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PROGRESS OF EMPHYSEMA IN SEVERE α_1-ANTITRYPSIN DEFICIENCY AS ASSESSED BY ANNUAL CT

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Abstract

Purpose: To assess serial CT as a measure of the progress of emphysema in patients with severe α_1-antitrypsin deficiency (phenotype PiZ).

Material and Methods: In a randomized placebo-controlled study of α_1-antitrypsin augmentation therapy, 22 patients with moderate emphysema were followed for 2–4 years with an annual lung CT. The images were analysed by means of semiautomatic lung detection, and the degree of emphysema was quantitated by the density-mask and the percentile methods. The influence of lung volume was standardised by a regression model.

Results: A highly significant decline in Hounsfield units (HU) was found in low-density areas, corresponding to a mean (SE) annual loss of lung tissue of 2.1 (0.4) g/l lung volume. Analysis of a single slice at 5 cm below the level of the carina gave comparable results: 2.4 (0.4) g/l.

Conclusion: Serial CT is a sensitive measure of the progress of emphysema in patients with severe α_1-antitrypsin deficiency.

Key words: Lung, ventilation; CT; density.

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The 1985 report of the National Heart, Lung, and Blood Institute's Division of Lung Diseases Workshop (18), USA, defines emphysema as "a condition of the lung characterized by abnormal, permanent enlargement of air spaces distal to the terminal bronchiole, accompanied by the destruction of their walls, and without obvious fibrosis". Several studies have compared the morphological assessment of emphysema in lungs or lobes at surgical resection or autopsy with that of CT (9, 19). Pointing out that the clinical diagnosis of emphysema is inaccurate and imprecise, BIERNACKI et al. have suggested that the progression of emphysema may be assessed more accurately by repeated quantitative CT than by measuring the first-second forced expiratory volume (FEV_1) (3).

Because visual assessment of CT of the lungs is subject to observer variability, methods have been developed to calculate densitometric parameters from the pixel attenuation values of the CT images for the quantitation of emphysema. FLENLEY's group in Edinburgh constructed frequency histograms of the Hounsfield units (HU) within the lung, and then used the HUs defining the lowest 5th percentile of the histogram to characterize the extent of emphysema (10). Another method, developed by MÜLLER's group in Vancouver (14), quantitates emphysema by a "density mask" that highlights pixels with densities below a threshold (e.g. –910 HU), thus defining lung regions of abnormally low attenuation as emphysematous.

The principal confounder of lung density measurements is the level of inspiration. In the range from full inspiration to full expiration, lung densities can more than double (16). The aim of our study was to adjust for the level of inspiration by regression analysis and then evaluate various densitometric parameters as measures of the progress of emphysema in serial CT of patients with severe α_1-antitrypsin deficiency.

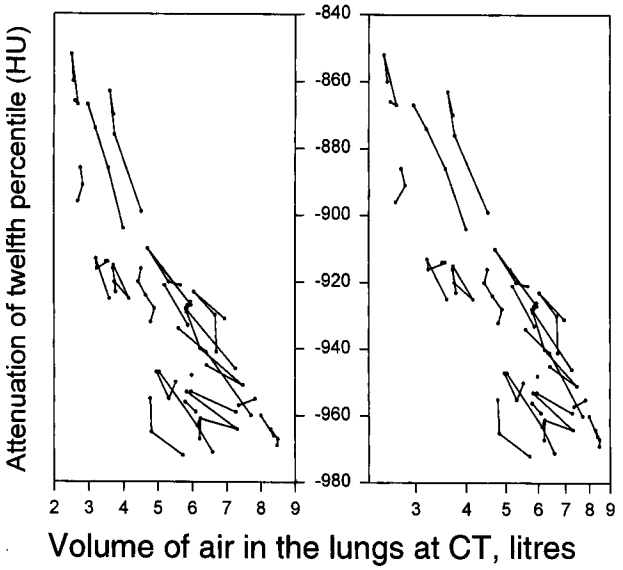

Fig. 1. Relation between level of inspiration as calculated from total lung CT and lung density as indicated by the 12th percentile (left). The 12th percentile is derived from the frequency histogram of HUs within the lung as the density value at which 12% of the pixels have lower densities. Each line represents the serial examinations of one of 22 subjects with severe α_1-antitrypsin deficiency (type PiZ) and moderate emphysema. Relationships linearise by logarithmic transformation of the volume of air (right).

Material and Methods

From 1991 to 1995, 22 patients with severe α_1-antitrypsin deficiency (phenotype PiZ, verified by isoelectric focusing) (7) and moderate emphysema (35% predicted<FEV_1<60% predicted) were followed with an annual CT of the chest. The patients participated in a randomized trial of augmentation therapy with α_1-antitrypsin vs placebo. All had stopped smoking at least 6 months before entering the study and their urinary cotinine was checked every 4 weeks during the trial. All patients were informed about the inherent radiation exposure and all agreed to participate in the study, which was approved by the local medical ethics committee.

The annual CT was performed on a Siemens Somatom DRG scanner that was calibrated daily with a water phantom. Thick-section CT images were obtained with 8-mm collimation at 8-mm intervals through the chest, and a note was made of the table positions at 4 anatomical levels: the level of the sternal notch, the level of the tracheal carina, 5 cm below the level of the carina, and 2 cm above the dome of the diaphragm. Furthermore, 5 thin-section images using 2-mm collimation were obtained: at the carina, and at 5 cm and 10 cm above and below the carina. Scanning parameters were 125 kVp, 88 mA, and 4 s imaging time. All subjects were imaged in the supine position during tidal breathing, i.e. at a lung volume close to the functional residual capacity in the sitting position. No contrast medium was injected.

The thick-section CT data were transferred to a Somatom Plus workstation and each examination was analysed with the Pulmo CT option. First, an automatic contour-tracing algorithm was used on each slice to separate the lung tissue from the thoracic wall and the mediastinum at a threshold of –200 HU for the soft-tissue lung interface. Then regions that were mistakenly included or excluded were corrected with the use of an interactive mode, and the trachea and large bronchi were always excluded. A frequency distribution (histogram) of the pixel attenuation values in the lung fields for each slice was subsequently generated and, by means of a serial interface, data were transmitted to a personal computer where they were stored. Finally, a total histogram for the whole lung was calculated by adding up the histograms of all the slices in the examination.

The thin-section images were assessed visually. Centrilobular emphysema, characterized by a nonuniform enlargement of the air spaces in the central portions of the lung lobules, was seen in the upper parts of the lungs whereas panacinar emphysema, identified by the presence of decreased parenchymal attenuation and diminished and distorted vascularity, predominated in the lower zones. Two experi-

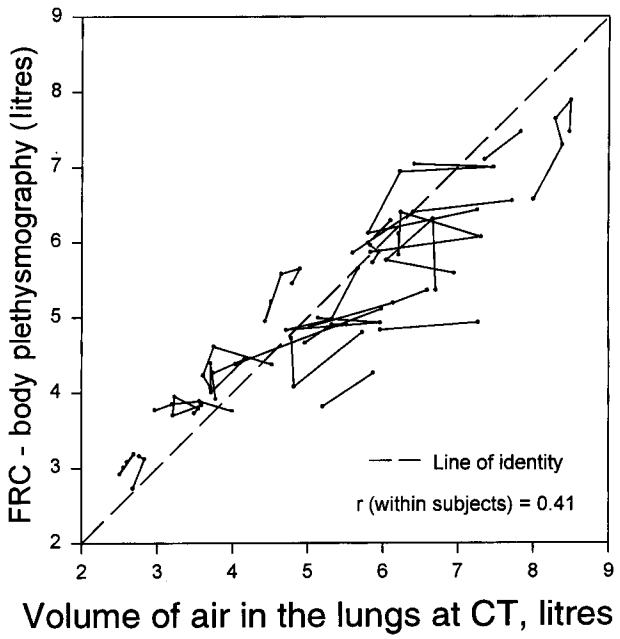

Fig. 2. Volume of air in the lung calculated from CT as compared to determination by body plethysmography. Each line represents the serial examinations of one of 22 subjects with severe α_1-antitrypsin deficiency (type PiZ) and moderate emphysema.

Table 1

Characteristics and respiratory function at enrollment of 22 subjects with severe α_1-antitrypsin deficiency (type PiZ) and moderate emphysema

	Mean	SD	% of prediction	SD
Sex, male/female	12/10			
Age, years	50	8.5		
Height, m	1.73	0.10		
Forced vital capacity (FVC), litres	4.54	1.42	113	15.8
Forced expiratory volume in 1 s (FEV_1), litres	1.61	0.42	50	12.1
Slow vital capacity (VC), litres	5.06	1.44	124	13.3
Total lung capacity (TLC) (by body plethysmography), litres	8.21	1.62	132	13.4
Residual volume (RV) (by body plethysmography), litres	3.43	0.69	173	38.8
Functional residual capacity (by body plethysmography) (FRC), litres	5.02	1.15	158	27.6
Functional residual capacity (by helium dilution) (FRC-He), litres	3.75	1.07	117	24.0
Carbon monoxide diffusing capacity ($D_{L_{CO}}$), $ml \cdot min^{-1} \cdot mm \cdot Hg^{-1}$	17.0	5.50	60	16.5
Diffusion constant (K_{CO}) calculated from the ratio of $D_{L_{CO}}$ to TLC, $ml \cdot min^{-1} \cdot mm\ Hg^{-1} \cdot litres^{-1}$	2.51	0.79	55	16.8

enced radiologists (M.F., K.O.), who were blinded to the clinical and functional findings on the progress of the disease, independently graded the trend of emphysema in the serial scans of each patient in broad outline as either "regressive", "stable", or "progressive".

CT was usually performed at 1:30 in the afternoon. In the morning of the same day the patient visited the respiratory laboratory. Pulmonary function testing was performed according to ATS and ERS recommendations (2, 5, 15). A constant volume body plethysmograph and a dry-rolling seal spirometer (Sensor Medics, 2800 and 2450, Anaheim, CA, USA) were applied. Fifteen minutes after bronchodilatation (nebulized terbutaline 5 mg), with the patient seated and with the nose clipped, a slow vital capacity (VC) manoeuvre was performed, followed by a forced vital capacity (FVC) manoeuvre from which the maximal flow volume loop and the FEV_1 were derived. Static lung volumes (i.e. total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV)) were measured by both the closed-circuit helium-dilution technique and plethysmography in which lung volumes and airway resistance were determined during panting with a frequency of less than 1/s. Carbon monoxide diffusing capacity ($D_{L_{CO}}$) was measured by the single-breath technique and, because the haemoglobin was always within normal limits, the values were not corrected for haemoglobin. The diffusion constant (K_{CO}) was calculated from the ratio of $D_{L_{CO}}$ to alveolar volume, the latter being obtained from the dilution of helium during the single-breath manoeuvre. All measurements were performed in triplicate except for the He-dilution. Gas volumes are reported with body-temperature and pressure-saturated (BTPS) corrections, and the results are expressed both in absolute values and as percent of predicted values that were calculated according to European reference equations (5, 15).

Data analysis

Initially two types of CT densitometric parameters and a volume-of-air parameter were derived from the frequency histograms of thick-section images. 1) A *density-mask parameter* was defined as the volume corresponding to pixels with attenuation values below a given threshold (14). 2) A *percentile parameter* was defined as the cutoff point in the histogram at a given percentile of the histogram (10). The 10th percentile was extracted from the histogram as the density value (HU) at which 10% of the pixels had lower densities. 3) The *volume-of-air parameter* (FRC_{CT}) was defined as the volume of air in the lung corresponding to the histogram. It was calculated from the histogram by assuming a water-equivalent density of evacuated lung tissue, and a direct linear relationship between pixel attenuation values and the actual physical density of the tissue, comprised in the voxel where 0 HU represented the density of water and −1000 HU the density of air.

Based on the total histogram of the whole lung, density-mask parameters were calculated with thresholds ranging from −1000 HU to −870 HU (at intervals of 10 HU), and percentile parameters were calculated with percentiles ranging from 1% to 50% (at intervals of 1%). Subsequently the power of the densitometric parameters to detect the progress of emphysema in serial CT was evaluated by a random-effects regression model with the densitometric parameter (DP) as the dependent variable, time of the CT (T) as the independent variable, the vol-

Table 2

Annual change in lung attenuation in 22 subjects with severe α_1-antitrypsin deficiency (type PiZ) and moderate emphysema

		Mean	SE	*p*
Whole lung				
Density-mask method*	−1000 HU	6.16%	4.25%	0.2
	−980 HU	5.80%	2.91%	0.06
	−960 HU	5.62%	1.77%	0.005
	−940 HU	4.98%	1.01%	0.00007
	−930 HU	4.79%	0.95%	0.00005
	−920 HU	4.54%	1.01%	0.0002
	−900 HU	3.95%	0.99%	0.0007
	−880 HU	3.04%	0.95%	0.004
Percentile method**	5%	−1.89 HU	0.42 HU	0.0002
	10%	−2.13 HU	0.38 HU	0.00001
	12%	−2.15 HU	0.38 HU	0.00001
	15%	−2.10 HU	0.39 HU	0.00002
	20%	−2.12 HU	0.41 HU	0.00004
	30%	−2.06 HU	0.47 HU	0.0002
	40%	−1.77 HU	0.54 HU	0.003
	50%	−1.44 HU	0.63 HU	0.03
Single slice (percentile method** only)				
Level of the sternal notch	10%	−0.15 HU	0.87 HU	0.9
	15%	0.16 HU	0.92 HU	0.9
	20%	0.35 HU	0.97 HU	0.7
Level of the tracheal carina	10%	−2.31 HU	0.63 HU	0.001
	15%	−2.18 HU	0.63 HU	0.002
	20%	−2.00 HU	0.61 HU	0.004
5 cm below the carina	10%	−2.29 HU	0.41 HU	0.00002
	15%	−2.37 HU	0.40 HU	0.00001
	17%	−2.42 HU	0.40 HU	0.00000
	20%	−2.35 HU	0.41 HU	0.00001
2 cm above the diaphragm	10%	−1.27 HU	0.40 HU	0.005
	15%	−1.33 HU	0.38 HU	0.002
	20%	−1.37 HU	0.42 HU	0.004

* The relative annual change (%) of lung volume below a threshold (HU).

** The annual change in attenuation value (HU) of a percentile of the histogram of HU within the lung.

ume-of-air parameter (FRC_{CT}) as a covariate, and patient (P) as a random factor:

$$DP=k_0+k_1 \times T+k_2 \times FRC_{CT}+U_P$$

where DP is either a density-mask parameter or a percentile parameter, k_0, k_1 and k_2 are constants, and U_P is normally distributed around zero (random levels) (6). k_1 is the annual change in DP and k_2 is the correction factor by the litre change in volume of air (FRC_{CT}).

Graphical assessment of the assumptions of linear regression indicated logarithmic transformation of density-mask parameters and FRC_{CT} (Fig. 1). The best model was defined as the model leading to the strongest predictions (F-statistics), and the best densitometric parameter was derived from this model.

Finally, with the purpose of reducing the radiation dose and the examination time in future examinations, a single-slice concept was explored by applying the best densitometric parameter to single slices at 4 preselected anatomical levels: the level of the sternal notch, the level of the carina, 5 cm below the level of the carina, and 2 cm above the dome of the diaphragm.

Results

Patient characteristics and respiratory function at enrollment are shown in Table 1. The two radiologists who visually assessed the thin-section (2 mm) CT images agreed on the total number of serial scans with a "stable" trend (6 vs 7) and a "progressive" trend (16 vs 15). The scans of 2 subjects were classified by both radiologists as showing a stable trend, and 11 were classified by both as showing a progressive trend. However, the two radiologists disagreed on the classification of the remaining 9 serial CT examinations. This means that agreement in the classification of subjects was the same as would be expected by chance (kappa=0.02).

The relation between total volume of air in the

lung as calculated from CT and the volume of air as measured by body plethysmography (FRC) a couple of hours earlier is shown in Fig. 2. The overall correlation coefficient was 0.91, and the within-subjects correlation coefficient was 0.41 (p=0.004).

The results of the quantitative analysis of the serial CT examinations are summarised in Table 2. In the CT examinations of the whole lung, results of higher statistical significance were obtained with the percentile method than with the density-mask method. The percentile method gave almost identical results within a broad range of percentiles from the 10th to the 30th.

Statistical significance peaked at the 12th percentile where the mean annual decline in lung density was 2.1 HU (95% confidence interval (CI): 1.4–2.9 HU). The median attenuation of the 12th percentile was –930 HU which corresponded to the optimal threshold of the density-mask method (Fig. 3). The correction factor (k_2) for change in volume of air in the lung (FRC_{CT}) steadily became greater with increasing percentiles. For instance, a doubling of FRC_{CT} implied a decrease in the correction factor which gave –46.4 HU at the 10th percentile, –58.9 HU at the 20th percentile, and –68.5 HU at the 30th percentile.

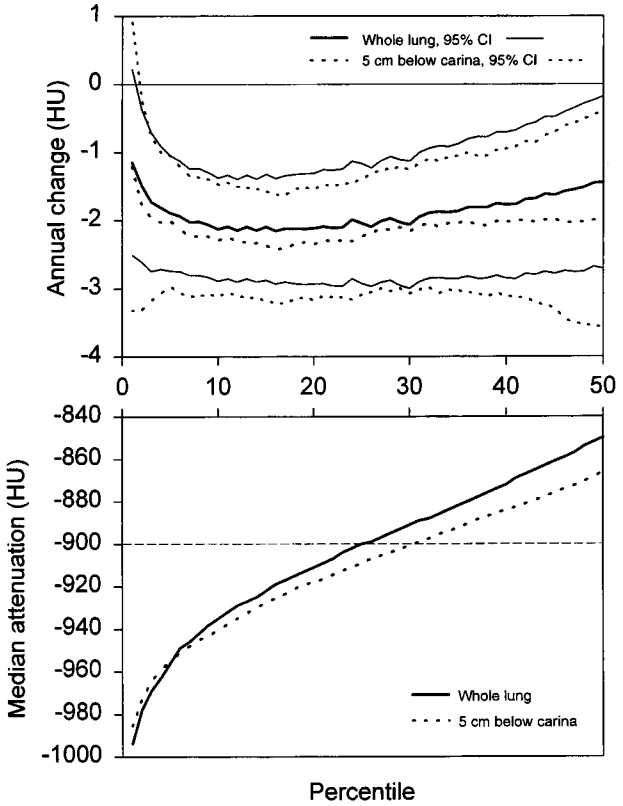

Fig. 3. The progress of emphysema in serial CT of 22 subjects with severe α_1-antitrypsin deficiency (type PiZ) and moderate emphysema. In the upper graph, the annual change of lung attenuation is indicated by percentiles ranging from the 1st to the 50th (the median). In the lower graph the median attenuation values of the percentiles are shown. The solid lines are derived from the quantitative analysis of whole-lung CT, and the dotted lines originate from a single slice at a level of 5 cm below the tracheal carina.

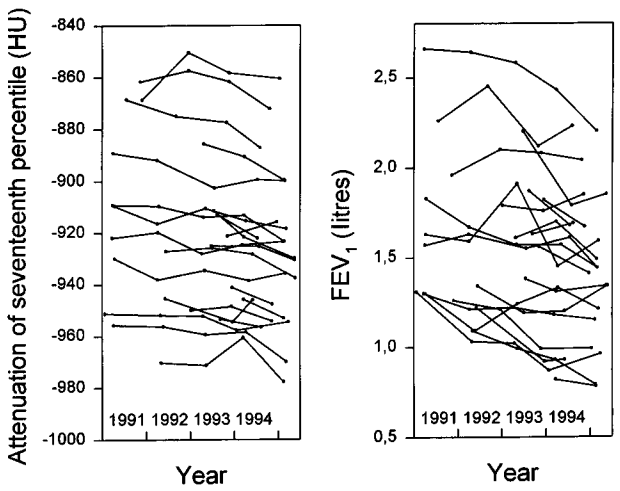

Fig. 4. Variability of lung density by annual CT at a level of 5 cm below the carina (left) and the variability of spirometry (right) in 22 subjects with severe α_1-antitrypsin deficiency (type PiZ) and moderate emphysema. Each line represents the serial examinations of one subject. The left graph shows the attenuation values (HU) of the 17th percentile at CT (Table 2), and the right graph shows the FEV_1.

For single slices, the highest statistical significance was achieved at a level of 5 cm below the tracheal carina. The results obtained with the 17th percentile of this slice (2.4 HU, 95% CI 1.6–3.2 HU) were fully comparable to those of the best percentiles in the whole-lung CT, although the range of useful percentiles was more narrow at this level. In Fig. 4, FEV_1 was chosen as the perfect example of traditional lung function tests for monitoring obstructive airways disease. For comparison, serial measurements of FEV_1 were plotted side by side with serial determinations of the 17th percentile derived from CT images at the level of 5 cm below the carina.

Discussion

The results suggest that serial CT density measurements of the lungs, standardised by volume of air, are a sensitive indicator of the progress of emphysema in patients with severe α_1-antitrypsin deficiency, even when the measurements are derived from a single slice only.

Histopathological evaluation remains the gold standard for assessing emphysemas since emphysema is defined in histological terms (18). However, histopathological assessment of emphysema in liv-

ing patients must be based on a biopsy and this does not accurately reflect the overall extent of emphysema in both lungs. CT density measurements on the other hand provide an objective quantitative assessment of the overall extent of emphysema in both lungs.

The X-ray attenuation in lung tissue largely depends on the volume of air inhaled and more than doubles from full inspiration to full expiration (16). Thus, defined volumes of inspiration have to be used for attenuation measurements in the lung. Several investigators have attempted to accomplish this by having the patients breathe through a spirometer during the examination for determining VC. As soon as a preselected inspiration level was reached, CT was initiated during breathholding (11). KALENDER et al. (11) tested the reproducibility of the level of respiration that triggered the CT exposures, and found a mean deviation of 1.0% in 10 healthy volunteers but a much larger deviation of 7.2% in 9 patients with obstructive ventilation disturbances (FEV_1 56±13%). No further information was given about the patients nor about how the deviations were documented, and the authors concluded that "... a general limitation of any spirometric technique for longitudinal measurements may result if the patient fails to reproduce the levels of full expiration and inspiration required for the measurements of vital capacity in successive examinations. This may occur in patients with obstructive respiratory disease".

In 24 adult patients of whom 4 had obstructive lung disease, KOHZ et al. (13) found an average difference of 89 ml (3.2%) in measurements of VC by spirometrically controlled CT performed twice with a 5-min interval. A comparison of results of the two consecutive examinations showed the average deviation in mean attenuation to be 10 HU. A variation in the position of the section scanned in the first and second examinations had the most important impact on results and was primarily a result of inaccuracies that occurred when the section position was drawn on the topogram. Even minimal variations in the position resulted in considerable alterations in lung attenuation, especially at the level of the carina. The imaging of hilar structures (pulmonary vessels and bronchi) was considerably altered by only minor changes in the section scanned, primarily as a result of the horizontal course of these structures.

Although this problem can probably be somewhat reduced by using the percentile method instead of mean attenuation, the variation of 10 HU is large as compared to our standard deviation for the annual loss of lung attenuation (Table 2). Several investigators believe that control of the level of respiration during scanning is mandatory for improving the reproducibility and accuracy of density measurements but this is not supported by our findings. Serial CT with adjustment for lung volumes by statistical modelling (regression analysis) seems to be more effective than spirometrically controlled CT. In future studies the two methods could be combined, making it possible to compare them under more equal conditions.

We calculated the volume of air from the histograms. Others have used the total CT lung volume (12). Because of partial volume effects, the boundaries of the lungs are not well defined. Marginal lung pixels usually contain little air and they thus contribute less to the total volume of air than to the total lung volume, which means that the total volume of air is less dependent on the arbitrary threshold value for the soft-tissue lung interface. A further advantage of using the total CT volume of air in the lungs is that it is in agreement with common lung function measurements such as FRC.

The density range of the lung varies between subjects. In a study of 17 smokers and nonsmokers with no evidence of emphysema at respiratory function testing, ADAMS et al. (1) found that the percentage of cross-sectional area in the density range of −1000 HU to −900 HU, a range commonly used to detect emphysema, varied from less than 1% to more than 50%. In our patients we also found a large variation in lung density as seen in Fig. 4. However, the time trend was fairly uniform after adjusting for volume of air in the lung and this trend was almost unimpaired when we restricted the analysis to a single slice at 5 cm below the carina.

In a broad range of pixels from the 10th to the 30th percentile (corresponding to densities ranging from −950 HU to −890 HU) the annual decline was 2 HU (Fig. 3) which corresponded to a loss of lung tissue of 2 mg/ml lung volume. We found that the largest decline in attenuation occurred in low-density areas. This is in keeping with the concept of emphysema as a condition characterized by the destruction of the walls of distal air spaces (18) because pixels with low densities mostly contain terminal bronchioles and alveoli. Pixels with higher attenuation values include larger bronchioles, vessels and partial volume areas, all of which are less affected by the emphysematous process.

In 1990 FLENLEY suggested the use of a "new CT method to assess the role of antiprotease therapy in preventing the progression of emphysema" (8). In considering the decline in density of a percentile as a surrogate marker by which to quantitate the progress of emphysema, an important problem to note is a possible normal change in lung attenuation

with increasing age. Two cross-sectional studies found no obvious effect of age on lung density in normal subjects (17, 20). For the sake of argument, let us suppose that the normal annual decline is about 0.5 HU and that antiprotease therapy might bring the decline half-way back to normal. This would indicate a mean decline of 2.5 HU in the placebo group and of 1.5 HU in the active treatment group. With the observed standard error of the mean, a decline of 0.4 HU (Table 2) would imply a 50% chance of observing a statistically significant treatment effect ($p<0.05$) in a 3-year study with 28 patients in each group. This compares very favourably with calculations by BURROWS in 1983 that were based on measurements of FEV_1 and showed that "300 to 500 subjects would be required for a therapeutic trial with a minimum follow-up of 3 years" (4). Thus, the decline in the density of any percentile in the 10th–30th range may prove to be a very sensitive measure of the progress of emphysema, at least in subjects such as ours with severe α_1-antitrypsin deficiency (phenotype PiZ).

Another important problem related to the use of CT for monitoring the progress of emphysema is radiation exposure. We explored the possibility of using only a single slice instead of a full-lung scan. We examined slices at 4 preselected anatomical levels: the level of the sternal notch, the level of the carina, the level of 5 cm below the level of the carina, and the level of 2 cm above the dome of the diaphragm, and found that the slice at 5 cm below the level of the carina gave results comparable to those of a whole-lung CT. The single-slice concept reduces the radiation dose by more than 95% which brings it into an acceptable range, making it possible to use CT in the routine follow-up of these patients.

The present study was confined to patients with severe α_1-antitrypsin deficiency (phenotype PiZ), and only future studies can show whether our results can be generalised to other types of emphysema. In smokers with normal α_1-antitrypsin, the distribution of emphysema (although most frequently involving the upper lung zones) may be less predictable. Therefore the particular single level used in the present study may not necessarily be representative of the emphysema burden of the whole lung in other patients.

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