

Pattern of Emphysema Distribution in α 1-Antitrypsin Deficiency Influences Lung Function Impairment

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FEV₁ is fundamental to the diagnosis and staging of chronic obstructive pulmonary disease. In emphysema, airflow obstruction usually coexists with impairment of gas exchange, but discordance is not infrequent. We hypothesized that variations in the distribution of emphysema would be associated with functional differences and therefore account for discordant physiology. We used quantitative computed tomography to assess emphysema severity and distribution in 119 subjects with α 1-antitrypsin deficiency (PiZ phenotype) and grouped them according to distribution pattern. In the 102 subjects with emphysema, 65 had a predominantly basal pattern ("basal"), but 37 (36%) had greater involvement of the upper regions ("apical"). Subjects from each group were matched for total volume of emphysema and age, and matched pairs analysis was used to relate emphysema distribution to clinical phenotype. Basal distribution was associated with greater impairment of FEV₁ (mean difference, 9.9% predicted; 95% confidence interval, 3.8 to 16.0; $p = 0.002$) but less impairment of gas exchange (PaO₂ mean difference, 0.5 kPa, 0.03 to 0.1; $p = 0.016$) and alveolar-arterial oxygen gradient (mean difference, 0.7 kPa; 0.2 to 1.2; $p = 0.007$) than the apical distribution. Emphysema distribution correlated with physiologic discordance ($r = -0.409$, $p < 0.001$). The use of single physiologic parameters as a surrogate measure of emphysema severity may introduce systematic bias in the staging of subjects with emphysema.

Keywords: α 1-antitrypsin deficiency; computed tomography; lung densitometry

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition that is defined by the presence of airflow obstruction that is "not fully reversible" (1), and spirometry therefore remains fundamental to the diagnosis and monitoring of the disease. However, the measurement of FEV₁ does not allow specific assessment of the individual components of COPD, and although a presumptive diagnosis of emphysema may be made from coexisting impairment of gas transfer, unexplained discordance of these two measures is not infrequent in subjects with emphysema (discussed later here).

In contrast to general COPD, emphysema is defined in morbid anatomic terms (2), and because quantification has historically required pathologic morphometry, the physiologic indices of FEV₁ and gas transfer have been employed traditionally as surrogate measures of emphysema in longitudinal studies. How-

ever, noninvasive quantification is now achievable with lung densitometry using computed tomography (CT) to measure the loss of lung tissue associated with emphysema. Various parameters derived from the frequency distribution histogram of lung voxel densities (Figure 1) have been described. The voxel index (VI) is defined as the proportion of lung voxels of low density below a defined threshold and the percentile point as the cutoff value in Hounsfield units below which a defined percentage of voxels are distributed. These methods have been validated against pathology (3–5) and used in previous clinical studies (6–9). Because pathology is already known to relate to physiology (10), quantitative CT can assess the pulmonary structure–function relationship *in vivo*, leading to improved interpretation of the physiologic measures employed in routine clinical practice.

α 1-Antitrypsin deficiency (AATD) is a hereditary disorder that is associated with a predisposition to develop early onset, rapidly progressive COPD where emphysema is a major component (11), and patients therefore provide a model for studies of emphysema. The "classic" description of AATD-associated emphysema as predominantly basal and panacinar originates from limited autopsy studies (12) and from patient series using imaging modalities now superseded by CT (13, 14). Accurate characterization of the distribution of emphysema may be important for diagnostic purposes (15) and because the pattern of emphysema distribution is likely to influence physiology. Indirect evidence for this derives from CT studies that have identified possible functional variation between different lung regions (16–18). Diffusing capacity has been shown to correlate better with upper zone indices of emphysema severity than lower zone indices, whereas measures of airflow obstruction correlate better with lower zone indices. In addition, different patterns of physiologic discordance (PD) are described in usual COPD and AATD. In usual COPD, where the emphysema is classically upper zone (9, 19), impaired diffusing capacity coincident with relative preservation of airflow obstruction has been described (20), whereas the opposite pattern (impairment of airflow with relative preservation of diffusing capacity) has been reported in AATD, where the emphysema is classically basal (21).

The purpose of this study was to characterize the distribution of emphysema in a population of subjects with AATD using CT lung densitometry and to identify variability in function by relating disease distribution to measures of physiology. We hypothesized that impairment of FEV₁ would be greater in predominantly basal emphysema, and impairment of gas transfer would be greater in apical emphysema. Consonant with this, if the pattern of physiologic impairment in those subjects with AATD and apical emphysema were similar to that described in usual COPD (20), then discordant physiology would therefore be a reflection of polarized emphysema distribution. This study examines this hypothesis in 119 patients. Some of the results of these studies have been reported previously in the form of an abstract (22).

METHODS

Subjects

One hundred nineteen subjects with severe AATD (PiZ phenotype) were selected consecutively from those attending our center. The α 1-anti-

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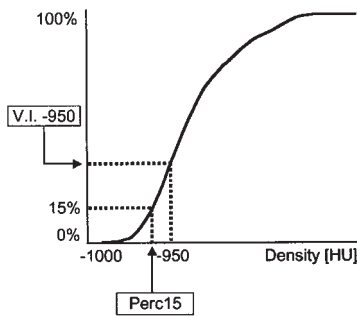


Figure 1. Cumulative voxel distribution histogram showing derivation of voxel index (VI) and percentile point parameters. The VI below -950 Hounsfield units (HU) (which may be the most appropriate threshold) (3, 4) is defined as the proportion of lung voxels of low density below a threshold of -950 HU and increases with worsening emphysema. The 15th percentile point (Perc15) is defined as the cut-off value in HU below which 15% of all voxels are distributed, and as a true measure of density, this parameter consequently decreases with worsening emphysema. These two parameters may therefore be regarded as having a reciprocal relationship.

trypsin concentration and phenotype were confirmed as described previously (23), and at the time of assessment, all subjects were in the stable clinical state.

CT

Patients were scanned at full inspiration with a “volume” protocol on a General Electric Lightspeed scanner in the helical mode and without the use of intravascular contrast (*see the online supplement*).

Lung Function Testing

Lung function testing was performed according to the British Thoracic Society/Association of Respiratory Technicians and Physiologists guidelines (24) as described previously (23) (*see the online supplement*), and results are expressed as a percentage of predicted values (25). An arterialized earlobe capillary sample was obtained to estimate Pa_{O_2} and Pa_{CO_2} and to derive the alveolar–arterial oxygen gradient (26) and the degree of relative hypocapnia (27) (*see the online supplement*).

Health Status

Health status was assessed using the St. George’s Respiratory Questionnaire (28) and the Short Form-36 Questionnaire (29), administered before the performance of lung function testing and with the patient well rested.

CT Densitometry

VI at a threshold of -950 Hounsfield units and the 15th percentile point (Figure 1) were measured for whole lung and additional single images selected from whole lung series representing the upper (level of the aortic arch) and lower (level of the inferior pulmonary veins) zones using computer software (Pulmo-CMS; MEDIS Medical Imaging Systems BV, Leiden, the Netherlands) as described previously (30) (*see the online supplement*).

Graphic representation of the VI for each consecutive slice in a series allowed visual assessment of the distribution of low attenuation areas from apex to base and enabled patients to be grouped according to distribution pattern. To explore the relationship between disease distribution and clinical phenotype, patients were grouped according to whether the emphysema was predominantly basal (“basal”) or affected predominantly the mid and upper zones, with or without involvement of the lung bases (“apical”) (Figure 2). Selection criteria for inclusion in the basal group was the presence of the peak VI within the lower third of the lung combined with a reduction in VI toward the middle and upper lung regions, whereas inclusion in the apical group was based on the presence of the peak VI within either the middle or upper third of the lung. Grouping was performed with blinding for other data.

Relationship between Emphysema Distribution and Clinical Phenotype

The influence of emphysema distribution on clinical phenotype was assessed by pairing individuals from each distribution group for overall

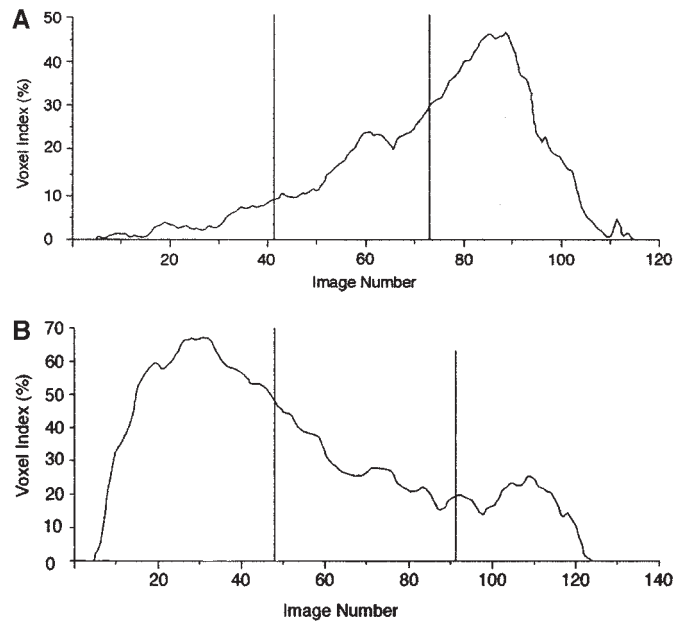


Figure 2. Examples of VI distribution profiles, indicating the patterns of emphysema distribution used for subject grouping. (A) Basal. (B) Apical (N.B. the variable scale on the vertical axis). Apical images are on the left, and basal images are on the right of the horizontal scale. The vertical black lines indicate the level of the upper (aortic arch) and lower zone (inferior pulmonary veins) images at the left and right, respectively.

emphysema severity, determined by the whole lung VI (WLVI), and age. A single investigator (D.G.P.) performed the matching without knowledge of other data during the matching process.

PD and Distribution of Emphysema

PD between FEV_1 and transfer coefficient (diffusing capacity of the lung for carbon monoxide [DL_{CO}/VA]) was defined by subtracting FEV_1 (percentage predicted) from the DL_{CO}/VA (percentage predicted) and the relative distribution of emphysema (Δ CT) by subtracting upper zone indices from lower zone indices using both VI -950 and the 15th percentile point (31).

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 11.5 (SPSS Inc., Chicago, IL). Differences between the basal and apical groups were determined by matched-pairs analysis, matching primarily for WLVI and secondarily for age. Matching performance was assessed in a post hoc analysis. Associations between categorical variables were examined using a chi-squared test and between paired variables using Pearson’s correlation coefficient and Spearman’s coefficient for non-normal variables.

RESULTS

All subjects were white, with a mean age of 52 years (range 23 to 74 years). Almost all (110) were index cases, and males outnumbered females (70 to 49). The majority had been cigarette smokers (75) or were currently smoking at the time of analysis (17), and 62 patients described symptoms of chronic bronchitis (32). The characteristics of the entire group are shown in Table 1.

Emphysema Distribution and Relationship of Densitometry to Physiology

Preliminary assessment of the relationship between physiology and CT densitometry indices in the whole group confirmed that

TABLE 1. SUBJECT CHARACTERISTICS

	Number	Mean	SD	Mean % Predicted
Age	119	52	10.2	N/A
Pack-years	119	16.4	14.8	N/A
FEV ₁ , L	119	1.7	0.9	54
VC, L	119	4.1	1.3	105
RV, L	117	2.8	1.0	135
TLC, L	117	7.3	1.8	117
DL _{CO} /V _A	117	1.0	0.4	64
Whole lung VI, %	119	16.1	11.5	N/A
Upper zone VI, %	119	10.1	10.5	N/A
Lower zone VI, %	119	18.1	13.1	N/A
Total Perc15	119	-943.4	28.1	N/A
Upper zone Perc15	119	-928.9	29.5	N/A
Lower zone Perc15	119	-945.7	28.2	N/A
SGRQ, total score	119	45.9	17.6	N/A
SF-36, physical	119	38.0	10.5	N/A
SF-36, mental	119	53.4	8.3	N/A

Definition of abbreviations: DL_{CO}/V_A = diffusing capacity of the lung for carbon monoxide (mmol/min/kPa/L); N/A = not applicable; Perc15 = 15th percentile point; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; SF-36 = Short Form-36 Questionnaire; TLC = total lung capacity (helium dilution); VI = voxel index.

The patient characteristics are given together with the number of subjects from whom data have been obtained. The average and SD for the group are shown together with the average values expressed as a percentage predicted. All lung function measurements were performed after dual bronchodilation with inhaled nebulized salbutamol (2.5 mg) and ipratropium (250 µg).

DL_{CO}/V_A correlated better with the upper zone than the lower zone indices but that FEV₁ correlated better with the lower zone indices (Figure 3), supporting the findings of our previous limited study (9). The degree of relative hypocapnia correlated with whole lung VI ($r = -0.535$, $p < 0.001$, $n = 119$) (Figure 4) and the 15th percentile point ($r = 0.526$, $p < 0.001$).

Emphysema distribution was assessed primarily using VI, although the correlation between VI and 15th percentile point was good ($r = 0.994$, $p < 0.001$), suggesting that either method could have been used for this purpose. The VI profiles in 17 subjects, all with a WLVI of less than 3%, demonstrated small random peaks that were considered to be inconsistent with significant emphysema. These subjects were excluded from further analysis, and their characteristics are shown in Table 2, indicating that they have essentially normal lung function, although the average DL_{CO}/V_A less than 100% predicted suggests a mild degree of impaired gas transfer. The majority of the remaining 102

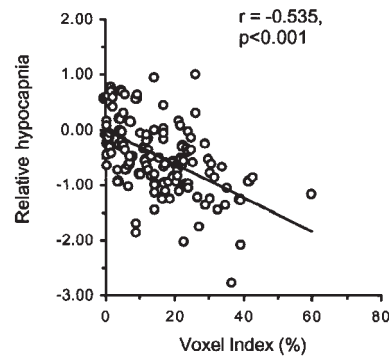


Figure 4. Correlation between total VI at a threshold of -950 HU and relative hypocapnia as defined by Burrows and colleagues (38) ($n = 119$, $r = -0.53$, $p < 0.001$).

patients (65 patients) had a VI profile consistent with basal emphysema (basal group), and 37 had emphysema extending into the upper lung region (apical group) (Figure 2).

Patients with emphysema were matched primarily for overall emphysema severity (WLVI) and secondarily for age by selecting 37 subjects from the 65 in the basal group to provide the best available match with the 37 patients in the apical group. The characteristics of the two groups and the results of the matched pairs analysis are shown in Table 3, with the key findings illustrated in Figure 5. Assessment of the matching process demonstrated no significant difference between the groups in overall emphysema severity (WLVI) or age, but evaluation of the distribution of emphysema in the two groups confirmed that there was a significant difference in the lower zone and upper zone VI (Figure 5A). The basal distribution pattern was associated with a lower FEV₁, VC, V_A, and alveolar-arterial oxygen gradient and a higher DL_{CO}/V_A and PaO₂ than the apical pattern (Table 3). Of importance, the mean difference (95% confidence intervals) in FEV₁ was -9.9% (-16.0 to -3.8) and in DL_{CO}/V_A was 6.1% (0.2 to 12.1), as summarized in Figure 5B. The difference between the two groups could not be explained by differences in sex, index status, smoking history, health status indices, or prevalence of chronic bronchitis (data not shown).

Relationship between PD and Emphysema Distribution

Discordance between FEV₁ and DL_{CO}/V_A (DL_{CO}/V_A percentage predicted - FEV₁ percentage predicted) was significantly related to the relative distribution of emphysema described by the difference between upper and lower zone CT indices (lower zone 15th percentile point - upper zone 15th percentile point, $r =$

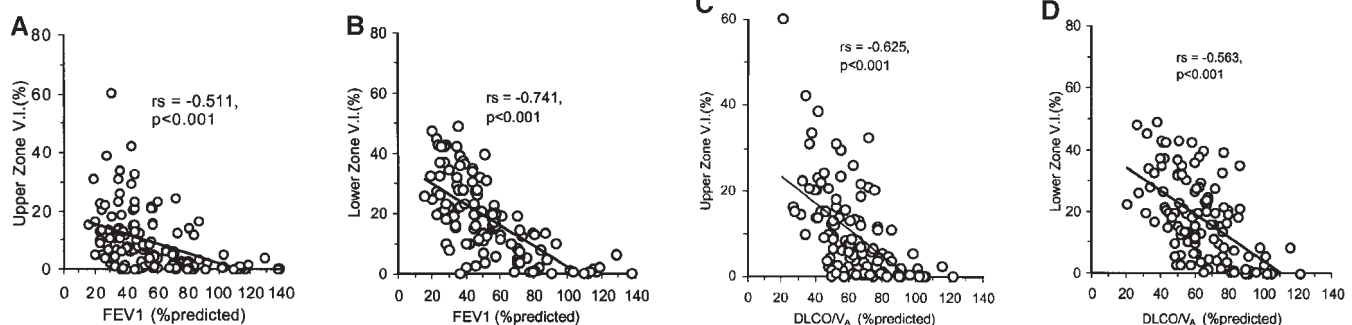


Figure 3. Preliminary assessment of the relationship between physiology and emphysema distribution correlating computed tomography (CT) densitometry indices derived from upper zone images (at the level of the aortic arch) and lower zone images (at the level of the inferior pulmonary veins) with airflow obstruction and gas transfer. (A) FEV₁ correlates better with lower zone VI ($r = -0.741$, $p < 0.001$) than (B) upper zone VI ($r = -0.511$, $p < 0.001$), whereas diffusing capacity of the lung for carbon monoxide (DL_{CO}/V_A) correlates better with (C) upper zone VI ($r = -0.625$, $p < 0.001$) than (D) lower zone VI ($r = -0.563$, $p < 0.001$).

TABLE 2. CHARACTERISTICS OF SUBJECTS WITH NO DEMONSTRABLE EMPHYSEMA

	Number	Mean	SD	Mean % Predicted
Age	17	44	10.5	N/A
Pack-years	17	7.4	11.5	N/A
FEV ₁ , L	17	3.1	0.8	100
VC, L	17	4.1	1.1	110
RV, L	17	1.8	0.6	100
TLC, L	17	6.1	1.4	108
DL _{CO} /V _A	17	1.5	0.3	87
Whole lung VI, %	17	1.0	0.7	N/A
Upper zone VI, %	17	0.7	1.2	N/A
Lower zone VI, %	17	0.8	0.7	N/A
Total Perc15	17	-889.9	19.34	N/A
Upper zone Perc15	17	-888.2	21.1	N/A
Lower zone Perc15	17	-890.3	19.9	N/A
SGRQ, total score	15	26.6	9.5	N/A
SF-36, physical	17	45.9	8.2	N/A
SF-36, mental	17	57.01	4.9	N/A

For definition of abbreviations see Table 1.

The patient characteristics are given together with the number of subjects from whom data have been obtained. The average and SD for the group are shown together with the average values expressed as a percentage predicted. All lung function measurements were performed after dual bronchodilation with inhaled nebulized salbutamol (2.5 mg) and ipratropium (250 µg).

-0.409, $p < 0.001$; and lower zone VI – upper zone VI, $r = 0.429$, $p < 0.001$). The individual data for PD and distribution (Δ CT) determined by the 15th percentile point are shown in Figure 6. The association of airflow impairment with relative preservation of diffusing capacity related to a predominantly basal pattern of emphysema, whereas the reverse pattern of discordance was related to predominantly apical emphysema.

DISCUSSION

We have shown that the relative degree of impairment in measures of airflow obstruction and gas exchange differs between

age-matched subjects with the same overall amount of emphysema in association with the pattern of emphysema distribution. Emphysema that is predominantly located in basal zones is associated with a greater degree of airflow obstruction but a lesser impairment of gas exchange than emphysema extending to the upper zones. These physiologic differences were consistently identified in further analyses that used alternative matching criteria. In the first of these analyses, subjects were matched using WLVI as described in METHODS; however, smoking history (pack-years) replaced age as the secondary matching criterion, and a further analysis matched subjects for overall emphysema severity using the 15th percentile point. The results of these two analyses are tabulated in the online supplement.

These findings have important clinical implications. The use of spirometry is recommended in the updated Global Initiative for Chronic Obstructive Lung Disease guidelines for the management of COPD (33) for confirming the diagnosis earlier in “at-risk” patients and for severity staging. It is likely that this will be increasingly performed in a primary care setting as the only physiologic measure. Consequently, it should be widely recognized that emphysema may occur without demonstrable airflow obstruction (namely, Global Initiative for Chronic Obstructive Lung Disease stage 0) but, nevertheless, with coexisting abnormalities in gas exchange. Our findings would suggest that this physiologic pattern is more likely to occur in subjects with usual COPD, in whom the emphysema is more commonly apical, than in AATD-associated COPD. Furthermore, the sole use of FEV₁ for the classification of disease stage in COPD may lead to the relative overestimation of severity in subjects with predominantly basal emphysema compared with subjects with apical disease. It is also of importance that recognition is given to the pattern of discordance described previously here in association with predominantly basal disease (namely, impairment of FEV₁ with relative preservation of DL_{CO}/V_A) because the diagnosis of AATD is not infrequently delayed (34), with symptoms ascribed to asthma rather than emphysema. The adherence to World Health Organization guidelines for AATD testing in all subjects

TABLE 3. MATCHED PAIRS COMPARISON OF SUBJECTS WITH “BASAL” AND “APICAL” EMPHYSEMA DISTRIBUTION

	Basal	Apical	Mean Difference (95% CI)	p Value
	Mean (SD)	Mean (SD)		
Age	53 (8.8)	55 (9.4)	-2.7 (-6.2 to 0.9)	0.133
Smoking, pack-years	18.8 (11.6)	18.3 (17.1)	0.6 (-7.0 to 8.1)	0.882
Whole lung VI, %	19.2 (10.1)	19.0 (9.9)	0.2 (-0.1 to 0.6)	0.219
Upper zone VI, %	8.4 (7.6)	17.7 (12.8)	-9.3 (-12.3 to -6.3)	< 0.001
Lower zone VI, %	24.0 (13.5)	19.9 (1.0)	4.2 (1.7 to 6.7)	0.001
Whole lung Perc15	-953.8 (17.6)	-952.9 (18.4)	-0.4 (-1.4 to 0.6)	0.436
Upper zone Perc15	-931.9 (21.3)	-950.2 (23.7)	16.1 (9.8 to 22.5)	< 0.001
Lower zone Perc15	-958.8 (17.2)	-956.2 (18.0)	-3.07 (-0.2 to -6.0)	0.039
FEV ₁ , % predicted	41.8 (16.3)	51.8 (18.5)	-9.9 (-16.0 to -3.8)	0.002
VC, % predicted	101.1 (25)	111.7 (21.6)	-10.6 (-20.6 to -7.1)	0.036
DL _{CO} /V _A , % predicted	59.4 (15.6)	53.9 (14.5)	6.1 (0.2 to 12.1)	0.044
V _A , % predicted TLC	93.0 (13.5)	99.5 (14.4)	-6.5 (-12.6 to -0.4)	0.037
Pa _{O₂} , kPa	9.0 (0.9)	8.5 (1.0)	0.5 (0.03 to 1.0)	0.016
A-a DO ₂	6.1(1.1)	6.8 (0.9)	-0.7 (-1.2 to -0.2)	0.007
Pa _{CO₂} , kPa	4.7 (0.5)	4.5 (0.6)	0.1 (-0.1 to 0.4)	0.280
Relative hypoxcapnia	-0.7 (0.7)	-0.6 (0.7)	-0.1 (-0.4 to 0.2)	0.365

Definition of abbreviations: A-a DO₂ = alveolar-arterial oxygen gradient; CI = confidence interval; DL_{CO}/V_A = diffusing capacity of the lung for carbon monoxide (mmol/min/kPa/L); Perc15 = 15th percentile point; VI = voxel index.

Pairs were successfully matched for total amount of emphysema and age with no significant differences between groups. Data are presented as mean with SD in parentheses. The mean difference (“basal” minus “apical”) and 95% CIs are shown, together with the significance of any differences between groups (p).

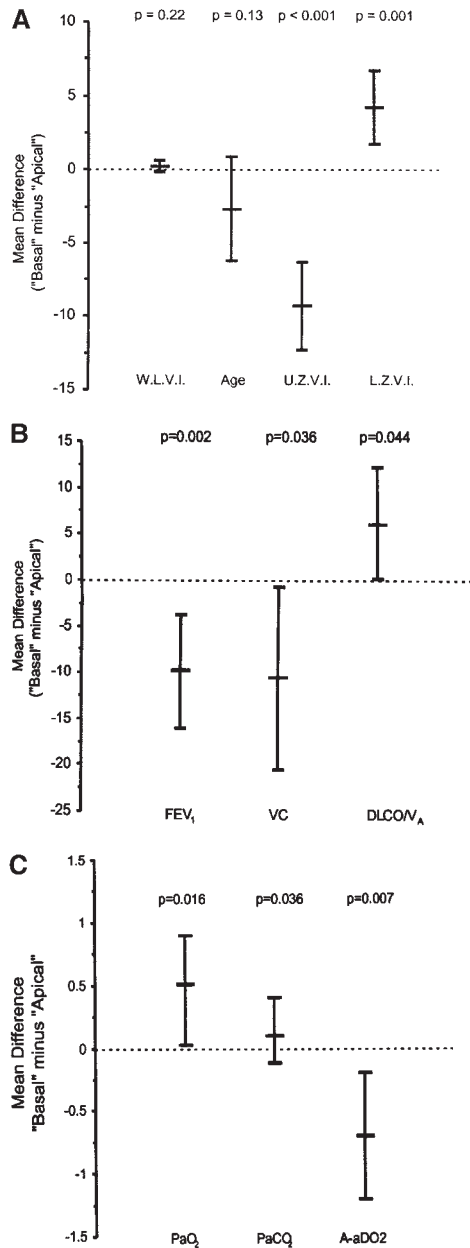


Figure 5. Key results of the matched-pairs analysis showing the mean difference between groups (basal minus apical) with the 95% confidence intervals. The significance of any differences are given (p). (A) Differences for whole lung VI (WLVI) and age are nonsignificant, indicating that the groups were well matched. Significant differences in upper zone VI (UZVI) and lower zone VI (LZVI) between groups demonstrates that the VI profile method used for grouping subjects successfully identified differences in the distribution of emphysema between the upper and lower lung regions. (B) Subjects with basal distribution have greater impairment of FEV₁ and VC than subjects with apical distribution but less impairment of gas exchange as shown by a higher D_{lco}/V_A and (C) higher PaO₂ and lower alveolar-arterial oxygen gradient.

with COPD or late-onset asthma should, however, prevent this from occurring (35).

In addition, our findings indicate that relatively greater involvement of the upper zones with emphysema may contribute an additive risk for development of pulmonary hypertension secondary to hypoxemia. FEV₁ has been an important predictor of mortality in usual COPD and AATD-associated emphysema,

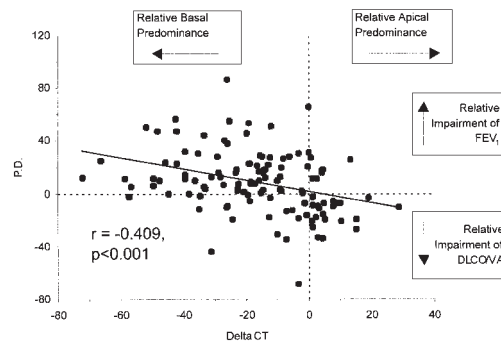


Figure 6. Relationship between physiologic discordance (D_{lco}/V_A percentage predicted – FEV₁% predicted) on the vertical axis and relative distribution of emphysema (lower zone Perc15 – upper zone Perc15) on the horizontal axis; Spearman’s correlation coefficient = 0.409, p < 0.001. Relative preservation of D_{lco}/V_A is associated with predominantly basal emphysema, whereas relative preservation of FEV₁ (“nonobstructive emphysema”) is associated with apical predominance.

but Dawkins and colleagues using a limited slice protocol have shown recently that CT densitometry applied to upper zone images is a better predictor of mortality in subjects with AATD (36). Mortality in this population is likely related to emphysema severity and consequently to the degree of CT abnormality, which is a more specific measure of emphysema than FEV₁. Our study suggests the possibility that this also has a physiologic explanation, namely, that measurement of the extent of upper zone emphysema may allow identification of a subgroup of patients at greater risk from hypoxemia and possible subsequent pulmonary hypertension. This effect could constitute an increased mortality risk, but further studies are needed to determine the validity of this hypothesis.

Previous studies have inferred regional differences in function from the strength of correlations between physiology and objective CT parameters acquired using limited sampling protocols (1, 16, 18, 37). The scanning protocol employed in this study enabled a comprehensive characterization of disease distribution, and by matching subject pairs for overall emphysema severity, we have provided the first direct evidence of different functional impairment between emphysematous involvement of the upper and lower lung regions. It is likely that the graphical display of lung density is an accurate reflection of both emphysema severity and distribution. Relative hypocapnia has previously been shown to predict emphysema severity (38), and the good correlation with lung density (Figure 4) in this study provides further evidence that CT densitometry relates well to physiologic measures of emphysema. Furthermore, the significant differences between pairs in upper zone and lower zone VI and the 15th percentile point confirms that the method of grouping into basal and apical identified differences in emphysema distribution using either method of calculation.

Emphysema in subjects with AATD is classically described as predominantly basal, but we have shown objectively using CT densitometry profiles that the pattern of emphysema distribution is more heterogeneous than recognized previously (8–10). The matched-pairs analysis and an additional analysis of all 102 patients (data not shown) did not identify any significant differences in age, index status, or smoking history to account for these different patterns of emphysema distribution. Our findings are of importance because guidelines published recently advise antitrypsin testing of subjects with basal emphysema with the implication that other patterns of distribution are not associated with AATD and that testing in these cases is unnecessary

(15). The current study in this group of patients suggests that this advice may be misleading in that 36% of patients with emphysema did not have basal predominance. Furthermore, there was sufficient heterogeneity to demonstrate an association between PD of FEV₁ and DL_{CO}/VA and emphysema distribution (*see* Figure 6). It is likely that the cases of discordance reported previously (20, 21) may also relate to the pattern of emphysema distribution as described in this study, particularly because we have similarly demonstrated a relationship between discordance and distribution in a study of subjects with usual COPD (22). However, the mechanism of this effect remains unclear.

The suggestion by Wilson and Galvin (21) that predominantly lower lobe disease may allow preservation of ventilation-perfusion matching so that diffusing capacity is relatively insensitive to the loss of surface area for gas exchange is likely to be only a partial explanation. It is possible that real physiologic differences do exist between the upper and lower lung regions and that these may be responsible for the differences in static lung function parameters and gas exchange that we have identified. The gravitational influences on diffusing capacity and FEV₁ measurements made in the sitting posture are likely to be affected by the pattern of emphysema distribution. In health, the ventilation-perfusion ratio varies between approximately 0.7 at the lung bases to 3 at the apex as a result of the changing relationship between ventilation and perfusion (26). The gravitational influences on the perfusion differential between lung apex and base would allow subjects with basal emphysema to maintain DL_{CO}/VA through the recruitment of underperfused disease-free lung units in the upper regions. This recruitment would result from the increase in pulmonary perfusion pressure arising secondary to emphysematous change. In contrast, subjects with apical emphysema would be unlikely to maintain gas exchange by similar recruitment of inferior disease-free lung units because these would already be well perfused. Impairment of FEV₁ when measured in a sitting position is likely to be greater in basal than in apical emphysema. The distending forces acting across airway walls reflect intrapleural pressure, and because this becomes less negative toward the lung bases, the distending airway forces and airway patency will therefore be less at the bases than at the apices (39). Furthermore, dynamic airway collapse resulting from reduced parenchymal tethering is likely to be greater in basal emphysema, leading to increased impairment of FEV₁.

In conclusion, variability in emphysema distribution pattern and its relationship with physiology have implications for the use of a single physiologic parameter in screening and in monitoring emphysema progression or response to treatment. Although it is accepted that optimal clinical practice indicates that full lung function testing should be performed in subjects with obstructive pulmonary disease (15, 40), this study demonstrates how the radiologist can obtain additional information derived from CT imaging to facilitate interpretation of physiologic status. The identification of subgroups within AATD is likely to be important in understanding the heterogeneity that exists in the natural history of disease progression in subjects with AATD, and this may also be applicable to usual COPD (41).

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References

1. Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. *Respir Care* 2001;46:798–825.
2. Snider GL, Kleinerman J, Thurlbeck WM, Bengali ZH. The definition of emphysema: report of a National Heart, Lung, and Blood Institute, Division of Lung Diseases Workshop. *Am Rev Respir Dis* 1985;132:182–185.
3. Gevenois PA, de Maertelaer V, De Vuyst P, Zanen J, Yernault JC. Comparison of computed density and macroscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med* 1995;152:653–657.
4. Gevenois PA, De Vuyst P, de Maertelaer V, Zanen J, Jacobovitz D, Cosio MG, Yernault JC. Comparison of computed density and microscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med* 1996;154:187–192.
5. Gould GA, MacNee W, McLean A, Warren PM, Redpath A, Best JJ, Lamb D, Flenley DC. CT measurements of lung density in life can quantitate distal airspace enlargement: an essential defining feature of human emphysema. *Am Rev Respir Dis* 1988;137:380–392.
6. Dirksen A, Friis M, Olesen KP, Skovgaard LT, Sorensen K. Progress of emphysema in severe alpha 1-antitrypsin deficiency as assessed by annual CT. *Acta Radiol* 1997;38:826–832.
7. Dirksen A, Dijkman JH, Madsen F, Stoel B, Hutchison DC, Ulrik CS, Skovgaard, LT, Kok-Jensen A, Rudolphus A, Seersholm N, *et al.* A randomized clinical trial of alpha(1)-antitrypsin augmentation therapy. *Am J Respir Crit Care Med* 1999;160:1468–1472.
8. Dowson LJ, Guest PJ, Stockley RA. Longitudinal changes in physiological, radiological, and health status measurements in alpha(1)-antitrypsin deficiency and factors associated with decline. *Am J Respir Crit Care Med* 2001;164:1805–1809.
9. Dowson LJ, Guest PJ, Hill SL, Holder RL, Stockley RA. High-resolution computed tomography scanning in alpha1-antitrypsin deficiency: relationship to lung function and health status. *Eur Respir J* 2001;17:1097–1104.
10. Morrison NJ, Abboud RT, Ramadan F, Miller RR, Gibson NN, Evans KG, Nelems B, Muller NL. Comparison of single breath carbon monoxide diffusing capacity and pressure-volume curves in detecting emphysema. *Am Rev Respir Dis* 1989;139:1179–1187.
11. Seersholm N, Kok-Jensen A. Clinical features and prognosis of life time non-smokers with severe alpha 1-antitrypsin deficiency. *Thorax* 1998;53:265–268.
12. Orell SR, Mazodier P. Pathological findings in alpha1-antitrypsin deficiency. In: Mittman C, editor. *Pulmonary emphysema and proteolysis*. New York: Academic Press; 1972. p. 69–89.
13. Brantly ML, Paul LD, Miller BH, Falk RT, Wu M, Crystal RG. Clinical features and history of the destructive lung disease associated with alpha-1-antitrypsin deficiency of adults with pulmonary symptoms. *Am Rev Respir Dis* 1988;138:327–336.
14. Gishen P, Saunders AJ, Tobin MJ, Hutchison DC. Alpha 1-antitrypsin deficiency: the radiological features of pulmonary emphysema in subjects of Pi type Z and Pi type SZ: a survey by the British Thoracic Association. *Clin Radiol* 1982;33:371–377.
15. American Thoracic Society/ European Respiratory Society. American Thoracic Society/European Respiratory Society Statement: Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency. *Am J Respir Crit Care Med* 2003;168:818–900.
16. 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 tests in unselected smokers. *Radiology* 1992;183:457–463.
17. 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;54:384–389.
18. Saitoh T, Koba H, Shijubo N, Tanaka H, Sugaya F. Lobar distribution of emphysema in computed tomographic densitometric analysis. *Invest Radiol* 2000;35:235–243.
19. Thurlbeck WM. The incidence of pulmonary emphysema: with observations on the relative incidence and spatial distribution of various types of emphysema. *Am Rev Respir Dis* 1963;87:206.
20. Klein JS, Gamsu G, Webb WR, Golden JA, Muller NL. High-resolution CT diagnosis of emphysema in symptomatic patients with normal chest

- radiographs and isolated low diffusing capacity. *Radiology* 1992;182:817-821.
21. Wilson JS, Galvin JR. Normal diffusing capacity in patients with PiZ alpha(1)-antitrypsin deficiency, severe airflow obstruction, and significant radiographic emphysema. *Chest* 2000;118:867-871.
 22. Parr DG, Stoel BC, Stolk J, Guest PJ, Stockley RA. Physiologic discordance in COPD relates to emphysema distribution. *Am J Respir Crit Care Med* 2004;169:A879.
 23. Dowson LJ, Newall C, Guest PJ, Hill SL, Stockley RA. Exercise capacity predicts health status in alpha(1)-antitrypsin deficiency. *Am J Respir Crit Care Med* 2001;163:936-941.
 24. Guidelines for the measurement of respiratory function: Recommendations of the British Thoracic Society and the Association of Respiratory Technicians and Physiologists. *Respir Med* 1994;88:165-194.
 25. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows: Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal: Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:5-40.
 26. West JB. Gas exchange: pulmonary pathophysiology: the essentials. Baltimore, MD: Williams and Wilkins; 1992. pp. 17-34.
 27. Burrows B, Niden AH, Fletcher CM, Jones NL. Clinical types of chronic obstructive lung disease in London and Chicago: a study of one hundred patients. *Am Rev Respir Dis* 1964;90:14-27.
 28. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145:1321-1327.
 29. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I: conceptual framework and item selection. *Med Care* 1992;30:473-483.
 30. Stolk J, Ng WH, Reiber JH, Rabe KF, Putter H, Stoel BC. Correlation between annual change in health status and computer tomography derived lung density in subjects with alpha-antitrypsin deficiency. *Thorax* 2003;58:1027-1030.
 31. Cederlund K, Tylén U, Jorfeldt L, Aspelin P. Classification of emphysema in candidates for lung volume reduction surgery. *Chest* 2002;122:590-596.
 32. Medical Research Council. Definition and classification of chronic bronchitis for clinical and epidemiological purposes: a report to the Medical Research Council by their Committee on the Aetiology of Chronic Bronchitis. *Lancet* 1965;1:775-779.
 33. Fabbri LM, Hurd SS. Global strategy for the diagnosis, management and prevention of COPD: 2003 update. *Eur Respir J* 2003;22:1-2.
 34. Stoller JK, Smith P, Yang P, Spray J. Physical and social impact of alpha 1-antitrypsin deficiency: results of a survey. *Cleve Clin J Med* 1994;61:461-467.
 35. Alpha 1-antitrypsin deficiency: memorandum from a WHO meeting. *Bull World Health Organ* 1997;75:397-415.
 36. Dawkins PA, Dowson LJ, Guest PJ, Stockley RA. High resolution thoracic CT scan predicts mortality in α_1 -antitrypsin deficiency. *Thorax* 2003;58:1020-1026.
 37. Knudson RJ, Kaltenborn WT, Burrows B. Single breath carbon monoxide transfer factor in different forms of chronic airflow obstruction in a general population sample. *Thorax* 1990;45:514-519.
 38. Burrows B, Niden AH, Barclay WR, Kasik JE. Chronic obstructive lung disease: II: relationship of clinical and physiological findings to the severity of airways obstruction. *Am Rev Respir Dis* 1965;91:665-678.
 39. Engel LA, Grassino A, Anthonisen NR. Demonstration of airway closure in man. *J Appl Physiol* 1975;38:1117-1125.
 40. British Thoracic Society. BTS guidelines for the management of chronic obstructive pulmonary disease. *Thorax* 1997;52:S1-S28.
 41. Nakano Y, Muro S, Sakai H, Hirai T, Chin K, Tsukino M, Nishimura K, Itoh H, Pare PD, Hogg JC, Mishima M. Computed tomographic measurements of airway dimensions and emphysema in smokers: correlation with lung function. *Am J Respir Crit Care Med* 2000;162:1102-1108.