

## Detection of Smoking Induced Emphysema: Visual Scoring versus Computerised Algorithms

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### Abstract

**Purpose:** Computed tomography (CT) has been applied to assess signs of early disease in a population study. Comparisons were made of histogram based methods to quantitatively determine lung density; relative area of emphysema below -910 and -950 Hounsfield units, and 15th percentile density (RA -910, RA -950 and PD15), as well as visual assessment of computed tomography (CT) images, to lung function indices in a population based study of smokers and non-smokers.

**Methods:** 138 subjects from a study of lung function in COPD were included in the study. Computerised assessments and visual scoring were used to analyse CT scans of different regions of identifying subjects with emphysema.

**Results:** Subjects visually diagnosed with centrilobular emphysema had significantly lower lung density (n=27, PD15=-932 HU, RA-950=6.6%) compared to subjects without emphysema (n=106, PD15=-917 HU, RA-950=2.3%). In the group with low PD15, the proportion with visually determined centrilobular emphysema was 38%, compared to 15% in the groups with high PD15.

**Conclusion:** Evaluation of patterns of lung attenuation by automated assessment and visual scoring provided similar classifications of disease in patients with mild COPD but differed in identifying regions of low density in healthy subjects. Visual assessment showed better correlation to both lung function and smoking habits than quantitative measures in this study. Quantitative measures should be used in the upper third of the lungs to detect smoking induced emphysema. Measurements of early attenuation changes within healthy subjects may require additional measures of validation by radiologists by visual assessment.

**Keywords:** COPD; Emphysema; Computed tomography

### Introduction

Chronic obstructive pulmonary disease (COPD) is a major and rising public health risk and the severity of airflow limitation is still a core element in diagnosis, assessment, and therapeutic management [1]. However, emerging data on COPD reveal substantial complexity, and it is generally accepted that the early pathological changes in COPD are not captured by spirometry only. Thus, a better understanding of the intricacy of COPD is important to improve current clinical practice and advance biomedical research and drug development. CT data should add another dimension into the description of COPD types and their progression.

Emphysema is often seen as co-morbidity to COPD and could even be regarded as a specific phenotype. CT imaging of the chest can be used to describe different structural expressions of COPD, as well as broad pathogenic sequences (such as: large airway disease, small airway disease, gas trapping and unique patterns of emphysema).

The speed and the low cost of the computerised quantitative CT methods are major advantages in studies with big numbers of CT scans. Furthermore, they are free from individual judgement bias. However, visual assessment of the pattern of emphysema and of airways disease, as well as of large airway abnormalities may provide information not readily assessed by current quantitative methods.

Although a useful tool, there is currently no standard for these computerised techniques. Knowledge on to what extent these measures

reflect actual COPD associated emphysema and correlates with other measures of the disease are increasing rapidly. Efforts have been made to find optimum thresholds [2], to use quantitative measures in indices [3] as well as more direct comparisons to lung function parameters [4]. Even though official guidelines do not exist the field was summarised in a workshop providing some clear recommendations [5] and reviewed recently [6].

The primary purpose of the present study was to compare computerised assessments and objective visual scoring of CT scans in twins with and without COPD. We also analysed the associations between CT emphysema and results from lung function tests with control for the influence of potential confounders such as sex, age, BMI, and tobacco consumption.

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## Methods

### Study population

All subjects were twins retrieved from the Swedish Twin Registry (STR), containing information on more than 80,000 twin pairs. Between 1998 and 2002, all living twins in the STR born in 1958 or earlier were contacted using a computer-assisted telephone interview [7], including a checklist of common diseases and respiratory symptoms, as well as smoking habits. From this telephone interview, 1,030 twins (in 515 pairs) were invited to participate in measurements of lung function [8]. The study was approved by the Ethical Committee at Karolinska Institute (# 03-461).

In total, 392 twins accepted the invitation to participate, and following spirometry screening 139 subjects with a FEV<sub>1</sub>/VC ratio 5 units below the predicted value, or FEV<sub>1</sub> below 90% of the predicted value were selected for CT. The FEV<sub>1</sub>/VC-ratio 5 percent units below predicted corresponds well with the fixed GOLD ratio in middle ages, but is age corrected (since the predicted value is) so that overestimation of COPD in the elderly could be avoided. Also twin siblings to these with impaired lung function were selected for computed tomography. After the exclusion of five subjects with poor quality or incomplete data, 133 subjects remained. The selection of subjects was initially conducted for a heritability study as described previously, in a manner that disease concordant and discordant twins were prioritized over symptom-free twin pairs [9].

### Image acquisition

Inspiratory CT image data were obtained in all subjects using a 4 slice a Siemens Volume Zoom CT scanner (Siemens Medical Solutions, Erlangen, Germany) in two modes:

1) A continuous helical scan (140 kV, 24-29 mAs, 750 ms rotation time) from apex to base with 5 mm axial slices reconstructed using a standard algorithm (B30s kernel).

2) Discrete 1 mm axial HRCT-slices (140 kV, 100 mAs, 500 ms rotation time) at three different levels; through the apices, at the hilar level and through the bases of the lungs, respectively, reconstructed using a B70f kernel.

The protocol was optimised for picture quality given the radiation constraints in this study including healthy volunteers. All images were stored electronically in the hospital PACS (picture archiving and communication system).

### CT densitometry

Quantitative assessment of CT lung density was performed using the VIDA Apollo software version 1.1 (VIDA Diagnostics, Inc, Coralville, IA, USA). Attenuation in the lung is expressed in Hounsfield units (HU), where zero HU corresponds to the attenuation of water and -1000 HU to air. The 15<sup>th</sup> percentile density (PD15), i.e. the HU value below which 15% of the lowest attenuation values are distributed, may also be expressed as density in g/L by adding 1000. The percentage of the lung volume with attenuation below the cut off values -910 HU and -950 HU (RA-910 and RA-950), as well as PD15 were calculated for the entire lungs, as well as separately for the upper, middle, and lower thirds of the lungs using the volumetric scan.

### Visual assessment of CT scans

Visual assessment was independently performed by two radiologists. The continuous 5 mm helical images (with edge enhancement) and the discrete HRCT-slices were viewed simultaneously on 30"

wide Eizo Rx430 screens with parenchymal window settings (width 1700 HU, center -400 HU). The radiologists, used to protocols with higher radiation doses judged the difference between clinical routine protocol and the one used in the study as negligible. Subject scans were individually classified as showing a predominant pattern of the parenchymal features: 1) normal, without areas of low attenuation; 2) centrilobular emphysema (CE); 3) distended or both distended and with CE. The term "distended" was used for describing low attenuation with a pattern that seemed to be due to hyperinflation of the lung rather than loss of parenchyma.

In this study with relatively mild disease we judged these classes to be sufficient. CE defined by one of the radiologists was considered sufficient for overall classification. Further abnormalities in radiological features were also recorded. Separate scoring was performed on scans of the whole lung and in the upper, middle, and lower zones of the lung.

### Spirometry

All lung function tests were carried out in a specialized clinic by an experienced team of three persons. Lung function (FEV<sub>1</sub>, VC and lung diffusion capacity for carbon monoxide; DL<sub>CO</sub>) was measured according to American Thoracic Society [10,11] using a SensorMedics Vmax Encore system (SensorMedics; Yorba Linda, CA, USA). FEV<sub>1</sub> was compared to the largest obtained VC, and individuals with an obstructive pattern also performed a new test 15 minutes after bronchodilation.

### Smoking

Self-reported cigarette smoking was assessed at the clinical examination and quantified as pack years. No smoking exposure was defined as <5 pack years.

### Statistical Methods

The characteristics of subjects with and without centrilobular emphysema were presented as medians for continuous variables and proportions for categorical data. The Mann-Whitney U-test and Pearson's chi-square tests were used to calculate the p-values.

The sample was categorized into four sex-specific similarly proportioned quartiles, according to the PD15 -values for the whole lung and for the upper lung separately. One-way analysis of variance was used to compare the continuous variables across the quartiles. P-values less than 0.05 were considered statistically significant. We also present p-values between 0.05 and 0.10 as tendencies. For all statistical calculations SPSS ver. 10 (SPSS Inc. Chicago, U.S.) was used.

### Results

The mean age of the included 133 subjects (47 men and 86 women) was 60.7 (±8.2 years, range: 47-81). Of them, 27 (20%) were considered to have centrilobular emphysema. Of these 27, one was classified as GOLD stage 0, thirteen as stage 1, eleven as stage 2, and two as GOLD stage 3.

In 17 subjects (13%) both readers defined the presence of CE. In 30 of the subjects there was a disagreement on the classification (Table 1). Of the remaining subjects, 2/27 subjects were visually assessed as paraseptal emphysema, and 1/27 as panacinar emphysema.

Subject characteristics (personal data, lung function, and smoking habits) according to visual assessment (CE or No CE) are given for each group in Table 2. FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, DL<sub>CO</sub>, and smoking showed statistically significant differences between subjects with and without emphysema. The group with emphysema tended to have higher RV/

	Class	Number	Percent
1	Centrilobular emphysema parenchymal destruction	6/14	4/10
2	Distended parenchyma/very even emphysema	14/26	10/18
3	Both (1 and 2)	21/8	15/6
4	All centrilobular emphysema (1 and 3)	27/22	19/16
5	Normal	97/92	69/65
6	Not valid for classification	3/1	2/0,7
7	Different opinion	30	21

**Table 1:** Classifications are presented in the form "radiologist one/radiologist two" both for numbers and percentages. Class 4 and 7 was not original class, but constructed afterwards.

	Centrilobular emphysema				P-value*
	No		Yes*		
	N	Median	N	Median	
Age (years)	106	59.5	27	61	0.29
Men, n (%)	106	34 (32)	27	13 (48)	0.18
BMI (kg/m <sup>2</sup> )	106	24.3	27	23.5	0.22
Height (m)	106	1.68	27	1.70	0.85
DLco (mmol/min/kPa)	106	21.3	27	16.1	<0.001
Smokers (%)	106	32 (30)	27	16 (59)	0.010
Packyears	99	8.5	27	31	<0.001
FEV1, % of PN	106	95	27	80	0.018
FVC, % of PN	106	114	27	112	0.44
FEV1/FVC	106	0.68	27	0.63	<0.001
RV/TLC	104	0.39	27	0.44	0.084
No COPD	26 (25%)	--	1 (3.7%)	--	0.003
GOLD 1	51 (48%)	--	13 (48%)	--	
GOLD 2	28 (26%)	--	11 (41%)	--	
GOLD 3	1 (0.9%)	--	2 (7.4%)	--	

\*Visually rated as centrilobular emphysema by at least one (out of 2) readers.

\*P-values calculated using Mann-Whitney U-test for continuous variables or chi-square test for dichotomous variables.

**Table 2:** Characteristics of subjects with and without centrilobular emphysema.

TLC ratio (p=0.084).

Quantitative CT measures of lung density in relation to visually assigned CE status are given in Table 3. For the whole lung, CE subjects showed significantly lower lung density scores than subjects without CE, both for relative area of emphysema (RA-950) and 15th percentile density (PD15). RA-910 for the whole lung was not significantly different between subjects with and without CE. The ratio between upper and lower lung was significantly different for RA-950, but not for RA-910 or PD15.

The computer derived lung density measurements were only partially concordant with the visual assessment in identifying the same individual as having centrilobular emphysema. This disconnect between the computer generated mean levels of lung density (HU as an index of emphysema disease), and the patterns of emphysema observable in images of the lung, occurred frequently. Computerised assessment identified 26/106 centrilobular emphysema free subjects as exhibiting PD15 scores less than the median PD15 score of subjects with visual assigned CE (median CE: -932 HU=68 g/l, non CE range -933 to -949 HU=68-51 g/l). Of these 26 subjects 15 further showed comparable relative area of emphysema<RA-950 HU scores to CE subjects (median CE% <-950 HU=6.6%, non CE range=6.6-14.2%). In terms of GOLD guideline definition, 17/26 of these patients were GOLD stage 1, three were GOLD stage 2, and four subjects were GOLD stage 3.

	Centrilobular emphysema		P-value
	No (N=106)	Yes (N=27)	
	Median	Median	
RA-910 whole lung	20.2	27.3	0.096
RA-910 upper	20.8	36.3	0.004
RA-910 middle	19.9	27.6	0.21
RA-910 lower	19.6	24.9	0.21
RA-950 whole lung	2.31	6.63	<0.001
RA-950 upper	2.39	7.22	<0.001
RA-950 middle	2.30	5.02	0.001
RA-950 lower	2.34	5.68	0.004
PD15 whole lung	-917	-932	0.010
PD15 upper	-916	-933	<0.001
PD15 middle	-916	-924	0.078
PD15 lower	-916	-925	0.091

**Table 3:** Quantitative CT measures of lung density given as PD15% (in HU), RA-910 and RA-950 (both in percent below) in relation to centrilobular emphysema, assessed in the whole lung, as well as for different regions of the lung.

	Whole lung: Sex-specific quartiles of PD15				P
	Q1	Q2	Q3	Q4	
N	32	34	34	33	
PD15 men	<-938	-938 - -929	-929 - -914	>-913	
PD15 women	<-929	-929 - -916	-915 - -901	>-900	
Age, years	62.9	61.7	60.0	58.5	0.02
Men,%	34	35	35	36	
Smoker,%	44	21	35	45	0.57
Pack-yrs	17.8	15.4	19.2	18.4	0.68
FEV1, % PN	87	93	88	90	0.84
FVC, % PN	118	116	109	109	0.01
FEV1/FVC	0.60	0.66	0.66	0.68	<0.001
DLco, (mmol/min/kPa)	19	22	21	22	0.09
RV/TLC	0.41	0.40	0.41	0.40	0.52
BMI	23.0	23.8	25.3	26.5	<0.001
Centrilobular emphysema, (%)	38	15	14	15	0.04

**Table 4:** Smoking, lung function measures and biomarkers in relation to sex-specific quartiles of PD15

	Upper third of the lung: Sex-specific quartiles of PD15				P
	Q1	Q2	Q3	Q4	
N	32	34	34	33	
PD15, upper third men	<-938	-937 to -929	-928 to -916	>-914	
PD15, upper third women	<-930	-930 to -916	-916 to -902	>-902	
Age (yrs)	62.2	62.6	60.1	58.1	0.021
Men%	34	35	35	36	
Current smoker%	47	29	26	42	0.68
Pack-years	20.8	15.0	18.1	17.3	0.65
FEV1, % PN	88	94	88	88	0.72
FVC, % PN	117	118	109	108	0.005
FEV1/FVC	0.62	0.65	0.66	0.68	0.003
DLco, (mmol/min/kPa)	18.6	22.1	20.4	22.2	0.063
RV/TLC	0.41	0.40	0.41	0.40	0.60
BMI	23.1	24.6	25.2	25.6	0.001
Centrilobular emphysema (%)	41	21	8.6	12	0.003

**Table 5:** Upper third of the lungs: Smoking, lung function measures and biomarkers in relation to sex-specific quartiles of PD15.

The relationships between the cut off (in HU) for PD15 in quartiles (standardized for sex) for the whole lung, smoking and physiological measures of lung function are presented in Table 4. The proportion with centrilobular emphysema was 38% in the group with lowest PD15, as compared to approximately 15% in the PD15-quartiles 2-4. There was no significant relationship between current smoking or pack-years and PD15. FEV<sub>1</sub> was similarly unrelated to PD15. DLCO tended to be lower in subjects with low density (i.e. low PD15). In an additional analysis the relationships between PD15 and centrilobular emphysema were slightly weakened when PD15 was adjusted for lung volume (not shown). Corresponding analyses were also done for the upper third of the lung only. However, the relationships were only slightly improved compared to using PD15 for the whole lung (Table 5).

A multiple linear regression model was used to explore variables associated with PD15 (Table 6). BMI and sex were significantly associated with PD15. Of the lung function measures, FEV<sub>1</sub>/FVC (low values) and FVC (high values) were associated with low PD15, as could be expected, but there was no relationship between smoking and PD15 in the upper third of the lungs. Neither DLco, FEV<sub>1</sub> (% PN), nor RV/TLC were associated with PD15 in this model. The results were essentially the same if the PD15 of the upper third of the lung was used.

## Discussion

In the present study computerised methods and visual assessment of computed tomography (CT) scans were compared in a population based study of COPD, to explore the relationships between CT findings, emphysema, smoking, and decreased pulmonary function. The purpose was to assess if quantitative measures could be helpful in early differentiation of risk for COPD.

In centrilobular emphysema the alveolar walls are destroyed starting at the centre of the lobule and the respiratory bronchioles are expanded. This sub-type occurs more commonly in the upper lobes and is closer related to cigarette smoking and COPD than other forms [12].

Computed tomography (CT) is increasingly used for the diagnosis of emphysema. Automatic methods provide qualitative and quantitative estimates of emphysema by acquiring point by point (by voxel position) attenuation measurements that identify locations in the lung with low density. Speed, repeatability and low cost are obvious advantages. Visual inspection by a radiologist has other benefits: a radiologist can visually recognize patterns and spatial distributions of low attenuation and map distributions of disease, especially for other findings than emphysema, in a way that most current automatic algorithms cannot [13]. This is also considered the most likely reason to the discrepancy between quantitative and qualitative measures in the present study. In 1984

Hayhurst et al. [14] demonstrated that quantitative CT measurements using a density threshold could be used to detect the presence of emphysema. Müller et al. [15] showed the highest correlation between pathology and CT-measures using the threshold RA-910 [%]. Gevenois et al. [16,17] recommended the use of RA-950 for thin-section CT. Both these thresholds, as well as the fixed ratio PD15 have been used in several studies for the purpose of assessing the degree of emphysema [18-22]. Further, these measures have been used obtained both at maximum inspiration and maximum expiration [23]. Both for the upper part and for whole lung PD15 was recommended by an expert group to be used in longitudinal studies [24].

PD15 showed higher values (more dense tissue) for females than males. This is in concordance with findings of Dransfield et al. [25] who reported larger areas below -950 HU for the same GOLD stage of COPD in men than in women. The reason for this is unclear; maybe this is associated with the generally slightly lower ratio between FEV<sub>1</sub> and FVC (i.e. that they are more obstructive), which could lead to a slight over inflation, or the more extensive growth of the male thorax during adolescence after the lung tissue is formed during the fetal period.

Our results show that centrilobular emphysema, assessed by two experienced radiologists, was significantly associated with smoking history, air flow limitation, DLco and GOLD-stage. On the other hand, PD15 showed no consistent relationship with smoking or DLco when measured in the whole lung, and relationships were only slightly improved when measured in the upper third of the lung. Using a fixed cut off the present study showed better agreement between visual scoring and the cut off at -950 HU than for -910 HU.

Even if it is widely accepted that smoking is a major causal risk factor of COPD and emphysema, previous studies of the relationships between smoking and lung density have not been unambiguous. In the present study, there was no significant relationship between pack-years and tissue density in smokers without COPD. One of the problems is that smoking itself tends to increase density of the lung parenchyma (by inflammation, cells, fluid etc), masking signs of emphysema, and making density less correlated to actual loss of alveolar septa. Hence the time relation between exposure and assessment is important [26-28]. In a sub-study from the ECLIPSE trial [29], there was a weak, but statistically significant relationship between pack-years and RA-950 in subjects with COPD. However, also in that study current smoking was strongly associated with higher densities, which outweighed the effects of decades of heavy smoking. This masking effect seems greater in subjects which has not yet acquired significant airflow limitation.

In our study of COPD the PD15 and other computerised algorithms did not show a better correlation to other measures of COPD than visual assessments. The reason is probably due to better pattern recognition in visual assessment, which is supported by findings by Gietema et al. [30]. Our findings are in concordance with a recent meta-analysis [31] in which emphysema detected visually on CT was found to be independently associated with increased odds of lung cancer, but not emphysema that was automatically detected. On the other hand another recent meta-analysis of these measures showed significant correlation between CT measurements of emphysema and airflow obstruction, with the strongest association found between CT emphysema measurements and the ratio FEV<sub>1</sub>/FVC, thus confirming correlations between morphology and function in COPD patients [32].

The physiological measures of lung function showed very different patterns for visually assessed centrilobular emphysema and measured low lung density. Visual assessment was associated with significantly

	PD15, whole lung		PD15, Upper third	
	Beta (+SE)	P	Beta (+SE)	p
Age (per 1 year)	-0.36 (0.22)	0.11	-0.79 (0.32)	0.017
Sex (women vs men)	12 (4.0)	0.004	8.8 (4.9)	0.075
BMI (per 1 kg/m <sup>2</sup> )	1.7 (0.60)	0.004	1.9 (0.74)	0.011
Pack-years (per 1 year)	-0.04 (0.10)	0.70	-0.16 (0.13)	0.21
FEV <sub>1</sub> /FVC (per 1%)	0.97 (0.22)	<0.001	0.90 (28)	0.002
FEV <sub>1</sub> (per 1%)	0.15 (0.11)	0.17	0.12 (0.13)	0.36
FVC (per 1%)	-0.21 (0.12)	0.08	-0.21 (0.15)	0.16
DLco (per mmHg/kPa x min <sup>-1</sup> )	0.33 (0.37)	0.37	0.71 (0.45)	0.11
RV/TLC (per 1%)	-0.31 (0.28)	0.26	0.16 (0.34)	0.65

**Table 6:** Results from multiple linear regressions with PD15 as dependent variable. Age, Sex, BMI, and pack-years were entered in the first step. The lung function measures were then individually adjusted for the variables in the first step.

reduced FEV1, FEV1/FVC, and DLco, and although not significantly, increased RV/TLC. This is what could be expected from a clinical point of view. In contrast, low lung density was associated with increased FVC. CT scans was performed at maximum inspiration, which in spirometric terms means at total lung capacity (TLC). However, as usual in routine CT scanning, the lung volume during scanning was not measured spirometrically, i.e. we have no means to investigate if the lung volume at scanning differed from TLC measured by spirometry, and slight differences in level of inflation could result in this correlation since more inflation will result in less density generally. If we could have corrected for lung volume at scanning this would have been an advantage.

Another thing that can improve accuracy is correcting density values using the HU value measured in the trachea. However, an automatic internal HU value calibration using tracheal air could not be performed in the present study due to the thick slices and the resulting challenges to accurately segment the airway tree.

There was an observed strong correlation between lung density and BMI, also seen previously [33]. While lung density is also artifactually influenced by scattered x-ray radiation, this contribution is expected to be relatively low when using a 4 slice CT scanner with a small cone beam angle. Even though low BMI is associated with low density, this association occurs in predominantly in advanced COPD disease, while in this group with only three subjects with GOLD Stage 3 (none stage 4). The alternative approach chosen to adjust for these effects was to include BMI as a co-variate in the multi-variate analysis.

To conclude, in this population based study measuring lung attenuation by CT in subjects with relatively mild degree of COPD, both quantitative automated assessment methods and visual scoring provided similar classifications of disease. Overall, both lung function and smoking showed closer statistical correlation to visual scoring than the software driven assessments. However, the advantages of using automated evaluation are several including cost and the non-biased but robust assessments of regions throughout the whole lung.

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#### Declaration of Interests

Dr Gerhardsson de Verdier, and Dr Nordenmark are employees at AstraZeneca, Dr Engström, Dr Fehniger and Dr Dahlbäck were employed at AstraZeneca at the time of the study. The authors have nothing else to report.

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