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CT emphysema distribution : relationship to clinical features in a cohort of smokers.

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Key Words

COPD
Emphysema
Low attenuation areas
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Distribution

ABSTRACT

Background

CT scanning allows precise assessment of both the extent and distribution of emphysema. There has been little work on the relation between the distribution of emphysema and clinical features of the disease. We investigated the association between clinical features and distribution of emphysema.

Methods

One hundred and twenty nine patients with smoking-related COPD had CT assessment of the extent and distribution of their emphysema (core/rind and upper/lower zone predominance). .

Results

Emphysema was predominantly in the upper-core zone and this distribution was related to the extent of disease. Core predominance was associated with lower FEV_1, FEV_1/FVC ratio and BMI; higher BODE index and MRC dyspnoea score. Upper zone predominance was associated with female sex and an increased total SGRQ. Using multiple linear regression age, sex and whole lung emphysema severity were independently associated with core/rind distribution; while sex and whole lung emphysema severity were independently related to upper/lower distribution.

Conclusions

Distribution of emphysema related best to clinical features when divided into core/rind predominance. However, these effects were not independent of the extent of emphysema. Increasing age and female sex were related to disease distribution independent of

emphysema severity. These findings may be related to differences in development of emphysema.

INTRODUCTION

Emphysema causes airflow limitation in chronic obstructive pulmonary disease (COPD) through destruction of the alveolar walls, resulting in decreased lung elastic recoil and airway collapse. [1] Emphysema leads to a marked decrease in lung tissue volume and an increase in airspace volume. These changes can be demonstrated by CT scanning as regions of reduced lung density. [2]

Advances in CT scanning and specifically designed software now allow precise assessment of the extent of emphysema. Areas of the lung with a density below a given threshold (commonly -950 Hounsfield Units) are designated as emphysematous. This technique has been validated against pathology [3, 4] and pulmonary function. [5, 6] In addition, the technology can be used to assess the *distribution* of emphysematous disease: an approach that has been utilised in assessing patients for (and in the outcomes of) lung volume reduction surgery, [7, 8] and also in monitoring changes in emphysema longitudinally in alpha-1 antitrypsin deficient patients. [9] The distribution of the parenchymal damage varies between individuals, but the reasons for this are not known. This heterogeneity is reflected in the wide variation in clinical features seen. Despite this, there is a paucity of studies which have investigated how differences in the distribution of emphysema relate to different clinical features among patients with COPD. [10, 11]

In this study we categorised patients according to the distribution of their emphysema. We hypothesise that clinical features should vary between patients with different

distributions. It is hoped that using CT we could identify patterns of disease which correlate with clinical severity. To our knowledge, other than with spirometry, such comparisons have not previously been made.

METHODS

Study Patients

Current and ex-smokers with a clinical history consistent with COPD defined by; symptoms of cough, sputum production and/or breathlessness and a >10 year pack years smoking history were recruited from primary care and through a respiratory outpatient clinic at the Royal Infirmary of Edinburgh. Diagnosis was confirmed with a post bronchodilator FEV_1/FVC ratio less than 70%. [1] Patients were studied when clinically stable, at least six weeks post-exacerbation. Subjects with other respiratory conditions, systematic inflammatory diseases or prescribed regular oral corticosteroids were excluded. One hundred and twenty nine patients were recruited. All studies were performed with the approval of Lothian Regional Ethics Committee, and written informed consent was obtained from all subjects.

Study Design

A structured questionnaire was administered by trained healthcare staff to record baseline characteristics including past medical history and smoking status. MRC chronic bronchitis score, MRC dyspnoea score, and the St George's Respiratory Questionnaire

(SGRQ) were recorded. Exacerbation frequency was assessed by patient recall over a one year period. An exacerbation was defined as an increase in symptoms requiring a course of corticosteroids or antibiotics. Corroboration was obtained in most cases by review of the patients hospital and /or general practitioner notes.

Patients performed a six minute walk according to ATS guidelines. [12] Spirometry was performed in triplicate (Vitalograph®, Ireland) with reversibility to salbutamol (2.5mg nebulised). Height and weight were measured to calculate body mass index (BMI). BODE index was calculated as described by Celli et. al. [13]

CT Protocol

Study subjects had a low dose quantitative thoracic CT scan at full inspiration. Patients were coached to achieve total lung capacity. No intravenous contrast was administered. A Toshiba Aquilion (16 slice CT scanner) was used with the following parameters: 135kV, 40mA, rotation time 0.5 sec, 16x 1mm collimation, pitch 1.45, reconstructed at 2.5mm intervals with 5mm thick slices and at 1mm intervals with 1mm slices, FC-03 filter. Slices were reconstructed to maximise on analyzable data; all slices were used in the quantitative analysis. The Hounsfield Unit (HU) for air was recalibrated using a method similar to that described by Stoel et. al. [14] to correct for the air offset in Toshiba CT scanners (about –985 HU instead of the nominal –1000 HU with this filter). All CT scans were reviewed by an experienced chest radiologist (JTM). On visual assessment any CT scans with other lung conditions (e.g. bronchiectasis, interstitial lung disease) resulted in exclusion of the patient from the study. Incidental lung nodules were followed with

interval CT scans according to the Fleischner Society recommendations. [15] None of these nodules were subsequently thought to represent a cancer.

CT Measurements

The number of pixels below -950 Hounsfield Units was used to quantify low attenuation areas (LAA) as a measure of emphysema. Software was developed to calculate the percentage of pixels below this threshold (%LAA-950) from the total number in each CT scan. To estimate the distribution of LAA, total lung volume was divided equally into upper and lower and also core and rind regions. The boundary for upper to lower was the CT slice that divided total lung volume into two equal regions, while the most peripheral 50% of lung area on each CT slice was defined as the rind region (Figure 1). This process was automated using an erosion algorithm originally described by Haralick et. al. [16]; in each cycle one layer of pixels at the outer boundary of the lung are removed until 50% of the initial lung area remains. The percentage of LAA in each region (core/rind and upper/lower) was then calculated from the total. This created two continuous variables for the distribution, i.e. 0-100% of LAAs in upper zone and 0-100%of LAAs in core zone. Each patient was then categorized as upper or lower zone predominant, and also as core or rind predominant when more than 50% of the LAA were in any distribution region. This allowed classification into one of four groups – upper rind, upper core, lower rind and lower core predominant.

Statistics

The %LAA-950 variable had a skewed distribution and thus was log transformed. Other non-normally distributed variables were analysed with non-parametric tests.

Pearson's correlation coefficient was used to determine relationships between normally distributed/log transformed variables; otherwise Spearman's rank test was used. Independent sample t-tests were utilised in comparing means between groups with dichotomous data. A one way ANOVA was used to compare the four distribution groups; with Tukey's post-hoc testing used to identify significant differences. Only comparisons with one consistent variable were analysed, as these would provide useful information. For example, upper/core compared to lower/core was analysed, while upper/core compared to lower/rind was not.

Multiple linear regression modelling was used to test for independent associations between clinical features and both the extent and distribution of emphysema. Variables found to be significant on univariate analysis - and potential confounders - were included in these multiple regression models. Some collinearity was found between FEV_1, BODE index and MRC dyspnoea, but this had little effect on the results and so these variables have been left in the analysis for completeness.

In all statistical analyses, significance was taken as a p-value <0.05.

RESULTS

The patient characteristics demonstrate a wide range of airflow limitation, six minute walking distance, Total SGRQ score and BODE index; reflecting the spectrum of disease encountered in clinical practice (Table 1). The extent of emphysema given as the total percentage of LAAs (%LAA-950) and how these are distributed as continuous variables are also shown; the mean for both core/rind and upper/lower distributions are each a little over 50%.

Table 1. Demographic data, clinical features and CT results for total group (n=129). Mean (standard deviation) shown for continuous variables, n (%) shown for dichotomous variables. * Denotes non-parametric distribution: median (interquartile range).

Gender	Male 85/129 (66%)
Age (years)	67 (8)
FEV_1 (%predicted)	52 (19)
FVC (%predicted)	82 (20)
FEV_1 / FVC (%)	49 (12)
Oxygen Saturations (%)	96 (1.9)
Smoking (Pack Years)	45 (20)
BMI (kg/m^2)	26 (6)
Six Minute Walking Distance (m)	361(118)
SGRQ Total	47 (20)
BODE Index	4 (2)
Exacerbation Frequency * (/year)	2 (1-3)
MRC Dyspnoea Score	3 (1)
MRC Bronchitis Score	1 = 63/119 (53%)
Smoking Status	Current 40/129 (31%)
%LAA-950*	5.5(1.6-17.5)
Upper % Below -950	57(23)
Core % Below -950	54(15)
Upper/Core % below -950 = $\frac{\text{Number of pixels below -950 in upper/core zone}}{\text{Total number of pixels below -950}} \times 100$	

Emphysema Distribution

For most patients there was a predominance of LAAs in upper, core regions (64% had upper, 66% core, 48% had both). The severity of emphysema in the whole lung (log %LAA-950) was associated with a higher percentage of emphysema in the upper (r=0.23,

p=0.008) and core regions (r=0.69, p<0.001). When the two distributions of emphysema were correlated, percentage upper zone distribution was significantly related to percentage core distribution (r=0.28, p=0.001), as shown in Figure 2.

Correlation of emphysema with Clinical Features

On univariate analysis (Table 2), several clinical features were associated with the extent of emphysema measured by CT. In nearly all cases, those same clinical features were significantly related to an increased percentage of core disease. Increased core distribution was associated with lower FEV_1 (r=-0.35, p<0.001), FEV_1/FVC ratio (r=-0.52, p<0.001) and BMI (r=-0.24, p=0.006); and higher BODE index (r=0.30, p=0.003) and MRC dyspnoea score (r=0.27, p=0.002). An increase in the upper zone distribution of emphysema was associated with female sex (mean 11.4% greater, p=0.006) and a higher total St George's score (r=0.18, p=0.039).

Table 2. Relationship between CT measured emphysema and clinical features. Correlations with extent (log %LAA-950) and distribution of emphysema. * Indicates use of non-parametric test, † indicates use of t-test (difference in means given). p-values are given if significant

	Extent	Distribution	
	Correlation with Log %LAA-950	Correlation with % Core Zone	Correlation with % Upper Zone
Age (years)	0.05	0.07	-0.09
Gender †	0.32	-5.01	-11.4 (p=0.006)
FEV_1 (%predicted)	-0.52 (p<0.001)	-0.35 (p<0.001)	-0.01
FVC (%predicted)	-0.04	0.11	0.03
FEV_1/FVC Ratio	0.70 (p<0.001)	-0.52 (p<0.001)	-0.03
Smoking Pack Years	-0.06	-0.03	-0.08
BMI (kg/m^2)	-0.48 (p<0.001)	-0.24 (p=0.006)	-0.03
Six Minute Walking Distance (m)	0.04	-0.15	-0.07
SGRQ Total	0.20	0.17	0.18 (p=0.039)
BODE Index	0.35 (p=0.022)	0.30 (p=0.003)	0.08
Exacerbation Frequency*	0.09	0.04	-0.10
MRC Dyspnoea	0.24	0.27 (p=0.002)	0.10
MRC Bronchitis †	0.18	2.10	1.43
Oxygen Saturation (%)	-0.34 (p=0.011)	-0.16	0.09

On comparing patients with predominantly upper/rind, lower/rind, upper/core or lower/core emphysema; FEV_1 %predicted, FEV_1/FVC ratio, oxygen saturations and MRC dyspnoea score were found to be significantly different. Post-hoc testing revealed that in all cases lower zone, core to rind differences were significant, while only oxygen saturations differed between upper and lower zones (Figure 3).

Using multiple linear regression modelling, only BMI and FEV_1 were significant and therefore independently related to the extent of emphysema (log %LAA-950). In assessing distribution, age, sex and extent of emphysema were independently associated with core/rind; while only gender and extent of emphysema were independently related to upper/lower (Table 3a-c).

Table 3a. Multiple linear regression model of emphysema extent on clinical variables. Shaded area shows overall result for model.

Model	Beta Coefficient (95% Confidence Interval)	Partial Correlations	p-value
Log %LAA-950 (r^2=0.33, p<0.001)			
Age	-0.02 (-0.05 – 0.02)	-0.09	0.380
Gender	0.46 (-0.17 – 1.01)	0.15	0.152
BMI	-0.09 (-0.15 – -0.04)	-0.33	0.002
FEV_1 (%predicted)	-0.04 (-0.06 – -0.02)	-0.35	0.001
BODE Index	-0.08 (-0.25 – 0.10)	-0.09	0.387
Oxygen Saturation	-0.05 (-0.22 – 0.11)	-0.07	0.524

Table 3b. Multiple linear regression model of core/rind emphysema distribution on clinical variables.

Core/Rind Distribution of Emphysema (r^2=0.62, p<0.001)			
Age	0.35 (0.11 – 0.59)	0.29	0.005
Gender	-9.52 (-13.9 – -5.16)	-0.41	<0.001
Log %LAA-950	7.18 (5.73 – 8.62)	0.72	<0.001
BMI	0.15 (-0.24 – 0.54)	0.08	0.455
FEV_1 (%predicted)	1.10 (-0.08 – 0.29)	0.12	0.258
BODE Index	0.33 (-1.79 – 2.46)	0.03	0.758
MRC Dyspnoea	1.52 (-2.15 – 5.19)	0.09	0.412

Table 3c. Multiple linear regression model of upper/lower emphysema distribution on clinical variables.

Upper/Lower Distribution of Emphysema (r^2=0.13, p=0.002)			
Age	-0.03 (-0.54 – 0.47)	-0.01	0.904
Gender	-11.3 (-19.8 – -2.73)	-0.23	0.010
Log %LAA-950	3.47 (0.92 – 6.03)	0.24	0.008
SGRQ Total	0.14 (-0.05 – 0.34)	0.13	0.147

DISCUSSION

CT assessment of COPD patients allows accurate measurement of emphysema extent and distribution. In a large cohort of 129 patients with COPD, we have examined whether the extent and distribution of CT measured emphysema related to clinical features. This is the first time such comparisons have been made to clinical parameters other than spirometry.

As expected, several clinical features of COPD were significantly related to total lung emphysema severity (%LAA-950) as measured using CT. Interestingly, when the distribution of emphysema is related to clinical features, core to rind differences in distribution are more significantly associated than upper to lower. Nearly all clinical features that correlate to total lung emphysema severity show significant relationships when distribution of emphysema is divided into core and rind (most notably, core emphysema is associated with a significant decrease in FEV_1 %predicted, a higher BODE index, a higher MRC dyspnoea score and a lower BMI). Two clinical features - SGRQ and gender- were related to upper/lower emphysema predominance (upper zone predominance of emphysema associated with an increased Total SGRQ score - worse health status - and is more common in women). When viewed in a one way ANOVA it is apparent that lower zone core/rind distributional differences are most related to changes in clinical outcome. This finding is rather surprising given that the majority of our patients have upper/core disease and that the extent of emphysema is correlated with both upper zone and core predominance. In other words, more severe upper zone, core

predominant emphysema is found in the majority of our patients, yet the more subtle lower zone disease shows the best correlation with clinical features.

This does however agree with other work published on emphysema distribution. Gurney et. al. found in a study of 59 smokers that severe upper zone emphysema was less related to spirometry than milder lower zone disease.[17] Similarly, our findings are in agreement with the only two published papers which describe smoking related emphysema (as distinct from alpha-1 antitrypsin deficiency related emphysema) distribution in terms of upper/lower and core/rind predominance. Nakano et. al. [11] also found that core disease was related to disease severity (as measured by pulmonary function tests), with lower/core disease more related to spirometry, and upper/core to carbon monoxide transfer factor. Haraguchi et. al. [10] found that centrally distributed emphysema had the strongest relationship to pulmonary function, and also that lower zone disease related better than upper.

On multiple linear regression, only FEV_1 and BMI were associated with the extent of emphysema (LAA-950), i.e. these are the only two clinical factors which actually relate to the CT measured severity of emphysema in our cohort. A similar outcome was observed in the distributional analyses: although a number of symptomatic features were associated with an increased percentage of core or upper zone disease on univariate analysis, after adjusting for confounding by emphysema severity and FEV_1, only age and gender remained associated. Therefore, we were unable to demonstrate that clinical features were related to differing distributions of emphysema in COPD.

The finding that upper-zone core disease was associated with emphysema severity was interesting. One possible explanation is that differences in mechanical forces in the lower and rind zones provide some protection to lung parenchyma such that only those with more severe or advanced disease develop emphysema at these sites. Our distributional analyses also demonstrate that women were most likely to have core disease in the upper zones, while increasing age was likewise associated with core predominance. These effects of age and sex were found to be *independent* of disease severity. It is possible then, that for most patients, smoking related emphysema predominates in the upper/core region with increasing severity; while for women and those of increasing age, the disease may begin with a predominantly core distribution regardless of severity.

Such ideas point to differences in the development of emphysema. One might suggest distribution patterns are related to the underlying pathological phenotype. Traditionally, centrilobular and paraseptal emphysema were thought to have upper lobe predominance and be more common in smokers, while panlobular emphysema was considered to predominate in the lower lobes in patients with alpha-1 antitrypsin deficiency. [18, 19] Until recently, information on gender related differences in emphysema has been limited. Results from the NETT trial showed that there is a core predominance of emphysematous disease in females: the authors postulated that sex differences in emphysema may be explained by an increased susceptibility of women to comparable degrees of cigarette smoke exposure. [20]

The association of core distribution with increasing age may in some way be related to the normal age-related decline in lung function: [21] it is possible this occurs predominantly in the core zones of the lung. However, pathological studies would be required to determine if CT assessment of emphysema distribution in this way is related to disease subtype; while issues of susceptibility and age related decline can only be resolved with longitudinal data.

Study limitations

Our study does have some limitations in design. Selection of our patients was opportunistic; those referred from primary care and attending a specialised clinic were recruited sequentially. Ideally a random selection of patients from a COPD population would have been more appropriate, but we believe that our cohort is nevertheless representative of the COPD population at large.

CT scanning was performed at maximal arrested inspiration and there is still some debate in the literature over the need for spirometric gating. [14, 22, 23, 24, 25] A recent international workshop however concluded that this was unnecessary, particularly if scans are not compared longitudinally as in our study. [26]

Assessment of exacerbation frequency was based on patient recall. This clearly has implications for accuracy, but for most patients their hospital and/or GP notes were used to corroborate.

In summary, a core predominant distribution of emphysema particularly in the lower zones shows the best relationship with clinical features. We have demonstrated that

assessing emphysema in this way not only relates well to spirometry, but also - for the first time in our study - to measures of functional status. We could not however, demonstrate that these associations are independent of the degree of emphysema, age or sex. Age and sex differences may be related to disease development but to determine whether emphysema distribution is merely a measure of severity or an independently related feature of the disease would require longitudinal studies.

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REFERENCES

1. Global Initiative for Chronic Obstructive Lung disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda, MD: National Heart, Lung and Blood Institute, World Health Organisation 2006
2. Goddard PR, Nicholson EM, Laszlo G, et. al. Computed tomography in pulmonary emphysema. Clinical Radiology 1982;33:379-87
3. Hayhurst MD, MacNee W, Flenley DC, et. al. Diagnosis of pulmonary emphysema by computed tomography. *Lancet* 1984;2:320-2
4. Muller NL, Staples CA, Miller RR, et. al. 'Density Mask' An objective method to quantitate emphysema using computed tomography. *Chest* 1988;94:782-7
5. Gould GA, Redpath AT, Ryan M, et. al. Lung CT density correlates with measurements of airflow limitation and the diffusing capacity. *Eur Respir J.* 1991;4:141-6
6. Haraguchi M, Shimura S, Hida W, et. al. Pulmonary function and regional distribution of emphysema as determined by high resolution computed tomography. *Respiration* 1998;65:125-9
7. Nakano Y, Coxson HO, Bosan S, Rogers RM, Sciurba FC, Keenan RJ, Walley KR, Pare PD, Hogg JC. Core to rind distribution of severe emphysema predicts outcome of lung volume reduction surgery. *Am J Respir Crit Care Med* 2001;164:2195-9
8. Stolk J, Versteegh MIM, Montenij LJ, Bakker ME, Grebski E, Tutic M,

Wildermuth S, Weder W, el Bardiji M, Reiber JHC, Rabe KF, Russi EW, Stoel BC. Densitometry for assessment of effect of lung volume reduction surgery. *European Respiratory Journal* 2007;29:1138-43

9. Parr DG, Stoel BC, Stolk J, Stockley RA. Validation of computed tomographic lung densitometry for monitoring emphysema in α1-antitrypsin deficiency. *Thorax* 2006;61:485-90

10. Haraguchi M, Shimura S, Hida W, Shirato K. Pulmonary function and regional distribution of emphysema as determined by high resolution computed tomography. *Respiration* 1998;65:125-9

11. Nakano Y, Sakai H, Muro S, Hirai T, Oku Y, Nishimura K, Mishima M. Comparison of low attenuation areas on computed tomographic scans between inner and outer segments of the lung in patients with chronic obstructive pulmonary disease: incidence and contribution to lung function. *Thorax* 1999;54:384-9

12. American Thoracic Society. ATS statement: Guidelines for the six minute walk test. *American Journal of Respiratory and Critical Care Medicine* 2002;166:111-7.

13. Celli BR, Cote CG, Martin JM, Casanova C, Montes de Oca M, Mendez RA, Plata VP, Cabral HJ. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *New England Journal of Medicine* 2004;350:1005-12

14. Stoel B.C, Stolk J. Optimization and Standardization of Lung Densitometry in the Assessment of Pulmonary Emphysema. *Investigative Radiology*

2004;39:681-688

15. MacMahon H, Austin JHM, Gamsu G, Herold CJ, Jett JR, Naidich DP, Patz EF, Swensen SJ. Guidelines for the management of small pulmonary nodules detected on CT scans: A statement from the Fleischner Society. *Radiology* 2005;237:395-400

16. Haralick RM, Sternberg SR, Zhuang X. Image analysis using mathematical morphology. *IEEE Pattern Analysis and MachineIntelligence* 1987;Vol PAMI-9 no 4: 532-550

17. Gurney JW, Jones KK, Robbins RA, Gossman GL, Nelson KJ, Daughton D, Spurzem JR, Rennard SI. Regional distribution of emphysema: Correlation of high resolution CT with pulmonary function test in unselected smokers. *Radiology* 1992;183(2):457-63

18. Thurlbeck WM, Muller NL. Emphysema: definition, imaging and quantification. *American Journal of Roentgenology* 1994;163:1017-25

19. Martelli NA, Hutchison DC, Barter CE. Radiological distribution of pulmonary emphysema. Clinical and physiological features of patients with emphysema of upper or lower zones of lungs. *Thorax* 1974;29(1):81-9

20. Martinez FJ, Curtis JL, Sciurba F, Mumford J, Giardino ND, Weinmann G, Kazerooni E, Murray S, Criner GJ, Sin DD, Hogg J, Reis AL, Han M, Fishman AP, Make B, Hoffman EA, Mohsenifar Z, Wise R, for the NETT research group. Sex Differences in severe pulmonary emphysema. *Am J Respir Crit Care Med* 2007;176:243-52

21. Omori H, Nakashima R, Otsuka N, Mishima Y, Tomiguchi S, Narimatsu A, Nonami Y, Mihari S, Koyoma W, Marubayashi T, Morimoto Y. Emphysema detected by lung cancer screening with low-dose spiral CT: prevalence, and correlation with smoking habits and pulmonary function in Japanese male subjects. *Respirology* 2006;11:205-10

22. Kalender WA, Rienmuller R, Seissler W, Behr J, Welke M, Fichte H. Measurement of pulmonary parenchymal attenuation: use of spirometric gating with quantitative CT. *Radiology* 1990;175:265-268

23. Gierada DS, Yusen RD, Pilgram TK, Crouch L, Slone RM, Bae KT, Lefrak SS, Cooper LD. Repeatability of quantitative CT indexes of emphysema in patients evaluated for lung volume reduction surgery. *Radiology* 2001;220:448-454

24. Moroni C, Mascalchi M, Camiciottoli G, Bartolucci M, Falaschi F, Battolla L, Orlandi I, Pistolesi M, Villari N. Comparison of spirometric-gated and ungated HRCT in COPD. *Journal of Computer Assisted Tomography* 2003;27(3):375-379

25. Bakker ME, Stolk J, Putter H, Shaker SB, Parr DG, Piitulainen E, Russi EW, Dirksen A, Stockley RA, Reiber JHC, Stoel BC. Variability in densitometric assessment of pulmonary emphysema with computed tomography. *Investigative Radiology* 2005;40:777-783

26. Newell JD, Hogg JC, Snider GL. Report of a workshop: quantitative computed tomography scanning in longitudinal studies of emphysema. *European Respiratory Journal* 2004;23:769-775

FIGURES

Figure 1. Defining emphysema distribution. All patients were classified as both core or rind predominant and also as upper or lower zone predominant. Zones were defined as shown below with white lines. The percentage of LAA-950 (shaded in black) in each zone was calculated from the total number of LAA-950. More than 50% LAA in any zone was considered to indicate predominance. This patient has core/upper predominance.

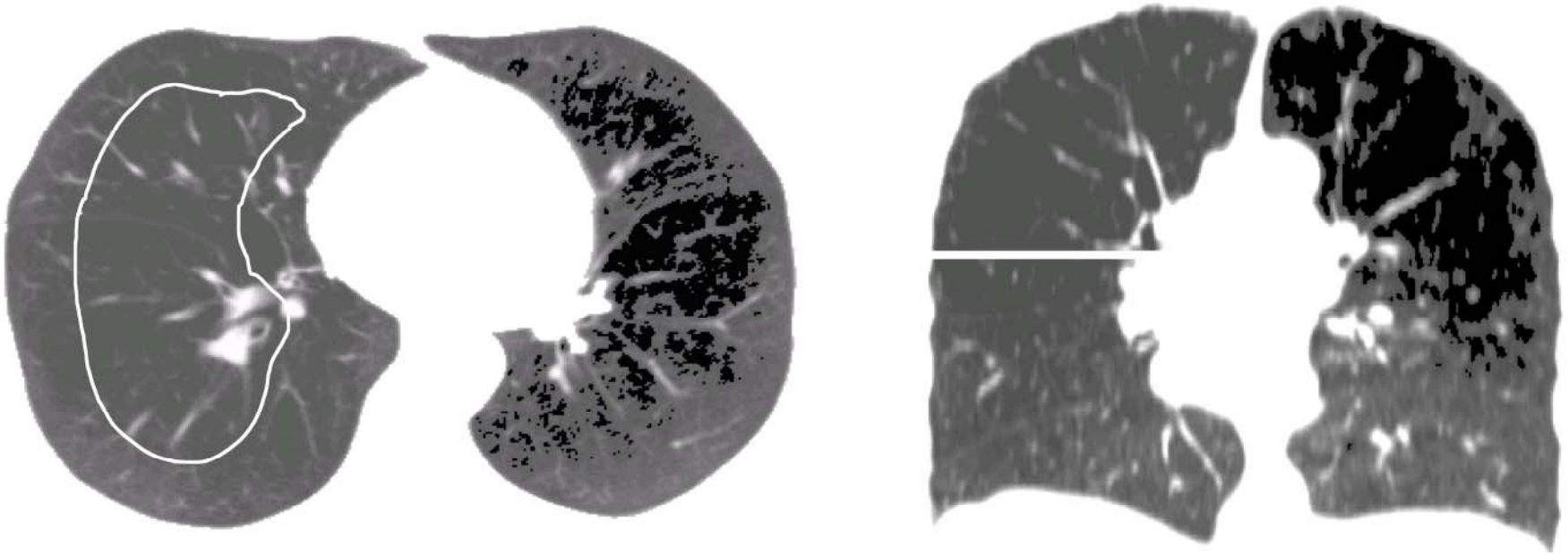


Figure 2. Distribution of low attenuation areas (LAAs) on CT when divided into core/rind and upper/lower zones.

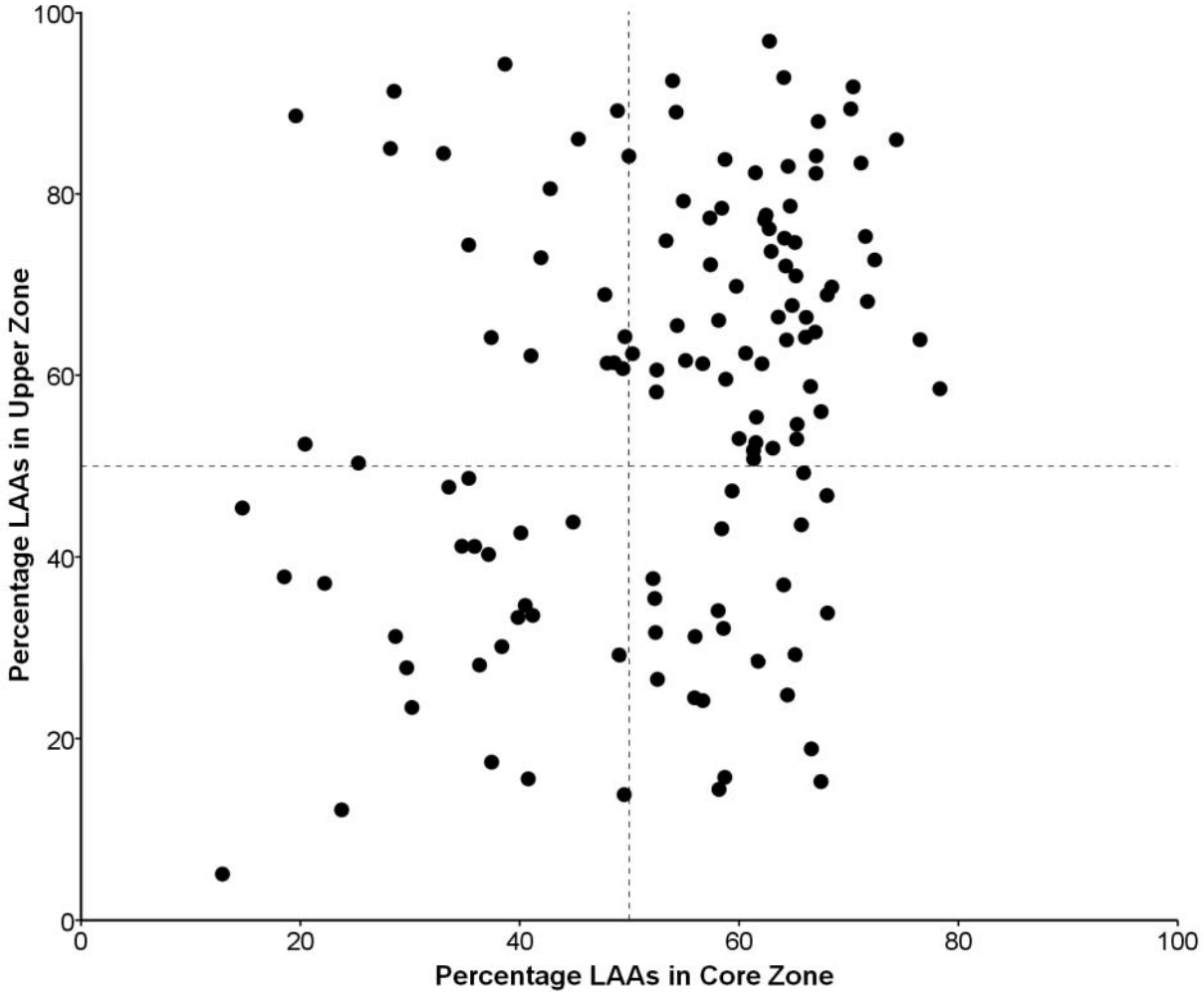
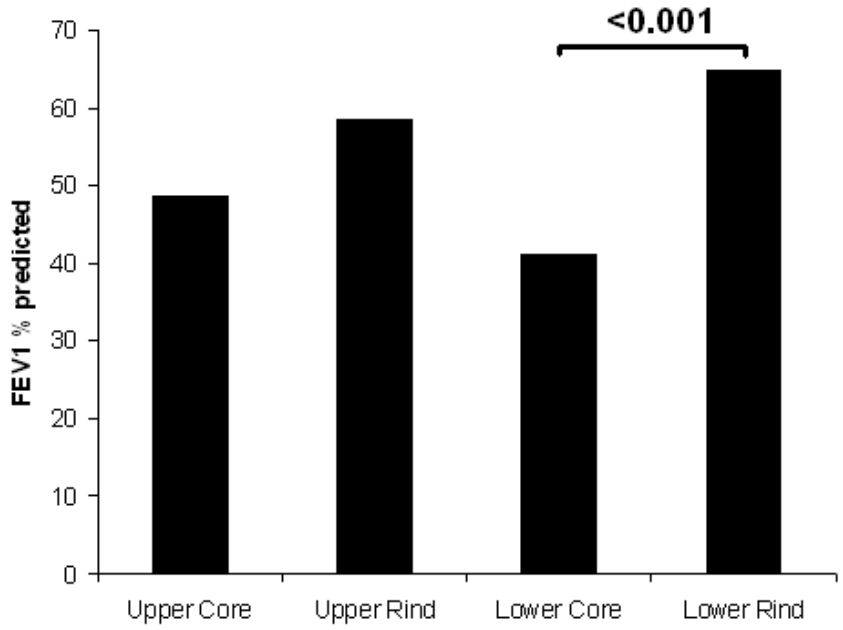
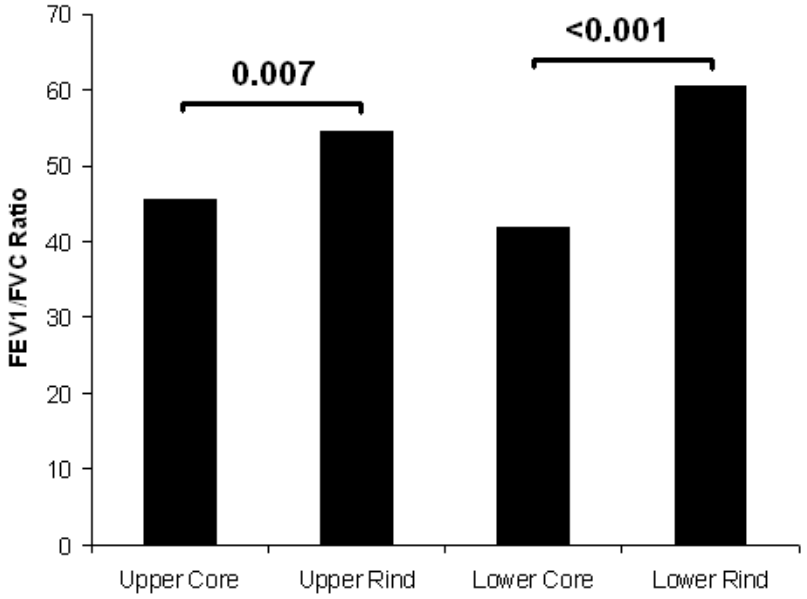
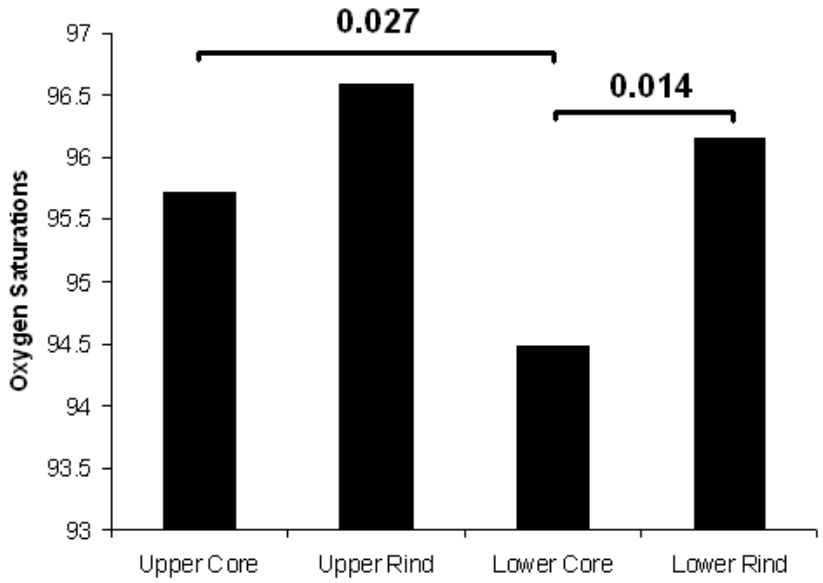
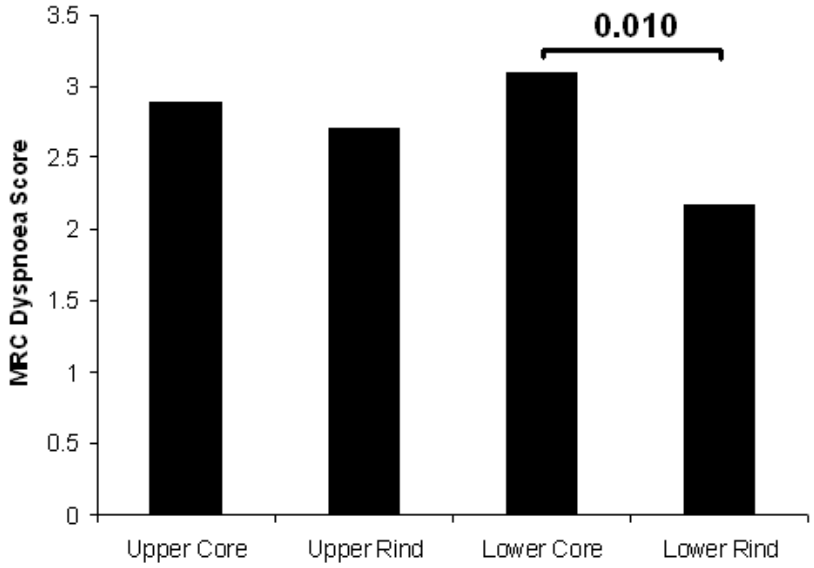


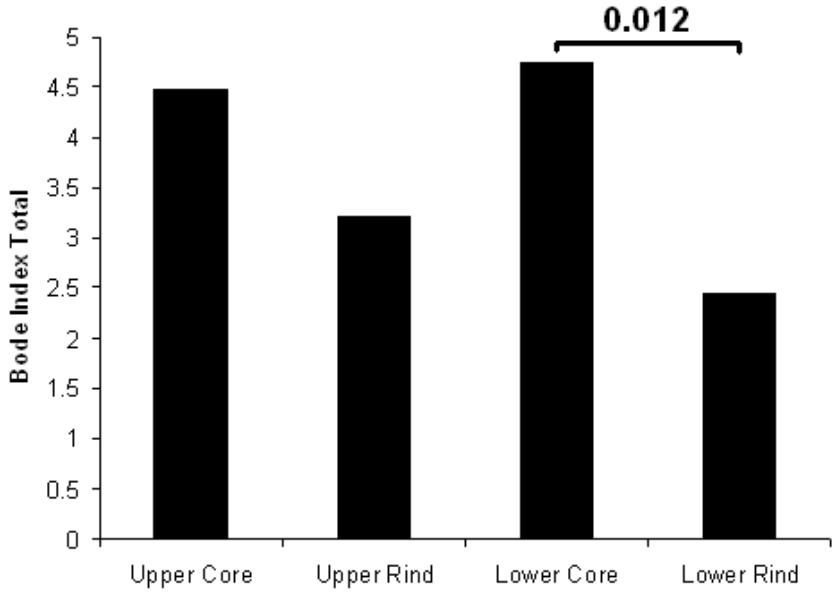
Figure 3. Results from ANOVA. Histograms represent the mean; % predicted FEV_1, FEV1/FVC ratio, oxygen saturations, MRC dyspnoea score, and BODE index in the different emphysema distributions. p-values indicate the results of Tukey's post-hoc testing.


FEV1 % predicted
70
60
50
40
30
20
10
0
<0.001
Upper Core
Upper Rind
Lower Core
Lower Rind


70
60
50
40
30
20
10
0
FEV1/FVC Ratio
0.007
<0.001
Upper Core
Upper Rind
Lower Core
Lower Rind


0.027
0.014
97
96.5
96
95.5
95
94.5
94
93.5
93
Oxygen Saturations
Upper Core
Upper Rind
Lower Core
Lower Rind


0.010
MRC Dyspnoea Score
3.5
3
2.5
2
1.5
1
0.5
0
Upper Core
Upper Rind
Lower Core
Lower Rind


0.012
Bode Index Total
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Upper Core
Upper Rind
Lower Core
Lower Rind