiration. The entire thorax was scanned with a slice thickness of 1·5 mm and a 3 cm inter-slice distance. Exposure data were 130 kV and 200 mA. The images were reconstructed with the sharp algorithm of Picker and six images were copied to each $14'' \times 17''$ film. The window width was set at 1400 HU and the level at $-400$ HU.

The images were analysed from the hard-copies by two experienced chest radiologists independently and without knowledge of whether the subject was a smoker or not. The radiologists analysed each slice in each lung. The diagnosis of emphysematous changes was based on findings of areas of low attenuation and/or presence of stretched, narrowed vessels. The degree of emphysema was scored as 0=no emphysema, 1=1–25% of the parenchymal area was involved, 2=26–50% involvement, 3=51–75% involvement and 4=more than 75%. The scores for each slice and lung were added and the sum divided by the number of slices obtained. In this way a score of total lung involvement could be calculated and the individual observer's evaluations compared. For comparison with the results of the lung function tests the mean of the two observers' results was used. To evaluate the interobserver agreement in the interpretation, a weighted kappa-analysis was used (10). All 1337 slices examined by both observers were compared. Slices with no score difference between the observers were weighted 1, a score difference of 1 was weighted 0·667 and of 2, 0·333. If the difference was 3 the weight factor was set to 0.

### LUNG FUNCTION METHODS

Spirometry was performed on a water sealed spirometer and according to the Official statement of the European Respiratory Society (11). Vital capacity (VC), forced expired volume in 1 sec ($FEV_1$) and its percentage of the VC (FEV%) were obtained. Total lung capacity (TLC) and residual volume (RV) was obtained using a body plethysmograph. The transfer factor ($D_L$CO) and the quotient between $D_L$CO and the alveolar volume ($V$A) ($D_L$CO/$V$A) were obtained by the single breath method (12) using standard equipment (SensorMedics 2200, SensorMedics Corporation, The Netherlands).

The results were expressed as a percentage of the expected (predicted) normal values. Normal values for VC, $FEV_1$ and FEV% were calculated according to Berglund *et al.* (13), TLC and RV according to Grimby *et al.* (14) and $D_L$CO and $D_L$CO/$V$A according to Salorinne (15).

## Results

### HIGH RESOLUTION COMPUTED TOMOGRAPHY

Emphysematous changes were demonstrated in 25 (44%) of the smokers but in only one (3%) of the never-smokers. The difference was highly significant ($P<0{\cdot}001$, Fischer's exact test). In the never-smoking person no low attenuation areas were demonstrated. The diagnosis was based on presence of

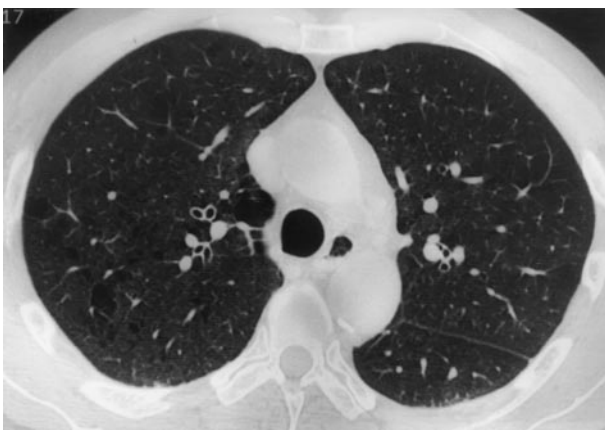

Fig. 1. Low grade of emphysematous lesions limited to the right lung.

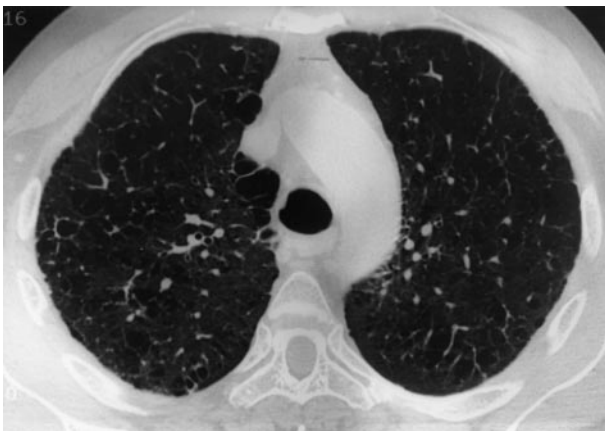

Fig. 2. Moderate emphysematous lesions in both lungs.

stretched vessels. There was a preponderance for upper lobe location in most persons (Figs. 1 and 2). In persons in whom emphysema was diagnosed by either of the observers the mean values of the emphysema scores ranged from 0·09–1·63. The never-smoker had an emphysema score of 0·17. The scores ranged from 0·14–1·69 (median 0·66) for observer A and from 0·00–1·56 (median 0·62) for observer B. The difference between the two observer's scores plotted against the averaged emphysema score appears in Fig. 3, a Bland and Altman diagram (16). The weighted kappa for all 1337 slices was calculated to be 0·78.

## LUNG FUNCTION TESTS

The results of the lung function tests appear in Table 1. The smokers had significantly lower $FEV_1$, FEV%, $D_LCO$ and $D_LCO/VA$ and higher RV. No significant difference between the groups, however, was demonstrated concerning TLC and VC. In an attempt to analyse whether the emphysematous changes or other consequences of smoking had had most influence on lung function the smokers with emphysematous lesions were compared to those without. The results appear in Table 2. There was a statistically significant difference only concerning $D_LCO/VA$. Furthermore a significant correlation was found between the emphysema score on HRCT and $D_LCO/VA$ (Fig. 4).

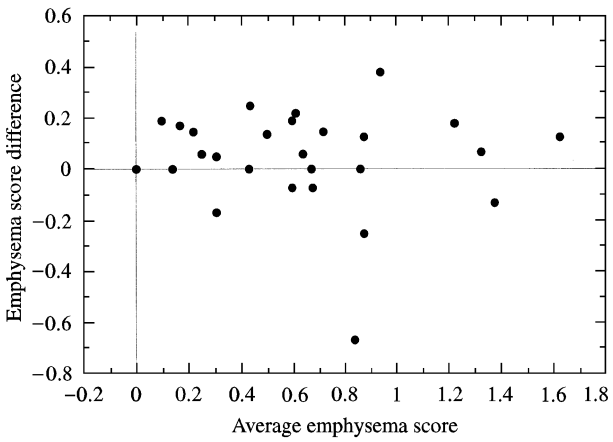


Fig. 3. A Bland and Altman plot illustrating the differences between the two radiologists scoring of emphysematous lesions in HRCT slices of 89 non-symptomatic male subjects. There were no emphysematous lesions according to both observers in 63 subjects.

TABLE 1. Lung function in 89 never-smoking and smoking men (percent of predicted values are given, statistical significance tested with Mann–Whitney *U*-rank test)

| | Never-smokers $n=32$ | | Smokers $n=57$ | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | *P*-value |
| TLC | 96 | 12 | 97 | 13 | n.s. |
| RV | 97 | 21 | 116 | 32 | <0·05 |
| VC | 94 | 13 | 88 | 13 | n.s. |
| $FEV_1$ | 108 | 16 | 94 | 17 | <0·001 |
| FEV% | 115 | 8 | 106 | 11 | <0·001 |
| $D_LCO$ | 97 | 13 | 82 | 13 | <0·001 |
| $D_LCO/VA$ | 94 | 13 | 83 | 16 | <0·001 |

For abbreviations see text.

# Discussion

Our study aimed at finding whether emphysematous lesions could be detected by HRCT in smokers without clinical symptoms. It might be anticipated that life in an urban area

TABLE 2. Lung function in 57 smoking men without and with findings of emphysema on HRCT (Percent of predicted values are given, statistical significance tested with Mann–Whitney *U*-rank test)

| | No emphysema $n=32$ | | Emphysema $n=25$ | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | *P*-value |
| TLC | 94 | 14 | 101 | 10 | n.s. |
| RV | 110 | 29 | 122 | 34 | n.s. |
| VC | 87 | 13 | 90 | 13 | n.s. |
| $FEV_1$ | 94 | 17 | 94 | 18 | n.s. |
| FEV% | 109 | 10 | 103 | 11 | n.s. |
| $D_LCO$ | 86 | 15 | 78 | 15 | n.s. |
| $D_LCO/VA$ | 88 | 15 | 75 | 15 | <0·01 |

For abbreviations see text.

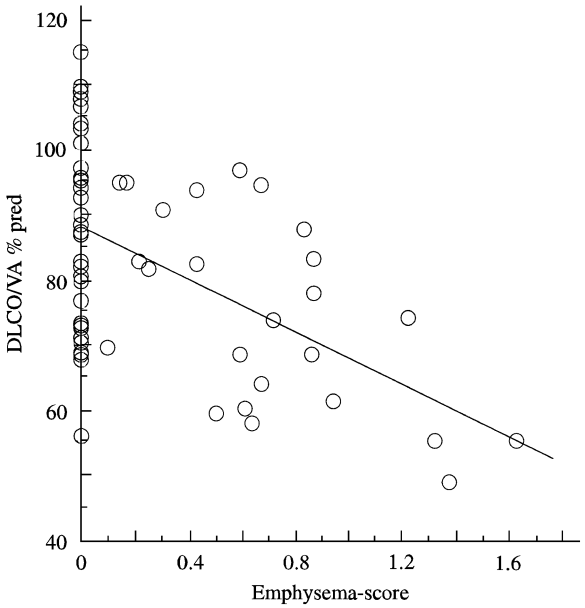


Fig. 4. Correlation between the CO-uptake/alveolar volume (transfer coefficient) and the mean emphysema score of the two observers in 26 non-symptomatic subjects with emphysematous lesion on HRCT. The Spearman rank correlation, Rho = −0·568.

with exposure for various infectious and pollutant agents for more than 60 years should leave some traces in the lung parenchyma. The influence of a noxious agent, in our case tobacco smoke would best be addressed by comparison with the appearance of the lung in an unexposed group, matched to age, sex and place of living. As a reference for the evaluation we therefore chose to include a group of men from the same epidemiological study who had never smoked. All persons, smokers and never-smokers, were selected at random and were of the same sex and age. All subjects were carefully interrogated and only those who previously had not sought medical attention due to pulmonary problems and who considered themselves healthy without symptoms of heart and/or lung disease were included. Smokers have been compared to never-smokers previously. We think, however, that our study has an advantage since little selection bias was involved and our results are therefore representative for the population studied. The conclusions drawn, however, are limited to men at the age of about 60 years.

The first report on diagnosis of pulmonary emphysema using computed tomography (CT) was published by Goddard *et al.* in 1982 (17). The technique, however, was not widely accepted until it had been refined with use of millimetre thin slices and high spatial resolution reconstruction algorithm (HRCT) (18). In most studies patients with symptoms of emphysema or chronic obstructive lung disease were investigated and good correlation has been found with lung function tests (19). The method has also been validated *in vitro* by comparison with specimens from lung surgery and post-mortem examinations and has been demonstrated to be accurate (20). Remy-Jardin *et al.* (21) reported a sensitivity of 100% and a specificity of 91% with use of targeted HRCT scans in comparison with pathology. Other reports, however, indicate that the earliest emphysematous changes may be overlooked (22). The latter authors, however, did not use HRCT.

When sensitivity for detection of pulmonary lesions is discussed it is important to consider the examination technique. In our study we used high resolution reconstruction algorithm and 1·5 mm thick slices spaced with 3 cm intervals. This is the usual technique for evaluation of generalized lung parenchymal disease. Use of non-contiguous slices, however, implies a risk that small lesions may be overlooked. Although emphysema may have an upper or lower lobe preponderance depending on the type of emphysema it still is to be considered a generalized disease and the risk that disease is not detected because of the examination technique may be considered small.

The main purpose of our investigation was to study the prevalence of smoking induced parenchymal lesions by HRCT and to compare this with a group of matched never-smokers. The evaluation was done by two experienced radiologists who did not have information of whether the subject was from the group of smokers or never-smokers. CT permits quantitation of the amount of emphysema (23). The usual way of doing this is by visual estimation of how much of a slice area is occupied by low attenuation parenchyma (18). The estimation may be refined by use of a grid (22), histogram analysis (24) or density mask (25). The density mask technique is based on computer analysis of how large a percentage of the pixels in a slice has HU-values below a certain cut off level (e.g. −950). We have analysed our material with this technique but found that although the technique can separate individuals with significant emphysema from those without, it cannot separate persons with the minor degrees present in our material, from those without. The human eye is more sensitive by recognizing differences in parenchymal pattern. We are trying to develop a computer technique for texture analysis which might improve the possibilities. We used visual estimation according to the method of Bergin *et al.* (20). This method gives an assessment of the extent of emphysema only. A single small emphysematous bulla gets the same score as emphysema involving up to 25% of the area of a slice. Since the scores of all slices were added and divided by the number of slices the final score constitutes a mean value for the entire lung, that is with a score of 1 there are emphysematous lesions in less than 25% of the lung. We did not try to differentiate between different types of emphysema. There was an upper lobe preponderance indicating centrilobular emphysema in most individuals but apart from the pattern of localization we do not think that it is possible to differentiate between different types of emphysema with HRCT.

Although the method was very crude it was considered good enough for our main purpose. Since several years we have been using WW 1400 and WL −400 HU for evaluation of the lung parenchyma. A lower level setting might have facilitated the detection of minor degrees of emphysematous changes but may instead introduce a risk of over-estimation of the degree. Our opinion is that

familiarity with the reading conditions is the most important factor and that these are kept constant. Our inter-observer variation was low (Fig. 3) and the kappa value shows a high rate of agreement and the scoring could be used for comparison with lung function tests (Fig. 4).

Changes which may be induced by smoking were very common in the group of smokers, emphysematous lesions being present in almost half (44%) of the men. The extent of the lesions was usually small which was to be expected since the group included only individuals without symptoms. The prevalence of these changes were higher than previously reported by Remy-Jardin *et al.* (7). The mean age of their subjects, however, was only 33 years and the smoking history therefore shorter probably explaining the difference.

Emphysematous lesions were also diagnosed in one subject in the never-smoking group. The extent of lesions, however, was small and the diagnosis was based on presence of stretched vessels. No predisposing factor could be demonstrated and the subject also had normal lung function. It is therefore impossible to tell whether the diagnosis of emphysematous lesions is correct or represents a false positive diagnosis.

## LUNG FUNCTION

Since emphysematous lesions, as demonstrated by HRCT, correspond to morphological emphysema the relationship between such lesions on HRCT and various lung function indices is of interest. From this relationship, conclusions may be drawn regarding the structural basis of various lung function indices.

In the present study, many healthy smokers had emphysematous lesions on HRCT and deteriorated lung function indices. These findings are in agreement with earlier HRCT-studies (26) and lung function studies (27,28,29). In the analysis of the relationship between structure and lung function indices only smokers were included. Otherwise smoking induced changes, not observable on HRCT, may be confounding factors. In the present analysis such hypothetical factors were assumed to affect all smokers similarly.

$D_L CO/VA$ expresses the ability, per unit alveolar volume, to transfer CO from alveolar gas to blood. This ability is dependent on the area of blood/air-contact per unit of alveolar volume. Emphysematous lesions are characterized by a reduced amount of alveolar septa per unit volume. Thus, both reduced $D_L CO/VA$ and emphysematous lesions reflect decreased blood/air-contact area. $D_L CO/VA$ was found to be significantly lower among those smokers who had emphysematous lesions compared to those without (Table 2). In addition, there was an inverse correlation between the emphysema score and $D_L CO/VA$ (Fig. 4), further supporting this relationship. This finding is in agreement with several previous reports on patients (8, 24, 30). Gelb *et al.* (31) studied patients with chronic obstructive pulmonary disease and reported a strong correlation between emphysema score on HRCT and $D_L CO/VA$ when $FEV_1$ was $>1$ 1. At lower $FEV_1$ there were no significant correlation indicating that airflow obstruction may cause reduced $D_L CO/VA$. In the present study, $FEV_1$ and FEV% were close to normal in most subjects and were almost identical among smokers with and without emphysematous lesions. Airway obstruction therefore appears to be an unlikely explanation for the reduction of $D_L CO/VA$. Figure 4 also indicates low $D_L CO/VA$ in subjects with minimal emphysema. This is almost certainly an expression of the expected methodological variation. The coefficient of variation of the never-smokers was 14% (Table 2) which is identical to the reference material (15). A somewhat higher coefficient of variation would be expected among smokers, thus explaining the scatter in Fig. 4.

TLC, RV, $FEV_1$ or FEV% were highly significantly different between never-smokers and smokers in accordance with previous observations (30,31). These variables were, however, not significantly different between smokers with and without emphysematous lesions. Thus emphysema appears not to be the main cause of these effects on lung volumes and forced expiratory flow. Other smoking induced effects on the lungs may be responsible, for example airway obstruction caused by inflammation.

It ought to be remembered that the present material consists of individuals with very mild radiological and functional defects. Relationships may exist in a material with more severe disease. On the other hand, this material is unique in as far as all subjects are of the same age and the same gender, reducing these sources of variability.

## CONCLUSIONS

Our study has shown that 1. smoking induced pulmonary lesions, that is emphysematous lesions, are common in non-symptomatic smoking men of about 60 years of age and born in Göteborg compared to a matched group of healthy never-smokers and that 2. smoking induced deterioration of lung function is mainly due to other factors than lesions identified on HRCT or that it is possible by HRCT to demonstrate morphological changes in a stage before symptoms develop. The structural basis for the emphysematous lesions identified on HRCT may, however, also be the basis for deterioration of $D_L CO/VA$.

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