ORIGINAL ARTICLE

High prevalence of emphysema and its association with BMI: A study of smokers with normal spirometry

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Abstract

Objectives. To evaluate to what extent emphysema was evident, as identified by High Resolution Computed Tomography (HRCT), in smokers with normal lung function and to relate age, gender, smoking history, and body mass index (BMI) to the HRCT results. A secondary aim was to study to what extent emphysema was present in smokers with lower normal values of lung function defined as FEV₁/FVC ratio percentage of predicted value (89–93% of predicted value for males and 90–93% for females) or FEF₅₀ ≤ 60% of predicted compared with smokers without this definition. **Methods.** Fifty-nine smokers, with a mean age of 53 years and with normal lung function, were examined with HRCT. **Results.** Emphysema evidenced visually by HRCT was present in 43% of the subjects. Using a 0–5 grade scale (0 = normal finding; 5 = emphysema in most slices), the degree of emphysema was almost exclusively 3–4. The type of emphysema was distributed as centrilobular emphysema predominant in 43.5%, paraseptal emphysema predominant in 43.5%, and as an equal mixture of these types in 13%. The presence of emphysema did not differ between the group of smokers with lower normal values of lung function and the rest of the smokers. Smokers with emphysema had significantly lower BMI than those devoid of emphysema, 24 and 27 respectively ($p < 0.0011$). **Conclusion.** There was a high occurrence of visual emphysema in middle-aged smokers with normal lung function. The densitometric quantitative analysis method is inadequate for detecting mild emphysema. High prevalence of emphysema was associated with low BMI.

Key Words: *Body mass index, computed tomography, family practice, pulmonary emphysema, smoking, spirometry*

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide [1,2]. Smoking cessation is the only intervention which has been shown to stop disease progression and lead to improvement of respiratory symptoms [3]. The treatment goal is to intervene as early as possible since smoking cessation before the age of 50 has been suggested to give the greatest health benefits and largest reduction in all-cause mortality in a COPD population [4].

In a previous study performed in primary care [5], a spirometry test to detect COPD at an early stage was offered free of cost to 40- to 55-year-old smokers. In that study, 371 smokers with normal

lung function and 141 smokers with COPD according to criteria of the European Respiratory Society (ERS) were identified [1]. Development of emphysema and gradual deterioration of lung function has been ongoing for several years before reaching the spirometric definition of COPD [6]. For the purpose of this study, we therefore defined a state of lower normal values of lung function, spirometry results in the form of a low forced expiratory flow at 50% of Vital Capacity (FEF₅₀) alone or a FEV₁/FVC ratio (FEV%) that was just above the diagnostic criteria for obstruction according to the ERS and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definitions [1,2].

Smokers with a mean age of 53 years had a high prevalence of emphysema detected by high resolution computed tomography (HRCT) despite having normal values assessed using spirometry.

- HRCT allows earlier detection of the noxious effects of smoking on lung parenchyma compared with spirometry.
- Tobacco smoke may have systemic effects causing loss of weight even before airway limitation is evident.
- The findings emphasize that smoking cessation is important irrespective of spirometric criteria for COPD.

Small airway disease and pathological lung function may exist in smokers who have spirometric measurements still within the normal range [6,7]. High resolution computed tomography (HRCT) may detect parenchymal lung abnormalities in healthy, symptom-free smokers [8]. HRCT is a sensitive method for detection of emphysema and studies suggest that HRCT could be used as a method for early detection of COPD [9,10].

The aim of this study was to evaluate to what extent emphysema was evident, as identified by HRCT, in middle-aged smokers with normal lung function. A secondary aim was to study to what extent emphysema was present in those smokers fulfilling the definition of lower normal values of lung function compared with smokers without this definition. An additional aim was to relate age, gender, smoking history and body mass index (BMI) to the HRCT results. Blood samples were taken for assessment of inflammatory activity by high sensitive C-reactive protein (hs-CRP) and eosinophil count.

Material and methods

Subjects

In a previous screening study in primary care, 371 smokers had normal spirometry according to conventional criteria [5]. Sixty of these 371 smokers were recruited in chronological order and invited to participate in this study. Excluded subjects were those with airway limitation evidenced spirometrically as $FEV_1\% < 88\%$ of predicted value for males and $< 89\%$ for females, in accordance with the ERS or signs and symptoms of asthma [1]. The study was performed at the University Hospital, Linköping, Sweden.

Anthropometric measurements, smoking habits, and blood samples

All participants answered a questionnaire concerning their current smoking habits. Height was measured, without shoes, to the nearest 0.5 cm. Weight was measured while the patient wore light clothing and no shoes. BMI, defined as weight in kilograms divided by the square of height in metres, was calculated. Eosinophil count and hs-CRP levels were determined using conventional methods.

Pulmonary function tests

Spirometry was performed by a trained technician using computerized equipment (MS-IOS Digital Instrument, Erich Jaeger AG, Würzburg, Germany). Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and forced expiratory flow at 25%, 50%, and 75% of Vital Capacity (FEF_{25} , FEF_{50} , FEF_{75}) were recorded and the best of three expirations was documented. Values were expressed as the percentages of predicted values (percentage of predicted). Reversibility tests were done 10 minutes after inhalation of four doses (0.4 mg/dose) of salbutamol (Ventoline Dischaler®, Glaxo Smith Kline, UK) and expressed as percentage change of FEV_1 . Reference values according to ERS [11] were employed. Prior to the spirometry, each subject rated breathlessness on a ten-grade Borg scale [12].

Definitions

Lower normal values of lung function: Post dilatation FEV_1/FVC ratio in percentage ($FEV_1\%$) 89–93% of predicted value for males and 90–93% for females or $FEF_{50} \leq 60\%$ of predicted value.

FEF_{50} : forced expiratory flow when 50% of the FVC has been expired.

COPD: $FEV_1\% < 88\%$ of predicted for males and $< 89\%$ for females, in accordance with the ERS [1].

Pack-year: A measurement of smoking exposure equivalent to smoking one pack a day for a year.

Formula: Number of years of smoking x average number of cigarettes smoked per day, divided by 20.

BMI: weight in kilograms divided by the square of height in meters.

HRCT protocol and evaluation of the degree of emphysema

In this study, HRCT was used as the gold standard as proof of parenchymal damage due to cigarette smoking. All CT examinations were performed with a General Electric Light Speed 8 slice machine.

Table I. Data showing the two groups of non-COPD individuals regarding gender, mean age, BMI, smoking history, and number of pack-years.

Characteristics	Lower normal values of lung function (n = 18)	Higher normal values of lung function (n = 36)
Female (%)	28	39
Age (years)	53.2 (4.1)	52.1 (4.3)
BMI (kg/m ²)	26.7 (4.0)	25.8 (3.5)
Smoking (years)	32.0 (7.8)	35.1 (5.7)
Pack-years	25.0 (11.7)	28.7 (11.9)

Notes: None of the differences was statistically significant. Data are presented as mean and standard deviation ($\pm$ SD); n = number of subjects; BMI = body mass index; pack-years = number of years of smoking $\times$ average number of cigarettes smoked per day, divided by 20.

Conventional 5 mm slices at 5 mm increments were reconstructed from a single breath hold with the patient supine in full inspiration. No contrast medium was administered. Separate non-single breath 1.25 mm HRCT slices were also collected from the whole thorax in 10 mm increments. The images were displayed on monitors with a 1600×1200 matrix at window width 1700 Hounsfield unit (HU) and window level -500 HU or at the viewer's own discretion to better view emphysema preferably by altering the window level to about -700 HU. The HRCT images were evaluated visually using structured forms by an experienced radiologist. Densitometric quantitative analysis (quantitative emphysema) of a 3D volume of the lungs with a cut off value of -950 HU as emphysema limit according to Park et al. [13] was carried out after selectively removing the trachea and main stem bronchi. The radiologist was blinded to spirometric values, clinical and smoking data. Any sign of centrilobular emphysema (CLE) or paraseptal emphysema (PSE) was noted and scored by the radiologist using a slightly modified version of the grading scale developed by Vehmas et al. [14]. The following scores were used: 0 = normal finding; 1 = faint abnormality/emphysema found in a single slice; 2 = distinct abnormality/emphysema in one to

two slices; 3 = abnormalities/emphysema in 2 to 5 slices; 4 = abnormalities/emphysema score in between 3 and 5; 5 = abnormalities/emphysema in most slices.

Statistics

Data were analyzed with Student's t-test for the continuous variables and a chi-squared test was used for categorical variables. Eosinophil count and hs-CRP were log transformed before the t-test. Data are presented using median values. All analyses were performed with SAS version 8.02.

Ethics

The study was approved by the Regional Ethics Committee, Linköping, Sweden.

Results

Sixty smokers with normal lung function from a previous study were invited and 59 consented to participate in the current study. Five smokers with spirometry values in accordance with the definition of COPD were excluded.

Table II. Findings of emphysema on HRCT in the group of smokers with lower normal values of lung function and the group with higher normal values of lung function: Grade and type of emphysema.

	Lower normal values of lung function (n = 18)	Higher normal values of lung function (n = 36)
Emphysema	8 (44%)	15 (42%)
Grade of emphysema		
0	10	21
3	3	7
4	5	7
5	0	1
Type of emphysema		
>CLE	6	4
CLE = PSE	1	2
>PSE	1	9

Notes: None of the differences was statistically significant. >CLE: centrilobular emphysema alone or predominant; >PSE: paraseptal emphysema alone or predominant; CLE = PSE: centrilobular emphysema = paraseptal emphysema.

Table III. Subjects allocated according to findings on HRCT. Data showing mean age, gender, number of pack-years, BMI, and lung function values.

	Emphysema on HRCT (n = 23)	No emphysema on HRCT (n = 31)
Female, %	43	39
Age (years)	52.7 (50.8–54.4)	52.3 (50.7–53.8)
BMI (kg/m ²)	24.2 (22.8–25.7)	27.4 (26.2–28.6)
Smoking (years)	34.2 (31.6–36.8)	34.0 (31.4–36.6)
Pack-years	29.4 (24.7–34.0)	26.0 (21.4–30.6)
FEV1 (% pred.)	103 (96–110)	103 (97–109)
FEF25 (% pred.)	104 (93–115)	106 (95–117)
FEF50 (% pred.)	76 (64–88)	78 (68–89)
FEF75 (% pred.)	52 (43–62)	56 (47–65)
FVC (% pred.)	110 (104–116)	109 (104–115)
FEV1/FVC ratio (%)	77 (74–79)	77 (75–79)
FEV1/FVC ratio (% pred.)	98 (96–101)	99 (97–101)
Rev-B2 (%)	3.5 (1.7–5.4)	4.2 (2.6–5.8)
HRCT, –950 HU (%)	1.096 (0.34–1.84)	0.665 (0.221–1.108)
CRP (mg/l)	2.05 (1.13–2.97)	3.43 (1.50–5.35)
Eosinophils (%)	0.186 (0.117–0.254)	0.145 (0.107–0.182)

Notes: There were no significant differences except for BMI. Data are presented as mean and standard deviation (SD); % pred = percentage of predicted; Rev-B2 = reversibility test with beta-2 agonist. T-tests were used for all variables and CRP and eosinophils were log transformed before the t-test.

In total 54 subjects were included, 18 of whom fulfilled the definition of lower normal values of lung function. There were more males than females. Subject characteristics and anthropometric measurements are shown in Table I. All but one subject rated his/her breathlessness between 0–2 on a ten-grade Borg scale. Subjects fulfilling the definition of lower normal values of lung function did not differ from the other smokers in terms of age, BMI, number of years of smoking, or pack-years (Table I).

Reversibility after inhalation of four doses (0.4 mg/dose) of salbutamol was significantly higher in the group of smokers defined as lower normal values of lung function than in the group with higher normal values of lung function ($p < 0.05$). Serum values of hs-CRP values were within normal limits, median 1.5 (range 0.28–27.5) mg/l, reference value < 10 mg/l and the median value of eosinophils was 0.13% (range 0.00%–0.78%), reference value 1%–4%. There were no differences between the groups regarding CRP in serum and eosinophils in differential counts.

HRCT scans

Emphysema was present by visual analysis in 43% ($n = 23$) of the subjects. There was no difference in the occurrence of emphysema between the two groups of lower and higher normal values of lung function ($p = 0.85$ Pearson's chi-squared test) (Table II).

The degree of emphysema was almost exclusively 3–4 (on a 5-grade scale) and did not differ between the groups ($p = 0.82$, Fischer's exact test). The type

of emphysema was distributed as CLE-predominant in 43.5%, PSE-predominant in 43.5%, and as an equal mixture of those two (CLE = PSE) in 13% and did not differ between the group of lower normal values of lung function and the rest of the smokers ($p = 0.11$, Fischer's exact test) (see Table II). The quantitative measurements of HRCT attenuation values (quantitative emphysema) did not differ significantly either between the two groups ($p = 0.11$). In total, by visual analysis, HRCT showed signs of emphysema in 23 of the 54 smokers with normal spirometry. When grouped according to the presence or absence of emphysema, BMI was found to be significantly lower in the group with emphysema ($p = 0.0011$). No differences were found when comparing spirometric parameters, CRP, eosinophils, smoking history, or pack-years (Table III).

Discussion

The main finding in this study was that emphysema evidenced visually by HRCT was highly prevalent in smokers with normal lung function. Among smokers ($n = 54$), who according to international guidelines all had normal pulmonary function, 43% had lung damage judged as emphysema using HRCT. Also, when applying the definition of lower normal values of lung function used in the previous study [5], the proportion with emphysema was similar. The hypothesis that the presence of lower normal values of lung function values, i.e. near the definition of COPD, was associated with higher prevalence of emphysema was not confirmed.

Limitations and strength

Our study has some limitations. We did not include a group of never-smokers since previous studies have shown that non-smokers generally do not develop emphysema [8,10,15]. In the studies by Tylen et al. and Vikgren et al. [10,15], which included considerably older subjects, 60–67 years old, emphysema was diagnosed in only one of 32 (3%) never-smokers and none of 26 never-smokers, respectively. It could be criticized that only one experienced thoracic radiologist evaluated the HRCT. However, previous studies have shown that inter-observer variation for assessment and grading of emphysema is low [8,10,14].

Our data are consistent with and confirm previous observations in other studies that found similar occurrence of emphysema in subjects with a higher mean age of 60 years than in the present study [10]. Additionally, a lower prevalence of emphysema (20%) was found in younger smokers with a mean age of 33 years [8].

Centrilobular emphysema is strongly associated with cigarette smoking [16]. In spite of previous opinions, paraseptal emphysema may also be smoking related [14,17]. Our study revealed that 43% of the smokers had predominantly paraseptal emphysema. However, none of the subjects in our study had isolated paraseptal emphysema.

The defined group of subjects with lower normal values of lung function had, by this definition, lower spirometry values compared with the rest of the smokers but there was no difference in the reported frequency of emphysema (see Table II).

In the latest versions of GOLD treatment guidelines stage 0: at risk has been omitted. The GOLD committee no longer categorizes a smoker having normal lung function, chronic cough, and sputum production to be “at risk” for COPD. Our results support the GOLD committee’s new classification since this study showed no difference in the occurrence of emphysema between smokers with lower normal values of lung function and the rest of the smokers. Respiratory symptoms are not helpful to recognize the most mild COPD in middle-aged smokers but a correlation has been found between respiratory symptoms as predictors of airflow limitation and the severity of airflow limitation in smokers aged 60 years and older [18,19]. Studies have shown a lack of correlation between mild COPD according to guidelines and degree of parenchymal damage detected using HRCT [9,20]. In established COPD, however, a correlation has been found between the severity of airflow obstruction and the extent of emphysema determined by HRCT [21,22]. HRCT attenuated values did not differ significantly either

between the groups of smokers. The study by Vikgren et al. showed that computer-attenuated measurements are inadequate for detecting mild emphysema [23].

In our study, smokers with proven emphysema had significantly lower BMI than those with no radiological signs of emphysema (see Table III). This difference in BMI, in these relatively young and healthy smokers, is an interesting observation since they had only slightly lower spirometry values that were within the normal level. In COPD, weight loss is probably multifactorial in origin. Besides the typical pulmonary pathology in COPD due to tobacco smoke, unexplained weight loss is a known and clinically relevant problem in patients with established COPD [24,25].

The reason for weight loss in these relatively young and healthy smokers is unclear. An accepted explanation of weight loss is excess energy expenditure due to the increased energy for breathing secondary to COPD [26,27]. Atrophy of skeletal muscle is generally the main cause of weight loss in established COPD [28,29]. COPD has recently been recognized as a disease not only restricted to airways, but also as a systemic disease [30,31]. Systemic inflammation may be a pathogenic factor that could explain the loss of weight in our subjects [32]. The inflammation in the lungs due to cigarette smoking may induce emphysema and weight loss before the airflow limitation is measurable by spirometry. We were unable to prove enhanced inflammatory activity as reflected by levels of circulatory C-reactive protein. Compartmentalization might be a possible explanation since a local inflammation in the pulmonary compartment may not necessarily be detected by measurements of C-reactive protein in the serum.

Conclusion

This study showed there was a high prevalence of emphysema detected by HCRT in smokers with a mean age of 53 years despite having normal values assessed by spirometry. Our findings suggest that HRCT allows earlier detection of the noxious effects of smoking on lung parenchyma compared with spirometry but not necessarily an earlier detection of COPD. These findings emphasize that smoking cessation is important irrespective of spirometric criteria. We also found that relatively young smokers with emphysema had significantly lower BMI than smokers with no emphysema, suggesting that tobacco smoke, in addition to the development of emphysema, may have systemic effects causing loss of weight even before airway limitation is evident.

Acknowledgements

The authors would like to thank the Health Research Council in the South-East of Sweden for their financial support, Mrs Elisabeth Forsström and Suzanne Martini for technical assistance, and professor Olle Zetterström for valuable advice with the manuscript.

Conflict of interest statement

No conflict of interest exists for any of the authors. None of the financial sponsors was involved in the study design, analysis, or interpretation of the data.

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