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Regional extravascular density and fractional blood volume of the lung in interstitial disease

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ABSTRACT Regional lung density (g lung/ml thoracic volume) and fractional pulmonary blood volume (ml blood/ml thoracic volume) have been measured by positron tomography in 10 patients with interstitial disease. From the measurements regional extravascular lung density (g tissue and interstitial water/ml thoracic volume) was derived, providing a non-invasive measurement of the interstitial reaction. Extravascular lung density was increased and large regional variations were observed. Fractional blood volume was reduced in patients with pulmonary fibrosis. In two patients with sarcoidosis, a reduction in extravascular lung density occurred after treatment with oral prednisone. Abnormalities in extravascular lung density and fractional blood volume correlated with abnormalities shown by tests of overall pulmonary function.

A technique for quantitative measurement of extravascular lung density (lung tissue and interstitial fluid per unit thoracic volume) and the fractional blood volume in the lung (volume of blood per unit thoracic volume) by means of positron tomography has recently been described.[1] The purpose of this study was to evaluate the use of this technique for investigation of interstitial lung disease.

Interstitial diseases are characterised by chronic interstitial inflammation and derangement of alveolar structures.[2] While some patients show spontaneous remissions, others progress to pulmonary fibrosis with permanent loss of lung function. Quantitative measurements of the disease process in the lung could be of value for monitoring the effect of treatment and are essental if the relation between the interstitial reaction and pulmonary function is to be clarified.

Methods

PATIENTS

Five patients with sarcoidosis and mild to moderate functional impairment (group 1) were studied. Details of the patients are presented in table 1. In all five patients a histological diagnosis had been made. Three of the patients were treated with prednisone (20 mg daily) for four to six weeks and subsequently restudied.

Five patients with severe functional impairment (group 2) were also studied. Three had end stage disease, two with fibrosing alveolitis and the other with sarcoidosis. The other two patients in this group had presented with breathlessness. In both patients crackles were found on physical examination and the chest radiographs showed basal nodular shadowing. Patient 9 had chronic hypoxaemia and finger clubbing. A clinical diagnosis of pulmonary fibrosis had been made. Both patients slowly deteriorated during the period of observation.

The study was approved by the research ethics committee of the Royal Postgraduate Medical School, and written informed consent was obtained from each patient.

PULMONARY FUNCTION TESTS

Standard pulmonary function tests were performed on the same day as the tomographic study. Vital capacity (VC) and forced expiratory volume (FEV_1) were recorded with a dry spirometer. Total lung capacity (TLC) was measured by body plethysmography. The single breath method was used for measuring the transfer factor for carbon monoxide (TLCO) and transfer coefficient (KCO). The results were expressed in relation to predicted values.[3 4]

POSITRON TOMOGRAPHY

The technique for measuring regional extravascular

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Table 1 *Details of patients studied*

Patient No	*Sex*	*Age (y)*		*Radiological appearance*	*Histology*
		At study	*At diagnosis*		
Group 1					
1	M	40	30	Widespread interstitial shadowing	Lung biopsy: NCG Kveim reaction positive
2	M	29	28	Bilateral hilar lymphadenopathy	Lung biopsy: NCG
3	F	36	34	Bilateral hilar lymphadenopathy, widespread nodular shadowing	Lung biopsy: NCG
4	M	32	26	Bilateral hilar lymphadenopathy, widespread nodular shadowing	Lung biopsy: NCG
5	F	47	44	Perihilar and apical stippling	Lung and lymph node biopsy: NCG Kveim reaction positive
Group 2					
6	M	65	65	Gross basal shadowing	Necropsy: Fibrosing alveolitis
7	M	66	46	Coarse reticular shadowing	Lung biopsy: Fibrosing alveolitis
8	M	41	31	Widespread interstitial shadowing	Lymph node biopsy: NCG Kveim reaction positive
9	M	76	72	Basal nodular shadowing	None; Kveim reaction negative
10	M	59	56	Basal nodular shadowing	None; Kveim reaction negative

NCG—non-caseating granulomas.

lung density and fractional blood volume has previously been described in detail,[1] and is only summarised here.

Positron tomography is based on coincidence detection of the pair of γ rays originating from the annihilation of a positron. In the instrument we used (ECAT II, EG&G ORTEC), annihilation events are recorded between pairs of detectors placed in a hexagonal array around the supine patient. The information is fed to a computer and subsequently used to reconstruct a transverse plane through the object in a way similar to that used in x ray computed tomography.

Protocol

In each study two measurements were made with the patient in the supine position. The first measurement was made with an external ring source containing a positron emitting isotope ($^{68}Ge/^{68}Ga$) placed between the patient and the array of detectors. The transmission tomogram thus obtained (fig 1, top left panel) showed the distribution of density in the plane chosen and provided a quantitative measurement of the density of the lung (g lung/ml thoracic volume). Tomograms were obtained at two levels of the chest: one roughly at the sternal insertion of the fourth rib and the other 8·5 cm in the cranial direction.

After this measurement the patient inhaled a quantity of ^{11}C carbon monoxide (^{11}CO) to label the blood pool. After the inhalation five minutes were allowed for mixing before emission tomograms were obtained at the same two levels. During the measurement venous blood was sampled and the concentration of ^{11}CO in peripheral blood subsequently measured in a well counter, cross calibrated with the ECAT. The emission tomogram showed the regional distribution of blood volume (fig 1, upper right panel). A quantitative measurement of the fractional blood volume in the lung (ml blood/ml thoracic volume) was obtained by dividing the regional concentration of ^{11}CO with the concentration in whole blood.

Data analysis

Since lung density and fractional blood volume can be expressed in the same units (g/ml thoracic volume), regional extravascular lung density (lung tissue and interstitial fluid per unit thoracic volume) can be calculated (fig 1, bottom panel) by subtraction.

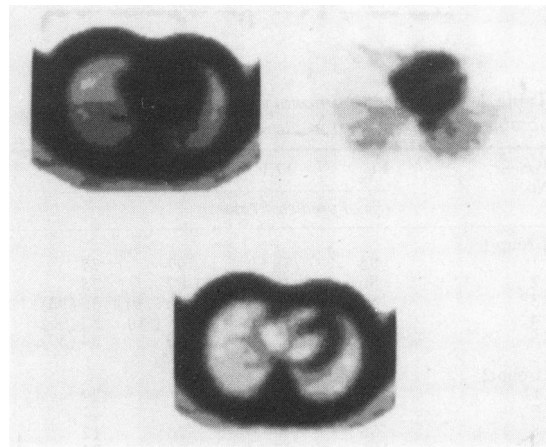

Fig 1 *Tomograms of lung density (top left), fractional blood volume (top right), and extravascular lung density (bottom) from a normal subject.*

The resolution in the reconstructed tomograms is 17 mm (measured as the full width at half maximum of the response to a line source of activity). Owing to the limited resolution, there is a gradual change in the measured density from the chest wall to the lung. This means that it is impossible to identify a distinct border of the lung in the tomogram, and that the peripheral part of the lung is affected by "spillover" from the chest wall (partial volume effect[5]).

For comparison with the results of lung function tests, extravascular lung density and fractional pulmonary blood volume were averaged over a large proportion of the lung by delineating the right and left lung fields in the caudal plane, a cut off density value of 0·85 g/ml being used to define the edge of the lung. The mean density and fractional blood volume in this volume were related to predicted values obtained from normal subjects.[6] Allowance for the partial volume effect was made by taking the size of the lung field into account.

Regional variations in extravascular lung density and fractional blood volume were analysed in two ways. Ventrodorsal (vertical in the supine subject) differences were measured within a 17 mm wide strip through the right lung field in the caudal plane (fig 5, inset). This strip was divided into 10 sections to account for differences in lung size. Sections 1 and 10 were disregarded because of the influence of the chest wall. Craniocaudal differences were analysed by selecting regions of interest of equal size in the middle of the right lung field at the same gravitational level.

The patients were compared with a reference group of 19 normal subjects (17 men and two women)[6] with a mean age of 35 years (range 20–56). Student's *t* test was used for statistical analysis.

Table 2 *Results of pulmonary function tests (values obtained after treatment in parentheses)*

Patient No	*VC*	*FEV_1*	*TLC*	*TLCO*
	(% of predicted values)			
Group 1				
1	86	58	97	77
2	86	80	87	75
3	85 (102)	89 (111)	106 (101)	55 (93)
4	96 (100)	98 (105)	95 (90)	82 (95)
5	60 (60)	62 (65)	60	54 (57)
Group 2				
6	74	65	—	29
7	44	50	—	—
8	55	50	76	12
9	105	87	96	32
10	72	23	109	71

VC—vital capacity; TLC—total lung capacity; TLCO—transfer factor for carbon monoxide.

Results

Results of the lung function tests are presented in table 2. In most patients a reduction in lung volumes and in the transfer factor for carbon monoxide was found. Although there was considerable scatter, impairment of lung function tended to be worse in patients in group 2 than in group 1.

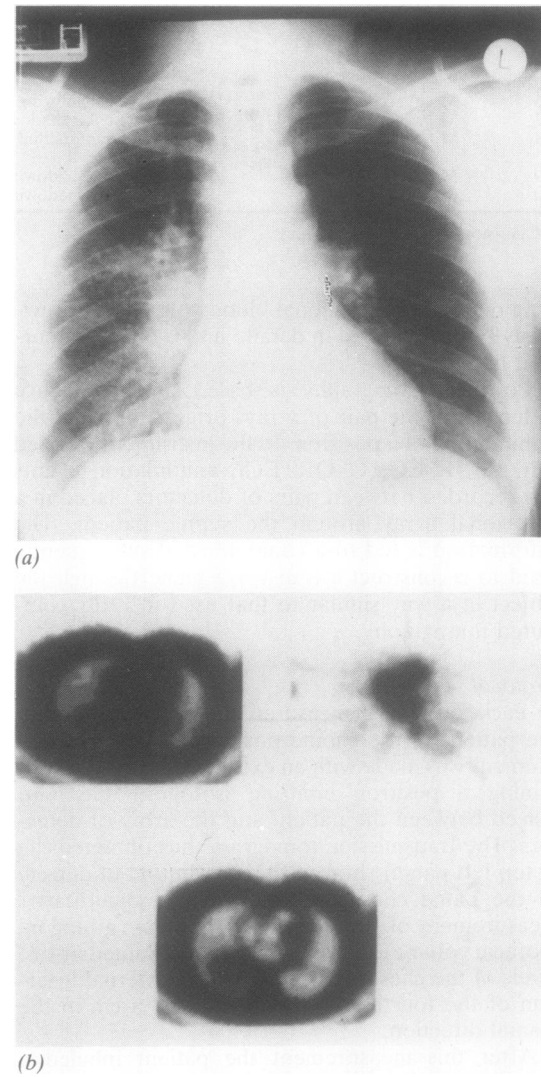

Fig 2 *Chest radiograph (a) and tomograms (b) from a patient with sarcoidosis. Lung density (top left) is increased owing to an increase in extravascular lung density (bottom). Fractional blood volume (top right) is reduced in the dorsal part of the right lung field, which corresponds to the lower lobe.*

TOMOGRAPHIC APPEARANCE IN RELATION TO CHEST RADIOGRAPH

Tomograms of lung density, fractional blood volume, and extravascular lung density from a normal subject are shown in figure 1. In normal subjects there is a ventrodorsal gradient of lung density (upper left panel), caused mainly by differences in fractional blood volume (upper right panel). Extravascular density (bottom panel) has a more uniform distribution.[1]

Chest radiographs and tomograms from a patient with sarcoidosis (patient 3) are shown in figures 2 and 3. In the pretreatment radiograph (fig 2*a*) there was gross bilateral lymphadenopathy and extensive shadowing in the right lung. Lung density (fig 2*b*, upper left panel) was greatly increased in the right lung field. Fractional blood volume (upper right panel) was reduced in the dorsal part of the right

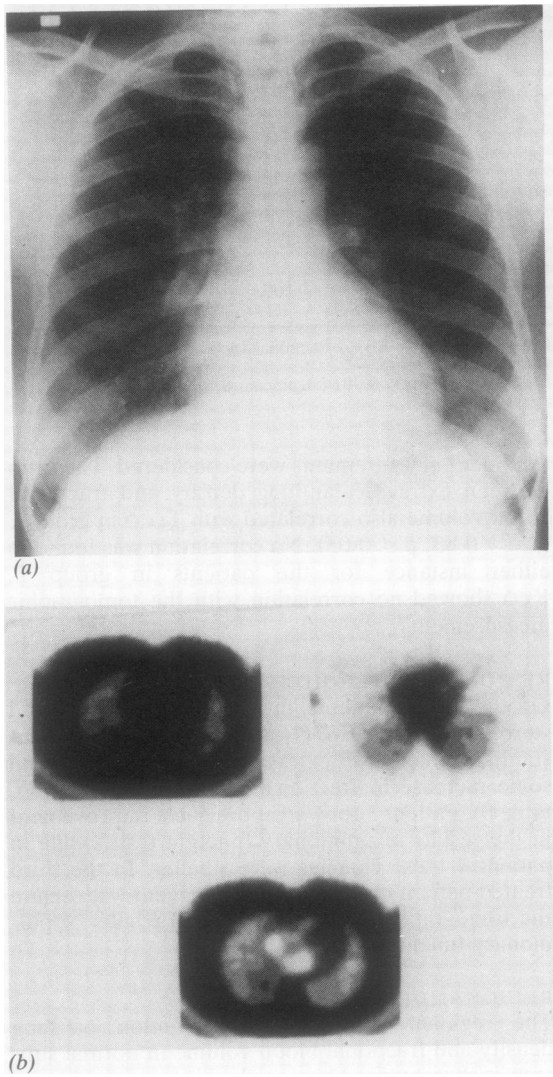

Fig 3 *Chest radiograph (a) and tomograms (b) from the patient with sarcoidosis shown in figure 2 after a period of steroid treatment. Improvement is seen in extravascular lung density (bottom) as well as in fractional blood volume (top right).*

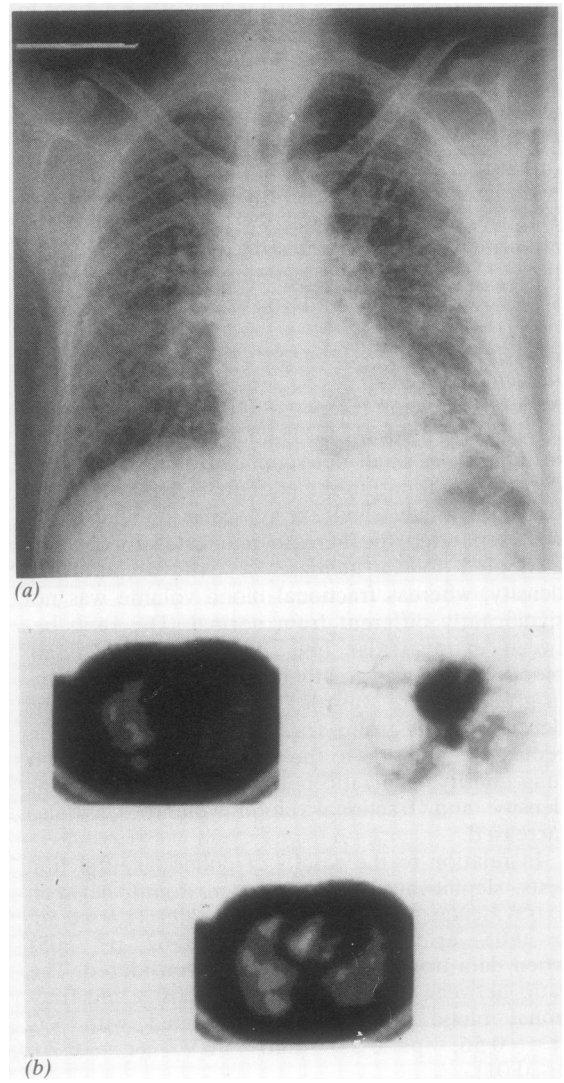

Fig 4 *Chest radiograph (a) and tomograms (b) from a patient with fibrosing alveolitis. Lung density (top left) and extravascular lung density (bottom) is increased, especially at the periphery of the lung. Fractional blood volume (top right) is reduced.*

lung field, corresponding to the right lower lobe. The increase in density was thus accounted for by abnormalities in the extravascular compartment (lower panel). After treatment with prednisone (30 mg daily) there was a reduction in the radiographic abnormalities (fig 3*a*). Fractional blood volume (upper right panel) returned to normal and extravascular lung density (lower panel) was greatly reduced. Major regional abnormalities in fractional blood volume were not seen in any other patient in group 1.

The chest radiograph and illustrative tomograms of lung density, fractional blood volume, and extravascular lung density from a patient in group 2 (No 6) with idiopathic pulmonary fibrosis are shown in figure 4. Lung density (fig 4*b*, upper left panel) was increased in the patient owing to an increase in extravascular lung density (lower panel). The abnormalities were greatest in the periphery of the lung. Fractional blood volume was reduced and showed an irregular pattern (upper right panel).

CORRELATIONS WITH RESULTS OF PULMONARY FUNCTION TESTS

Mean density and fractional blood volume throughout the lung fields for the caudal plane are presented in table 3. A small but significant increase in lung density was found in the patients in group 1. When the intravascular and extravascular compartments were separated, the increase in lung density could be attributed to an increase in extravascular lung density, whereas fractional blood volume was not significantly different from normal. The ratio between extravascular lung density and fractional blood volume was greatly increased. In the patients in group 2 there was also a small increase in lung density. In this group, fractional blood volume was reduced in addition to the increase in extravascular lung density. The ratio between extravascular lung density and fractional blood volume was also increased.

In relation to the results of pulmonary function tests, significant correlations were found between extravascular lung density and VC ($r = -0{\cdot}56$, $p < 0{\cdot}05$) as well as FEV_1 ($r = -0{\cdot}62$, $p < 0{\cdot}05$) when data from both groups were considered. The ratio between extravascular lung density and fractional blood volume also correlated with VC ($r = -0{\cdot}56$, $p < 0{\cdot}05$) and FEV_1 ($r = -0{\cdot}70$, $p < 0{\cdot}01$).

No correlation was found between the tomographic measurements and TLCO when data from both groups were considered. In group 1, however, a significant correlation between mean fractional blood volume and TLCO was found ($r = 0{\cdot}73$, $p < 0{\cdot}05$) when both pretreatment and post-treatment measurements were considered. The ratio between extravascular lung density and fractional blood volume also correlated with TLCO in group 1 ($r = -0{\cdot}83$, $p < 0{\cdot}05$). No correlation was found in either instance for the patients in group 2. KCO showed no correlation with the tomographic measurements.

Table 3 *Mean lung density, fractional blood volume and extravascular lung density measured in the lung fields in the caudal plane (values obtained after treatment in parentheses)*

Patient No	*LD*	*FBV*	*ELD*	*ELD/FBV*
	(% of predicted values)			
Group 1				
1	110	103	115	114
2	112	92	124	138
3	100 (100)	76 (98)	114 (101)	164 (107)
4	122 (114)	112 (122)	131 (108)	113 (85)
5	106 (102)	90 (89)	115 (111)	141 (137)
Mean	110**	95	120***	134***
SD	8	14	8	21
Group 2				
6	107	66	132	206
7	122	75	154	194
8	110	88	125	134
9	101	79	116	132
10	106	58	139	217
Mean	109**	73***	133***	177***
SD	8	12	14	41
Normal subjects (n = 19)				
Mean	100	100	100	100
SD	4	11	6	13

LD—lung density; FBV—fractional blood volume; ELD—extravascular lung density.
**$p < 0{\cdot}01$; ***$p < 0{\cdot}001$ (significant deviation from normal).

RESPONSE TO STEROID TREATMENT

Of the three patients in group 1 who received steroid treatment, two (Nos 3 and 4) showed a substantial reduction in extravascular lung density and some increase in fractional blood volume (fig 3*b*, table 3). Patient 3 showed appreciable improvement in the results of pulmonary function tests, while in patient 4 these changes were smaller. In the third treated patient only minor improvement was seen in the tomographic measurements and results of pulmonary function tests.

REGIONAL DIFFERENCES

The regional ventrodorsal distribution of lung density and fractional blood volume in normal subjects is characterised by a gradual increase in density and blood volume from the ventral to the dorsal part of the lungs (fig 5). The distribution of extravascular lung density is more uniform in the normal subjects. Most patients in group 1 showed a non-uniform increase in lung density and extravascular lung

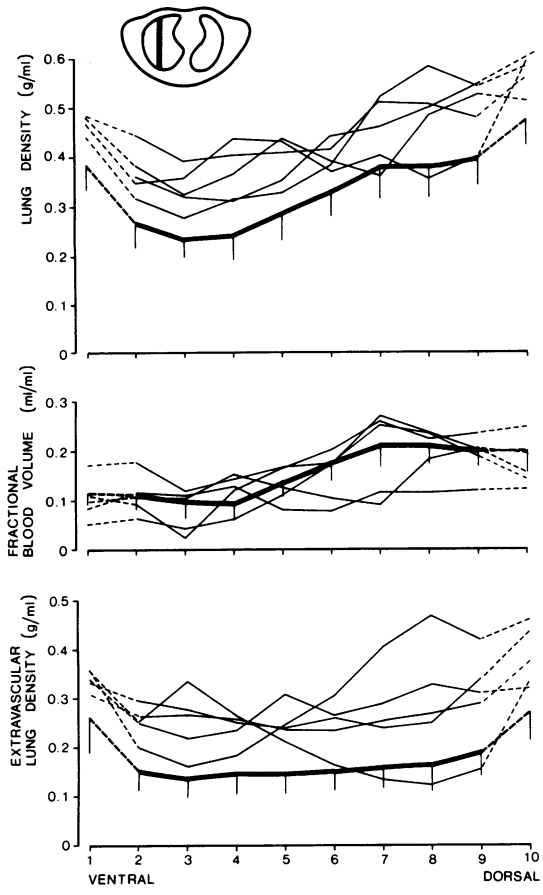

Fig 5 *Regional lung density, fractional blood volume, and extravascular lung density in a ventrodorsal strip through the right lung (inset) in the patients in group 1. Thin lines represent individual patients. The thick line represents the mean of 19 normal subjects and vertical bars one standard deviation. Segments 1 and 10 are influenced by the chest wall.*

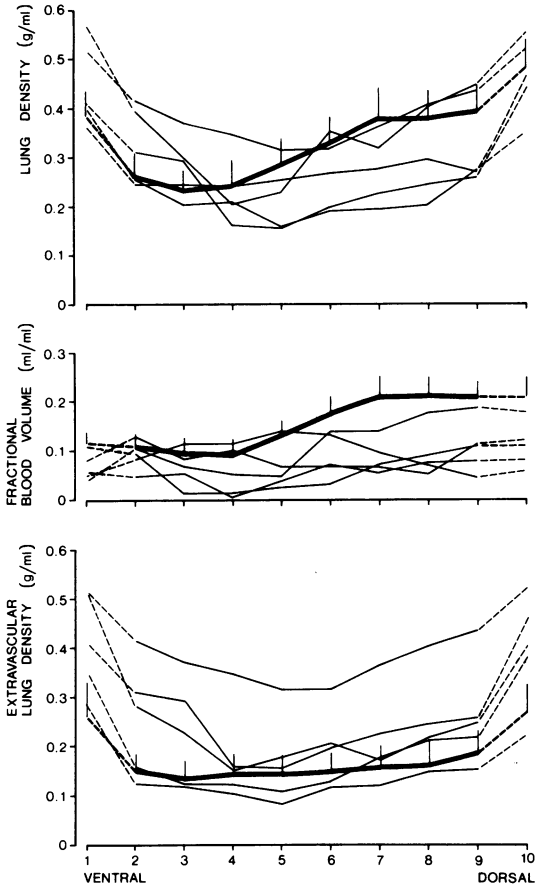

Fig 6 *Regional lung density, fractional blood volume, and extravascular lung density in a ventrodorsal strip through the right lung in the patients in group 2. Symbols as in figure 5.*

density, but no commom pattern in the abnormalities could be identified. Three patients had a normal ventrodorsal distribution of fractional blood volume, whereas in the other two blood volume was reduced in the dorsal part of the lung. In one of the latter patients (No 3), the ventrodorsal distribution of blood volume returned to normal after steroid treatment (cf fig 3*b*).

In some patients in group 2 lung density was lower than normal in the central part of the lung (fig 6). Fractional blood volume was reduced at all levels in most patients, and the ventrodorsal gradient was absent. There was a tendency for extravascular lung density to be lower in the central part of the lung than in the outer parts. (Note that the periphery of the lung is omitted from the analysis because of influence from the chest wall.)

The analysis of craniocaudal differences in lung density, fractional blood volume, and extravascular lung density also showed large regional variations, but there was no common pattern of abnormalities in any of the groups.

Discussion

The many structural abnormalities occurring in interstitial lung disease include thickening of alveolar walls, interstitial inflammation with accumulation of inflammatory cells, formation of granulomas in sarcoidosis, and eventually interstitial fibrosis.[2] Of the many different techniques for evaluating interstitial lung disease, only lung biopsy provides a complete picture of the interstitial reaction. In this study

a technique[1] based on positron tomography was used to obtain measurements of extravascular lung density. This comprises lung tissue as well as interstitial water and accumulated inflammatory cells, and thus reflects all types of interstitial abnormalities in the lung. Differentiation between different causes of increased extravascular density would require specific cellular or interstitial markers.

The tomographic measurements were made during tidal breathing in the supine posture. The acquisition time for the tomograms is five to 10 minutes, and each measurement represents a large number of breathing and cardiac cycles. The partial volume effect introduces difficulties in the measurement of extravascular lung density and fractional blood volume in the peripheral part of the lung. When either density or blood volume is averaged over the entire lung field, the whole transverse section of the lung is included in the measurement and allowance for the partial volume effect is made by comparison with normal subjects.[6] In the regional assessment it is necessary to omit a section of the lung underlying the chest wall from the analysis.

Lung density, fractional blood volume, and extravascular lung density are all affected by the degree of expansion of the lung, and the possibility that our results may in part be explained by a reduction in lung volume must be considered. A moderate reduction in lung inflation can be expected to be associated with increased fractional blood volume and extravascular lung density. The ratio between extravascular lung density and fractional blood volume, however, would be less affected. In group 1, the patients with mild to moderate functional impairment, the reduction in lung volumes was small. Fractional blood volume was normal while extravascular lung density was increased. Modest reductions in lung inflation are unlikely to make major contributions to the increase in extravascular lung density. The finding of a substantial reduction in extravascular lung density in combination with small changes in lung volumes after treatment in patient 4 also indicates that extravascular lung density is not heavily dependent on lung inflation. In the patients with severe functional impairment (group 2) there was greatly reduced fractional blood volume and increased extravascular lung density. This is unlikely to result from deflation of the lung per se.

Extravascular lung density averaged over the lung fields in the caudal plane was consistently increased in both groups of patients. The values tended to be higher in group 2 than in group 1, although the difference between the two groups of patients was not significant. The reduction in extravascular lung density after steroid treatment in two patients with sarcoidosis was associated with improvement in radiological appearance and the results of pulmonary function tests. This shows the feasibility of measuring quantitatively and non-invasively the response to treatment in interstitial disease.

The regional analysis showed the distribution of interstitial abnormalities to be very non-uniform in patients in group 1. This is in keeping with previous radiological findings in patients with sarcoidosis.[7] The patients in group 2 also showed large regional variations in extravascular lung density. The lowest values were often seen in the centre of the lung field, which suggests a peripheral distribution of fibrosis (cf fig 4*b*).

Only one patient with sarcoidosis of recent onset (patient 3; figs 2 and 3) showed a substantial reduction in fractional blood volume. This seemed to be confined to the right lower lobe and was reversible after steroid treatment. The reduction of fractional blood volume in this patient may be due to obstruction of hilar vessels by the enlarged hilar lymph nodes, as disease of intraparenchymal vessels is likely to be irreversible.

All patients in group 2 had a reduced fractional blood volume, which may result from structural abnormalities of the pulmonary vasculature. It is well established that capillary blood volume can be reduced in interstitial lung disease, especially in later stages.[8-11] The magnitude of the abnormalities seen in this study suggests that larger vessels as well as capillaries are affected. This is supported by a post-mortem arteriographic study[12] showing a reduced number of branches and diffuse narrowing of distal arteries in areas with severe fibrosis.

Histological appearances correlate with reductions in vital capacity in patients with sarcoidosis[13 14] and other interstitial disease.[15] Similarly, we found a relatively weak correlation between vital capacity and extravascular lung density. The transfer factor shows significant correlations with histological indices in sarcoidosis,[13 14 16] but not in pulmonary fibrosis[17] or interstitial pneumonia.[15] Correspondingly, fractional blood volume and the ratio between extravascular lung density and fractional blood volume correlated with TLCO in patients with sarcoidosis but not in the patients with fibrotic lungs in group 2.

This study shows the feasibility of assessing non-invasively the structural abnormalities in the lung in interstitial disease and of monitoring the effects of treatment. In combination with tomographic techniques for measuring alveolar ventilation[18] or ventilation perfusion ratios,[19] the measurement of extravascular lung density could be useful for studies of the relationship between lung structure and function on a regional basis.

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