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High-resolution computed tomography scanning in α_1-antitrypsin deficiency: relationship to lung function and health status

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High-resolution computed tomography scanning in α_1-antitrypsin deficiency: relationship to lung function and health status. L.J. Dowson, P.J. Guest, S.L. Hill, R.L. Holder, R.A. Stockley. ©ERS Journals Ltd 2001.

ABSTRACT: The development of computed tomography (CT) has enabled emphysema to be assessed noninvasively. Objective quantification of lung density correlates well with lung function in patients with chronic obstructive pulmonary disease and has been shown to be a sensitive tool for monitoring disease progression.

In order to determine the clinical impact of changes seen on high-resolution computed tomography (HRCT), the relationship between the objective quantification of emphysema on HRCT, lung function and health status in 111 patients with α_1-antitrypsin deficiency was examined (PiZ).

The degree of HRCT scan abnormality correlated well ($p < 0.001$ for all comparisons) with forced expiratory volume in one second (r = -0.60 – -0.75), specific airway conductance (r = -0.67 – 0.76), residual volume/total lung capacity (r = 0.46 – 0.58) and transfer factor of the lung for carbon monoxide (r = -0.64 – -0.81). In addition, the CT scans correlated ($p < 0.001$) with health status as assessed by the St. George's Respiratory Questionnaire (SGRQ total: r = -0.38 – 0.50) and the Short-Form health survey (*e.g.* physical functioning: r = -0.39 – 0.54).

In summary, other workers have shown high-resolution computed tomography to be a sensitive indicator of disease progression. This study confirms the relationship between high-resolution computed tomography and lung physiology, and suggests the relationship is even stronger in patients with predominantly lower zone pan-lobular emphysema than in usual chronic obstructive pulmonary disease. High-resolution computed tomography also relates to patients disability and impairment as defined by health status questionnaires and, therefore, should be considered as an alternative outcome measure particularly in α_1-antitrypsin deficiency.

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α_1-antitrypsin deficiency (α_1-ATD) predisposes to the development of emphysema and other features of chronic obstructive pulmonary disease (COPD), particularly in smokers [1]. Traditionally, as with usual COPD, this group of patients have been characterized and monitored by spirometric measurements including the forced expiratory volume in one second (FEV1). This measurement is simple to obtain, is useful in defining short-term response to therapy and is of prognostic value [2]. However, the FEV1 is effort-dependent, suffers from inherent measurement variability and is relatively nonspecific, reflecting many different aspects of lung pathology in patients with COPD. Furthermore, its relative insensitivity to disease progression meant that the numbers of patients required for a sufficiently powered, randomized, placebo-controlled trial of augmentation therapy in α_1-ATD, have generally been prohibitive [3].

Pulmonary emphysema is defined pathologically and diagnosis in life is difficult since simple radiography is relatively insensitive [4]. However, computed tomography (CT), particularly high-resolution computed tomography (HRCT), detects emphysema accurately at a relatively early stage and allows objective measurements of the degree of abnormality to be made [5–7]. Several studies have shown that CT scores derived from radiological densitometric data are related to pathological changes [5, 8, 9] and pulmonary physiology (including FEV1) [6, 10, 11] in patients with emphysema. Perhaps more importantly, several studies have demonstrated that CT is a relatively sensitive measure of emphysema progression [12–14].

Subjective measures using health status questionnaires are now widely recognized as important indicators of impairment and disability and are increasingly being incorporated into intervention trials involving patients with COPD. This is partly because they provide information that cannot be attributed to changes in lung function, as demonstrated by consistently weak correlations between these two modes of patient assessment [15–17].

Because of its sensitivity to change [13], CT scanning would be a good surrogate to assess the efficacy of augmentation therapy in α_1-ATD. However, in order to support CT scanning as a tool for monitoring emphysema in intervention studies it is important to establish its relationship to other conventional outcomes. This study was, therefore, designed to confirm the relationship between HRCT and lung function in this well-defined group of patients with relatively pure panlobular emphysema and to define the relationship between HRCT and health status.

Methods

Subjects

A total of 125 patients with α_1-ATD (PiZ) were assessed. The phenotype was confirmed by analysis of finger prick blood spot (Heredilab, Salt Lake City, UT, USA). The current study was designed to address the relationships between HRCT, physiological impairment and health status in patients with emphysema. Therefore, six patients with clinically significant liver disease were excluded, together with eight patients who had marked macroscopic changes on HRCT that would distort the relationship between the CT quantification of the amount of emphysema present and the physiological and health status measures. These included interstitial changes (n=3), a single giant bulla in otherwise normal lungs (n=2), lung malignancy (n=1) and previous single lung transplant (n=2). The remaining 111 subjects included 85 index cases and 26 identified by family screening.

All subjects were assessed in the stable clinical state at least 2 months after any acute exacerbation. The programme was approved by the University Hospital Birmingham National Health Service Trust ethics committee and all subjects gave informed consent.

Computed tomography

HRCT scanning was performed using a GE Pro Speed Scanner (General Electric Medical Systems, Milwaukee, USA). Slices of 1 mm were taken at 10 mm intervals throughout the thorax, during breath-holding at full inspiration with the subjects in the supine position. The examination was repeated during full expiration at 30 mm intervals, beginning 30 mm above the aortic arch and progressing caudally. Scans were examined visually for the purpose of quality control and in order to assess the presence of macroscopic changes of emphysema [18]. Objective quantification of the extent of emphysema was obtained by determining the relative area of pixels representing lung tissue with a density below -910 Hounsfield Unit (HU). This threshold was selected, based on the available published data comparing conventional CT with pathological [9, 11] and physiological [10] assessment of emphysema. The resulting pixel index was determined for a single slice at the level of the aortic arch (upper zone) and the inferior pulmonary vein (lower zone).

Pulmonary physiology

Full lung function testing was carried out on the same day as the clinical assessment and after administration of the health status questionnaires. Dynamic flow rates were determined using wedge-bellows spirometry (Vitalograph Ltd, Buckinghamshire, UK) after the patients had refrained from using bronchodilators for an appropriate period (6 h for short-acting preparations and 12 h for longer-acting preparations). Bronchodilator reversibility was then assessed by repeating flow rates, 30 min after nebulized salbutamol (5 mg) or terbutaline (5 mg) if that was their usual therapy. Patients then received nebulized ipratropium bromide (0.5 mg) and the tests were repeated after a further 30 min to assess any individual or added response to the anticholinergic agent. Lung volumes were determined by helium dilution and gas transfer by the single breath carbon monoxide technique ($T_{L,CO}$) corrected for effective alveolar volume (K_{CO}). The majority of subjects (n=99) also had airway resistance measured by constant volume plethysmography (Autolink, Morgan Medical, Kent, UK) from which specific airways conductance (sG_{aw}) was calculated. A flow/volume loop was also recorded using a pneumotachograph with a timing facility (Autolink, Morgan Medical, Kent, UK) from which the forced mid-expiratory flows ($FEF_{25\%-75\%}$) were obtained in order to evaluate small airways disease (n=105). All tests were performed according to British Thoracic Society/Association of Respiratory Technicians and Physiologists guidelines [19].

Health status

Indices of health status were obtained using questionnaires administered by a member of the research team with the patient well rested and prior to pulmonary function testing. The data was collected directly onto a computerized database from which the patient was able to select one of the permitted responses for each item.

The St. George's Respiratory Questionnaire (SGRQ) [15] is a disease specific measure containing 76 items divided into three domains: symptoms (relating to cough, sputum production, wheeze and breathlessness), activity (relating to physical activity limited by breathlessness) and impacts (relating to employment, control, panic, stigmatization, medication and expectations). The responses to each item are empirically weighted according to estimates of the distress caused, resulting in scores 0–100 for each domain with 0 indicating no impairment. A summary score (total) was derived from the responses to the three domains and also scored 0–100.

The Short-Form health survey (SF-36) is a generic measure that assesses health concepts representing basic human values that are relevant to functional status and well being [20]. It includes one multi-dimensional scale measuring each of eight health concepts: physical functioning, role limitations due to physical health problems (role physical), bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional problems (role emotional), and mental health (psychological distress and well being). The data was again transformed to a 0–100 scale separately for each health concept, where a score of 0 indicates the most severe disability.

Statistical analysis

The data was analysed using a computerized statistical package (Statistical Package for the Social Sciences (SPSS) version 8.0, SPSS Inc., Chicago, USA). The overall frequency distributions of most of the variables analysed were non-normal and hence the median and interquartile ranges were used to describe the data. Differences between subgroups were determined by the Mann-Whitney U-test for continuous data and Chi-squared test for categorical data. Differences in paired variables required the Wilcoxon signed rank test and correlations between paired variables were examined using Spearman's rho. A p-value <0.05 was taken as statistically significant for all analyses.

Results

Baseline characteristics

The demographic features, HRCT and physiological results for the 111 subjects are summarized in table 1. Of the 82 patients (74%) with a history of >1 pack-yr cigarette consumption, nine continued to smoke. The median number of pack-yrs of tobacco consumption amongst the current and exsmokers was 23 (range 2–66).

Table 1. – Subject characteristics, lung function and pixel indices

	N	Median	IQR
Gender M:F	74:37	na	na
Age yrs	111	50	43–55
Lung function*			
FEV_1	111	41.7	29.2–76.2
FEV_1/VC	111	43.9	29.7–71.7
$FEF_{25\%-75\%}$	105	14.0	9.6–36.2
sG_{aw}	99	33.3	19.7–49.8
TLC	109	119.1	105.3–132
RV	109	135.7	101.3–169.1
RV/TLC	109	115.8	93.4–137.6
$T_{L,CO}$	109	61.0	50.0–85.0
K_{CO}	109	67.4	51.3–90.4
P_{a,O_2}	99	9.2	8.4–10.3
HRCT pixel index % pixels <-910 HU			
Upper zone inspiratory	111	35.3	19.7–49.8
Upper zone expiratory	111	22.0	6.8–39.7
Lower zone inspiratory	111	53.0	31.5–63
Lower zone expiratory	111	44.4	20.6–56.2

N: number of patients; IQR: interquartile range; FEV_1: forced expiratory volume in one second; VC: vital capacity; $FEF_{25\%-75\%}$: forced midexpiratory flows; sG_{aw}: specific airways conductance; TLC: total lung capacity; RV: residual volume. *: postbronchodilator values (where available, see methods) expressed as % predicted.

High-resolution computed tomography

Ninety patients (81%) had macroscopic evidence of emphysema seen on HRCT with areas of low attenuation or frank bullous disease. Figure 1 shows the range of pixel indices for the patients with and without macroscopic evidence of emphysema on visual inspection of the HRCT films and demonstrates that the two groups are separated, most notably on the expiratory scans ($p<0.001$ for all comparisons). The group of 21 subjects with no macroscopic evidence of emphysema on CT were younger compared to those with macroscopic emphysema (median age, 39 *versus* 51 yrs, respectively, $p=0.001$). They also included a higher percentage of never-smokers (62% *versus* 17%, $p<0.001$) and nonindex cases (71% *versus* 12%, $p<0.001$). As expected, their pulmonary function and health status was better than the patients with macroscopic emphysema ($p<0.01$ for all measures of pulmonary function, and all domains of the SGRQ (data not shown)).

The pixel indices indicated that both upper and lower zones were affected (table 1) with a good correlation between the severity of emphysema seen ($r=0.74-0.79$; $p<0.001$). However, as a group, the pixel indices were higher in the lower zones indicating more extensive emphysema in this region ($p<0.001$) (fig. 2).

Lung function

Lung function data indicated a wide range from normal to severe airflow obstruction, with gas trapping and impairment of gas transfer (table 1). Eighty-three patients (75%) had airflow obstruction as

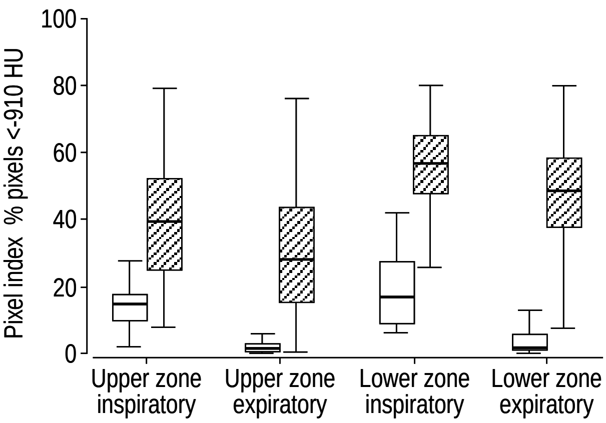

Fig. 1. – The pixel index (PI) in patients with (▨, n=90) and without (□, n=21) macroscopic evidence of emphysema on visual reporting. The median (horizontal bar), interquartile range (box) and range (whiskers) are displayed for each group. Outliers (values >1.5 box lengths away from the top or bottom of the box) are not displayed. The PI for the scans from subjects with emphysema is significantly greater ($p<0.001$) for all scans. HU: Hounsfield Units.

determined by an FEV1 < 80% predicted and an FEV1/vital capacity ratio < 0.7. The median pre-bronchodilator FEV1 for these subjects was 0.78 L (interquartile range (IQR) 0.63 – 1.11) which increased to 0.91 L (IQR 0.76 – 1.44) following β_2-agonist ($p < 0.001$) and 1.08 L (IQR 0.83 – 1.47) following the addition of ipratropium bromide ($p < 0.001$).

Health status

The SGRQ and SF-36 indicated a wide range of health status, from normal to markedly reduced. The median values for the SGRQ suggested moderate-to-severe impairment from respiratory problems (symptoms: 72.8, normal range 9 – 15; activity: 73, normal range 7 – 12; impacts: 40.2, normal range 1 – 3; total: 55.5, normal range 5 – 7) and this was accompanied by marked abnormality in the SF-36 domains relating to physical activity and general well being (physical functioning: 40; role physical: 50; general health: 25; vitality: 40) with a milder reduction in social functioning (median 75). The scores for the remaining domains relating to bodily pain, emotional and mental health problems were similar or better than the scores of the general population [20] (data not shown).

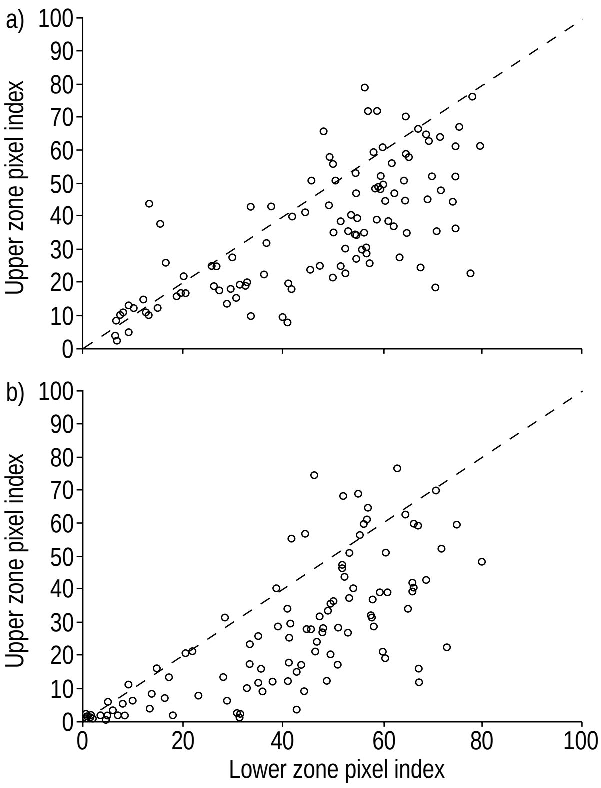

Fig. 2. – Scatter diagram showing the relationship between upper and lower zone high-resolution computed tomography pixel index for: a) inspiratory (rho = 0.72; $p < 0.001$) and b) expiratory (rho = 0.80; $p < 0.001$) phase scans. The line of equality is drawn in with subjects lying below the line displaying predominantly lower zone disease.

Relationship of high-resolution computed tomography to lung function

The pixel indices obtained from all HRCT scans showed highly significant correlations ($p < 0.001$) with all physiological indices. The correlations between HRCT scans and lung function as well as the individual data for FEV1 are shown in table 2, *s*Gaw *s*Gaw and *T*L,CO are summarized in figure 3.

Relationship of high-resolution computed tomography to health status

HRCT correlated significantly with all domains of the SGRQ ($p < 0.001$) and the SF-36 ($p < 0.05$) with the exception of bodily pain, mental health and reported health transition in the latter. The correlation coefficients for the relationships of HRCT pixel indices and the SGRQ are shown in table 3. Figure 4 summarizes the health status expressed as total SGRQ score related to bands of pixel index divided according to severity from normal (pixel index < 5%) to the presence of extensive emphysema (pixel index > 50%). The data confirms the wide scatter of scores but demonstrates a significant decrease in health status for each band of pixel index. This relationship was maintained for both inspiratory and upper zone scans (data not shown).

Relationship of lung function to health status

Lung function was also related to health status and significant correlations were observed between all domains of the SGRQ and postbronchodilator lung function (table 3). This relationship was maintained for the physical functioning, general health and social functioning domains of the SF-36 ($p < 0.04$ for all correlations). Individual data for the relationship

Table 2. – Spearman correlation coefficients (rho) for the relationship between high-resolution computed tomography (HRCT) and lung function*

	HRCT pixel index⁺			
	Upper zone		Lower zone	
	Inspiratory	Expiratory	Inspiratory	Expiratory
FEV1	-0.60	-0.72	-0.64	-0.75
FEV1/VC	-0.72	-0.79	-0.70	-0.78
FEF25%–75%	-0.60	-0.69	-0.70	-0.76
*s*Gaw	-0.67	-0.76	-0.68	-0.76
TLC	0.63	0.70	0.54	0.61
RV	0.61	0.58	0.43	0.41
RV/TLC	0.47	0.58	0.46	0.56
*T*L,CO	-0.76	-0.81	-0.64	-0.72
*K*CO	-0.79	-0.77	-0.61	-0.62

FEV1: forced expiratory volume in one second; VC: vital capacity; FEF25%–75%: forced midexpiratory flows; *s*Gaw: specific airways conductance; TLC: total lung capacity; RV: residual volume; *T*L,CO: transfer factor of the lung for carbon monoxide; *K*CO: carbon monoxide transfer coefficient. *: expressed as % predicted; $^+$: percentage of pixels < -910 HU. All correlations are highly significant ($p < 0.001$).

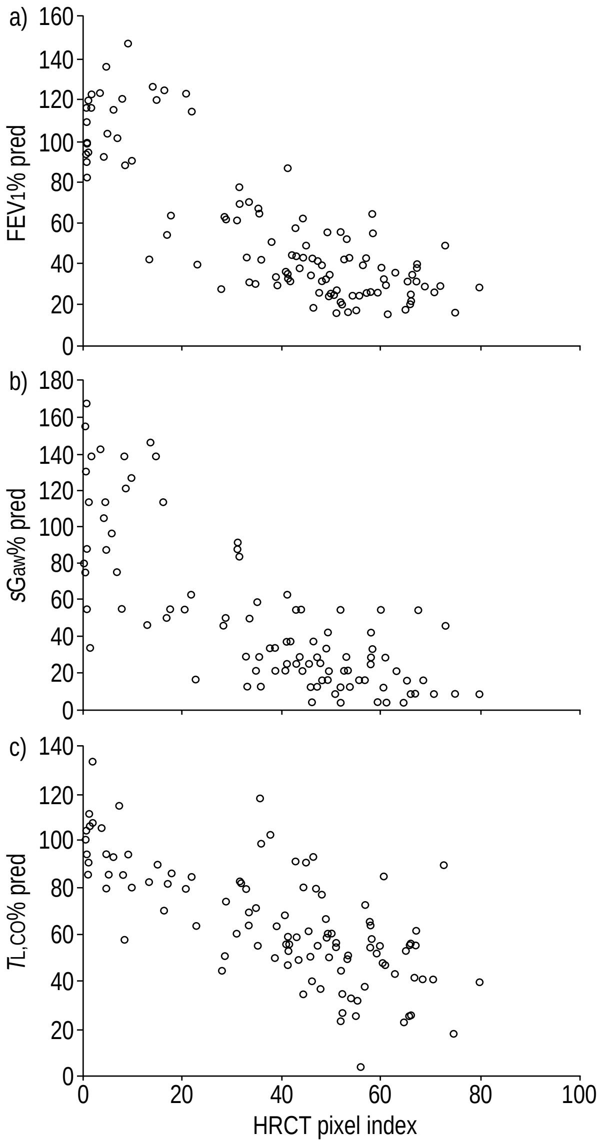

Fig. 3. – Scatter diagram showing the relationship between the pixel index (% pixels <-910 Hounsfield Units) for lower zone expiratory scans and: a) postbronchodilator forced expiratory volume in one second (FEV1) (rho=-0.75; p<0.001), b) specific airways conductance (*s*Gaw) (rho=-0.76; p<0.001) and c) carbon monoxide gas transfer (*T*L,CO) (rho=-0.72; p<0.001). Physiology results are expressed as a percentage of predicted normal. HRCT: high-resolution computed tomography.

between SGRQ total and FEV1, *s*Gaw and *T*L,CO are shown graphically in figure 5.

Discussion

The current study demonstrates that the pixel index obtained from a single HRCT slice is closely related to abnormalities in lung physiology in patients with α_1-ATD and predominantly lower zone pulmonary emphysema (fig. 2). In addition, the extent of emphysema relates to impairment and disability as assessed by both disease specific and generic health status questionnaires.

Table 3. – Spearman correlation coefficients (rho) for relationships between disease-specific health status and measures of lung function and high-resolution computed tomography pixel index

	St. George's Respiratory Questionnaire			
	Symptoms	Activity	Impacts	Total
Lung function*				
FEV1	-0.45	-0.60	-0.47	-0.55
*s*Gaw	-0.46	-0.66	-0.52	-0.60
RV/TLC	0.47	0.51	0.49	0.52
*T*L,CO	-0.43	-0.57	-0.46	-0.53
*K*CO	-0.36	-0.43	-0.39	-0.43
HRCT pixel index+				
Upper zone inspiratory	0.31	0.42	0.31	0.38
Upper zone expiratory	0.38	0.53	0.37	0.46
Lower zone inspiratory	0.31	0.44	0.36	0.39
Lower zone expiratory	0.41	0.58	0.44	0.50

FEV1: forced expiratory volume in one second; *s*Gaw: specific airways conductance; RV: residual volume; TLC: total lung capacity; *T*L,CO: transfer factor of the lung for carbon monoxide; *K*CO: carbon monoxide transfer coefficient. *: expressed as a percentage of predicted; +: percentage of pixels <-910 HU. All correlations are highly significant (p<0.001).

This study represents a comprehensive assessment of subjects with α_1-ATD (PiZ) where all investigations have been carried out in a single centre, using the same equipment and staff. The data confirms that the majority of subjects had predominantly but not exclusively lower zone emphysema identified by

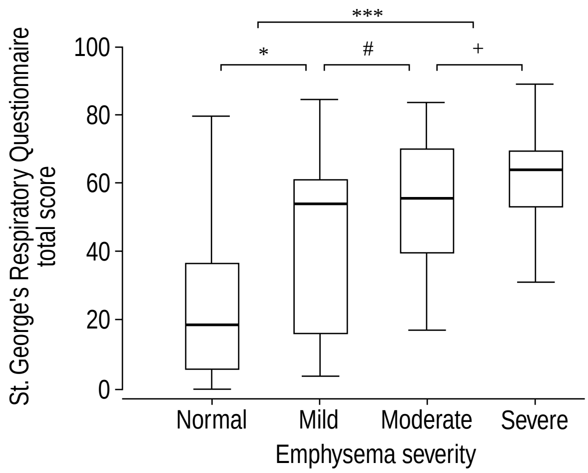

Fig. 4. – Health status as assessed by the St. George's Respiratory Questionnaire in patients with different degrees of emphysema (Normal: pixel index (PI)<10, n=21; Mild: 10<PI<30, n=12; Moderate: 30<PI<50, n=37; Severe: PI>50, n=41) defined by lower zone expiratory high-resolution computed tomography pixel index. The median (horizontal bar), interquartile range (box) and range (whiskers) are displayed for each group. ***: overall p-value is <0.001 (Kruskal Wallis test); significance of the differences between each consecutive group (Mann-Whitney U-test), *: p=0.024; #: p=0.153; +: p=0.046.

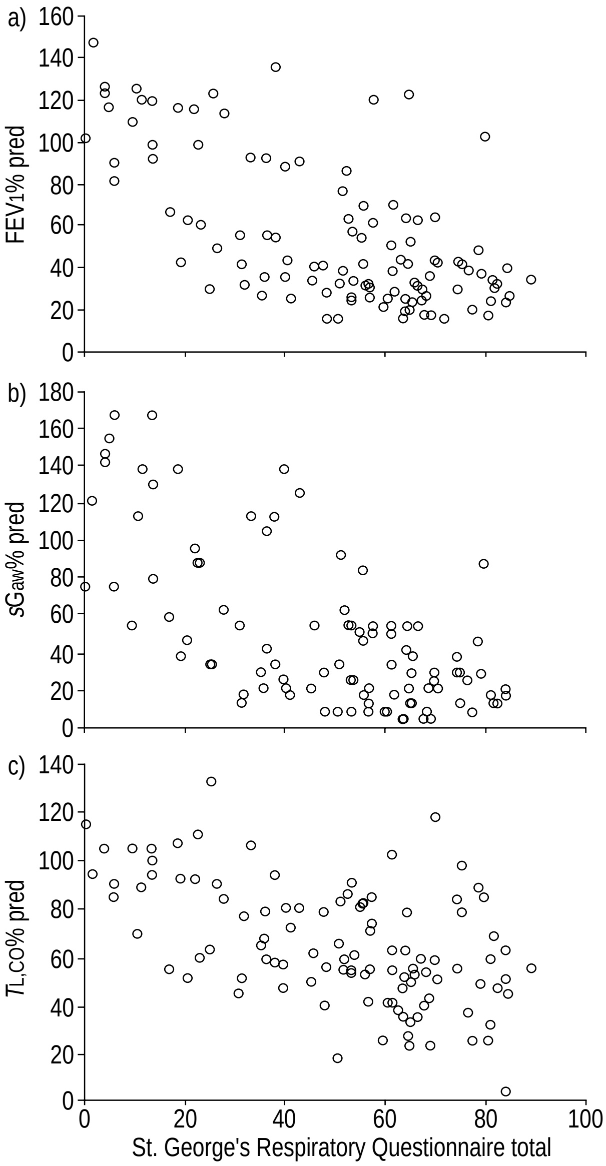

Fig. 5. – Scatter diagram showing the relationship between St. George's Respiratory Questionnaire and a) postbronchodilator forced expiratory volume in one second (FEV1) (rho=-0.55; $p<0.001$), b) specific airways conductance (*s*Gaw) (rho=-0.60; $p<0.001$) and, c) carbon dioxide gas transfer (*T*L,CO) (rho=-0.53; $p<0.001$). Physiology results are expressed as a percentage of predicted normal.

HRCT scanning. Physiologically, the results indicated marked airflow obstruction, air trapping and a reduction in diffusing capacity. In addition, the reduction in FEF25%–75% and *s*Gaw suggest small airways involvement, although it is not clear whether this represents inflammatory changes in the airways or simply reduced elastic recoil and airway collapse. However, recently published pathological data showing bronchiolar involvement in this group of patients [21] suggested that intrinsic changes in the airways themselves may be of more importance than has been previously thought [22].

In this study, using a threshold of -910 HU, the HRCT pixel index was closely related to all measures of pulmonary function. The expiratory scans were most closely related to markers of airway obstruction and gas trapping, although there was a relatively wide scatter of results reflecting the different anatomical influences on airway diameter. The inspiratory scans were as strongly related to *K*CO which itself is strongly related to emphysema as assessed by the area of walls of distal airspaces per unit of lung volume [5].

There are several methods for analysing and expressing densitometric data from CT scanning, including mean values, percentiles and different density thresholds. However, consensus has yet to be achieved regarding the most appropriate protocol. A value of -910 HU was chosen as the threshold based on the data available at the time the study was initiated and in the belief that the expiratory phase scans would be the most reproducible. Studies published since then have suggested that other thresholds may be more appropriate, at least for the inspiratory phase scans [8]. In addition, there is some uncertainty concerning the ventilatory phase that demonstrates the pathological changes most effectively. In the current study, the inspiratory phase scans demonstrated a wider range of pixel indices than the expiratory scans. Also, a small number of asymptomatic patients with pulmonary function tests within the normal range and a normal HRCT scan macroscopically had abnormally high pixel indices. It is possible that these individuals have early, subclinical emphysema not visible macroscopically or that they represent the tail of a normal distribution of lung density which is known to vary with age and total lung capacity in healthy subjects [23]. However, it remains most likely that the use of -910 HU as the threshold for the inspiratory scans, results in the overestimation of the extent of emphysema in these subjects.

In support of this possibility, GEVENOIS *et al.* [24] found that -910 HU was the appropriate threshold for determining macroscopic emphysema from expiratory scans but found that the correlation between -950 HU applied to inspiratory HRCT and pathological changes was stronger [8]. However, 94% of the patients included in these studies were undergoing surgical resections for lung cancer and by necessity had relatively mild emphysema (median value <10%). It is possible that GEVENOIS *et al.* [24] may have found a different threshold to be more appropriate if, as in the current study, a wider range of impairment was examined including patients more likely to be seen and treated for COPD in practice and intervention trials. If -950 HU had been used for the inspiratory scans, specificity for the detection of emphysema may have improved but milder disease may also have been missed.

Nevertheless, despite the limited slice protocol and absence of respiratory gating in the current study, the correlations between CT emphysema scores and lung were at least as strong and frequently stronger than those previously noted in usual COPD [10, 11, 24–26]. There may be several reasons for this, including the wide range of disease severity studied, the relatively young age group, the use of high-resolution rather than conventional CT, and the fact that all investigations were carried out in a single centre using the same equipment and staff. Also, patients with α_1-ATD represent a relatively homogenous group of subjects with pan-lobular emphysema rather than patients with nondeficient COPD where centrilobular emphysema predominates or may even be absent. In addition, as demonstrated in figure 2, the lower lobes are affected predominantly in α_1-ATD and there is some evidence that this may have a proportionally greater physiological impact [27, 28].

Although these results do not indicate that the method of CT analysis used in this study is superior to methods used by other workers, it does confirm the usefulness of this approach in the objective assessment of emphysema. However, it is clear that in order to allow comparison between different centres and to facilitate multicentre studies, a consensus is required concerning the most appropriate method. It may be that the aims of individual studies should be taken into account when selecting a CT density threshold. For instance, if the aim is to monitor progression of emphysema in patients with relatively mild disease, then the sensitivity provided by using a more dense threshold may be preferred over the specificity of a lower one. However, further studies are clearly required to explore this possibility.

The development and validation of health status tools have enabled them to become an increasingly important part of disease assessment. Such measures are reproducible and sensitive to change. In studies of COPD patients, FEV1 relates to health status but accounts for only a minor proportion ($<10\%$) of the disability encountered [15, 16, 29, 30]. The current study is the first to explore the relationship between emphysema (as assessed by HRCT) and health status. The data showed a clear relationship between the pixel index and the disease-specific SGRQ scores as well as many of the domains of the generic SF-36. However, the relationship between lung function and health status was even stronger. Again, the correlation coefficients indicated stronger relationships than those previously noted in COPD not due to α_1-ATD [16–18] and may reflect the homogeneity of the group studied as indicated earlier.

In summary, the current study confirms that high-resolution computed tomography is closely related to physiological changes in patients with emphysema and α_1-antitrypsin deficiency. Despite the theoretical limitations of the relatively simple protocol employed here, the correlations are stronger than those observed in previous studies and importantly, involved a lower dose of radiation. This may be of particular importance if computed tomography fulfils its promise as a method for monitoring disease progression and the effects of medical intervention. Furthermore, if an intervention is shown to influence disease progression as assessed by high-resolution computed tomography, the current data suggests that this will not only be associated with preservation of lung function, but also benefits in terms of health status. Although discrepancies between the present data and data from studies in usual chronic obstructive pulmonary disease suggest caution when applying these conclusions more generally, the current study suggests further studies are required to determine whether high-resolution computed tomography can be considered an appropriate outcome measure in addition to or even replacing forced expiratory volume in one second or health status.

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References

1. Anonymous. Alpha 1-antitrypsin deficiency: memorandum from a WHO meeting. *Bull World Health Organ* 1997; 75: 397–415.
2. American Thoracic Society. Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin. The Alpha-1-Antitrypsin Deficiency Registry Study Group. *Am J Respir Crit Care Med* 1998; 158: 49–59.
3. Burrows B. A clinical trial of efficacy of antiproteolytic therapy: can it be done? *Am Rev Respir Dis* 1983; 127: S42–S43.
4. Thurlbeck WM, Simon G. Radiographic appearance of the chest in emphysema. *Am J Roentgenol* 1978; 130: 429–440.
5. Gould GA, MacNee W, McLean A, *et al.* 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. 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.
7. Miller RR, Muller NL, Vedal S, Morrison NJ, Staples CA. Limitations of computed tomography in the assessment of emphysema. *Am Rev Respir Dis* 1989; 139: 980–983.
8. 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.
9. Muller NL, Staples CA, Miller RR, Abboud RT. "Density mask". An objective method to quantitate emphysema using computed tomography. *Chest* 1988; 94: 782–787.
10. Kinsella M, Muller NL, Abboud RT, Morrison NJ, DyBuncio A. Quantitation of emphysema by computed tomography using a "density mask" program and correlation with pulmonary function tests. *Chest* 1990; 97: 315–321.
11. Knudson RJ, Standen JR, Kaltenborn WT, *et al.* Expiratory computed tomography for assessment of suspected pulmonary emphysema. *Chest* 1991; 99: 1357–1366.
12. Coxson HO, Rogers RM, Whittall KP, *et al.* A quantification of the lung surface area in emphysema using computed tomography. *Am J Respir Crit Care Med* 1999; 159: 851–856.

13. Dirksen A, Dijkman JH, Madsen F, *et al.* A randomized clinical trial of alpha-1 antitrypsin augmentation therapy. *Am J Respir Crit Care Med* 1999; 160: 1468 – 1472.
14. Stolk J, Zagers R, Vrooman HA, *et al.* Assessment of the progression of emphysema by quantitative analysis of spirometrically-gated CT images. *Eur Respir Rev* 1997; 43: 154 – 158.
15. 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.
16. Ketelaars CA, Schlosser MA, Mostert R, Huyer Abu-Saad H, Halfens RJG, Wouters EF. Determinants of health-related quality of life in patients with chronic obstructive pulmonary disease. *Thorax* 1996; 51: 39 – 43.
17. Tsukino M, Nishimura K, Ikeda A, Koyama H, Mishima M, Izumi T. Physiologic factors that determine the health-related quality of life in patients with COPD. *Chest* 1996; 110: 896 – 903.
18. Naidich DP. High-resolution computed tomography in cystic lung disease. *Semin Roentogenol* 1991; 26: 151 – 154.
19. Anonymous. 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.
20. Ware JE. SF-36 Health Survey. Manual and Interpretation Guide. 1. Boston, Massachussetts, Nimrod Press, 1999.
21. Theegarten D, Teschler H, Stamatis G, Konietzko N, Morgenroth K. Pathologic-anatomic findings in surgical lung volume reduction of advanced emphysema. *Pneumologie* 1998; 52: 702 – 706.
22. Black LF, Hyatt RE, Stubbs SE. Mechanism of expiratory airflow limitation in chronic obstructive pulmonary disease associated with alpha1-antitrypsin deficiency. *Am Rev Respir Dis* 1972; 105: 891 – 899.
23. Gevenois PA, Scillia P, de Maertelaer V, De Vuyst P, Yernault JC. The effects of age, sex, lung size and hyperinflation on CT lung densitometry. *AJR* 1996; 167: 1169 – 1173.
24. Gevenois PA, De Vuyst P, Sy M, *et al.* Pulmonary emphysema: quantitative CT during expiration. *Radiology* 1996; 199: 825 – 829.
25. 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 – 146.
26. Heremans A, Verschakelen JA, Van Fraeyenhoven L, Demedts M. Measurement of lung density by means of quantitative CT scanning. A study of correlations with pulmonary function tests. *Chest* 1992; 102: 805 – 811.
27. Gurney JW, Jones KK, Robbins RA, *et al.* Regional distribution of emphysema: correlation of high-resolution CT with pulmonary function tests in unselected smokers. *Radiology* 1992; 183: 457 – 463.
28. 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 – 129.
29. Renwick D, Connolly M. Impact of chronic obstructive airways disease on quality of life in older adults. *Thorax* 1996; 51: 520 – 525.
30. Wijkstra PJ, Ten Vergert EM, van der Mark ThW, Postma DS, Kraan J, Koeter GH. Relation of lung function, maximal inspiratory pressure, dyspnoea, and quality of life and exercise capacity in patients with chronic obstructive pulmonary disease. *Thorax* 1994; 49: 468 – 472.