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Serial pulmonary function tests in progressive systemic sclerosis

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ABSTRACT Serial pulmonary function tests were performed on nine patients with progressive systemic sclerosis over a mean period of ten years. Abnormality was seen to develop both early and late in the course of the disease, and the earliest abnormality observed was impairment of the transfer factor. Deterioration of some aspect of pulmonary function was noted in each case, evidence of restriction or air trapping being seen with equal frequency. Two patients died, both of causes unrelated to their pulmonary involvement, and even pronounced early involvement of the lungs did not necessarily imply a bad prognosis.

There have been numerous studies describing the abnormalities of pulmonary function found in systemic sclerosis. These abnormalities characteristically consist of a reduction of the transfer factor with or without reduction in lung volumes but with some patients showing a pattern of functional impairment more typical of airflow obstruction (Miller *et al*, 1959; Adhikari *et al*, 1962; Catterall and Rowell, 1963; Hughes and Lee, 1963; Ritchie, 1964). We know, however, of only two reports of serial changes in pulmonary function in this condition. Hughes and Chapman (1966), commenting only on gas transfer, noted a gradual deterioration in all but two of ten patients followed up for up to five years. Conversely Colp *et al* (1973) reported a progressive reduction of vital capacity and transfer factor in only three of 16 patients tested over a mean duration of 4·5 years.

In an attempt to resolve this apparent contradiction we present the results of serial studies in nine patients with progressive systemic sclerosis over a mean period of ten years.

Patients and methods

Clinical data on the nine patients are shown in table 1. All were women with ages ranging from 29 to 68 years at the time of first testing. The duration of disease was derived from the time of onset of the first symptom that could be attributed to the illness. In seven patients this was Raynaud's phenomenon and in two arthralgia. All had typical skin changes and evidence of systems other than the lung being affected, and none had an overlap syndrome with features of another connective tissue disorder. Eight patients admitted to some breathlessness on exertion, and this was noted to progress to grade 2 (grading according to Medical Research Council questionnaire) over the course of the study in two patients (nos 7 and 9). In addition patient 4 became severely dyspnoeic with the onset of cardiac failure attributed to the disease affecting the heart. Two patients have died: no 1 suddenly after a haematemesis complicated by a myocardial infarction and no 4 from cardiac and renal failure developing during the last year of life. The vital capacity and transfer factor had already fallen before these complications occurred.

All the patients received steroids during their illness. There was no evidence to suggest that this treatment significantly affected the natural history of the disease so far as the lungs were concerned.

Each patient performed tests of peak flow rate, forced expiratory volume in one second, and forced vital capacity. Lung volumes were determined by helium dilution, and the transfer factor was recorded as the mean of two estimations by the single breath carbon monoxide method using a Resparameter. The methods used in the laboratory for these tests have been previously described (Hughes and Empey, 1972). Figures for predicted values on each occasion were those of Cotes (1975).

Table 1 *Clinical details of patients studied*

Case no	*Age**	*Duration (years)*	*Smoking history*	*Pulmonary symptoms*	*Pulmonary signs*	*Chest radiographic changes*	*Other systems affected*
1	55	16	No	Dyspnoea	Nil	Basal reticular shadowing	Oesophagus, small bowel
2	41	2	No	Dyspnoea, cough	Basal crepitations	Normal	Oesophagus, small bowel
3	29	10	Yes	Dyspnoea, cough	Nil	Normal	Oesophagus, joints
4	53	14	No	Dyspnoea, cough	Basal crepitations	Basal ground glass shadowing increased heart size	Oesophagus, joints, heart, kidneys
5	68	6	No	Dyspnoea	Nil	Basal reticular shadowing	Oesophagus
6	59	29	No	Dyspnoea	Nil	Basal mottling	Oesophagus, small bowel, colon
7	53	21	Yes	Dyspnoea, cough	Basal crepitations	Basal reticular shadowing	Oesophagus, heart
8	37	5	Yes	Nil	Nil	Normal lung fields, prominent pulmonary arteries	Joints, heart
9	48	28	No	Dyspnoea	Basal crepitations	Reticulonodular shadowing throughout both lung fields. Maximal at right base	Oesophagus, joints, small bowel

*Age at time of first lung function tests.

Results

The results of the first and the last of the serial pulmonary function tests in each of the nine patients, with intervening tests where either of these was incomplete, are shown in table 2.

At the initial testing three patients had normal results (nos 1, 2, and 3), two had impaired transfer factor (nos 4 and 5), and three had some restriction of lung volumes and a reduced transfer factor (nos 6, 7, and 8). One patient had a reduced residual volume to 71% of predicted as the only possible abnormality (no 9).

In each of the three patients with initially normal results the transfer factor fell to between 60 and 70% of predicted normal, and was the first abnormality to develop. In addition, in patient 1 there was a progressive fall in lung volumes, suggesting some degree of restriction. In patient 3 (fig 1) there was evidence of air trapping, reflected by a rise in residual volume (RV) and residual volume/total lung capacity (RV/TLC) ratio. In the two patients with initially impaired transfer factor alone this fell further, albeit with some fluctuation, with accompanying reduction in lung volumes in patient 4 and a rise in RV and RV/TLC ratio in patient 5.

In the case of the three patients with initial reduction in lung volumes and transfer factor the latter was below 50% of predicted normal in each case both at initial and final testing, although again showing some fluctuation in the intervening period. In patient 7 (fig 2) the reduction in lung volumes slowly progressed; in patients 6 and 8 there was a rise in RV and RV/TLC ratio. In patient 9, with an initial slight reduction of RV, there was a fall in transfer factor and lung volumes.

Evidence of restriction, therefore, was initially present in four patients and subsequently developed in a further two, but in only one patient (no 7) did the final values for vital capacity, TLC, or RV lie below 60% of predicted normal. In four patients evidence of air trapping developed, but in only one (no 8) was there an associated low FEV_1/FVC ratio. Two of these patients were cigarette smokers. By the time of the final testing the transfer factor was below the predicted normal range in every patient although only in patient 2 was it the sole abnormality present.

The variable changes in lung volume have been noted. It therefore seemed appropriate to consider changes in transfer factor per unit of lung volume, as measured by transfer coefficient (Kco) (McGrath and Thomson, 1959). Such changes in Kco are shown in the right hand columns of table 2. Kco fell with time in all patients but in two instances was within the normal range at a time when the transfer factor was considered to be abnormal. This was in patients 1 and 9, both of whom had shown definite reduction in lung volumes, and this accounts for the reduced transfer factor but normal Kco.

Discussion

Restriction of lung volumes, airways obstruction, and a mixed pattern combining features of both have previously been described in systemic sclerosis

Table 2 *Initial and final pulmonary function results*

Case no	*No of tests*	*Date*	*VC*		*TLC*		*RV*		*RV/TLC ×100*	*FEV₁/FVC ×100*	*TLCOSB*		*KCO*	
			ml	*% Predicted*	*ml*	*% Predicted*	*ml*	*% Predicted*			*mmol/min/kPa*	*% Predicted*	*mmol/min/kPa/l*	*% Predicted*
1	4	1963	2600	106	4150	110	1850	119	41	77	6·97	94	1·67	100
		1970	1880	90	3760	94	1560	99	41	83	4·50	65	1·40	86
		1972	1630	74	—	—	—	—	—	94	—	—	—	—
2	4	1970	2650	93	4140	90	1500	96	35	98	6·73	80	1·70	96
		1978	2960	112	4510	102	1610	104	36	88	5·18	64	1·15	67
3	4	1966	4325	131	6025	116	1825	114	30	75	9·14	96	1·42	76
		1973	3300	103	5900	117	2400	150	41	79	6·22	69	1·11	61
4	5	1968	2475	95	4125	94	1650	103	40	90	3·10	40	1·05	62
		1973	1750	70	2900	68	1050	64	36	83	—	—	—	—
		1976	1800	75	—	—	—	—	—	75	2·24	30	0·73	45
5	3	1968	2820	125	4200	100	1700	101	41	83	4·48	64	1·12	70
		1978	1750	83	4030	101	1950	108	52	88	2·79	42	0·73	48
6	2	1968	2000	67	4190	81	1590	78	38	79	2·41	29	0·88	54
		1978	1640	71	4120	98	2030	113	49	79	2·17	31	0·o2	39
7	7	1967	1470	60	2875	69	1075	69	38	79	3·62	48	1·22	72
		1978	1260	56	1930	48	840	52	23	67	2·93	43	1·07	66
8	10	1962	2500	83	3350	71	950	63	28	76	2·93	32	1·06	59
		1978	2080	79	4020	90	1880	114	47	69	2·83	36	0·98	58
9	8	1963	2100	86	3150	79	1000	71	32	85	6·22	82	2·18	126
		1977	1400	69	2305	66	945	65	41	86	4·66	69	1·92	119

Conversion: SI to traditional units—TLCO and KCO: mmol min^{-1} kPa^{-1} = 2·9 ml min^{-1} mmHg^{-1}.

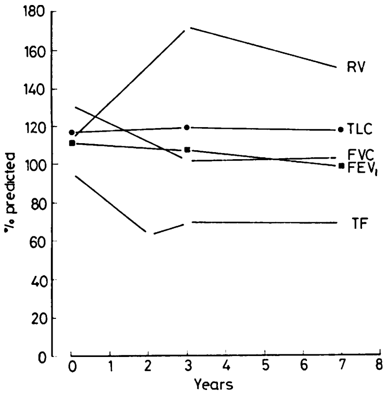

Fig 1 *Patient 3. Serial studies of pulmonary function.*

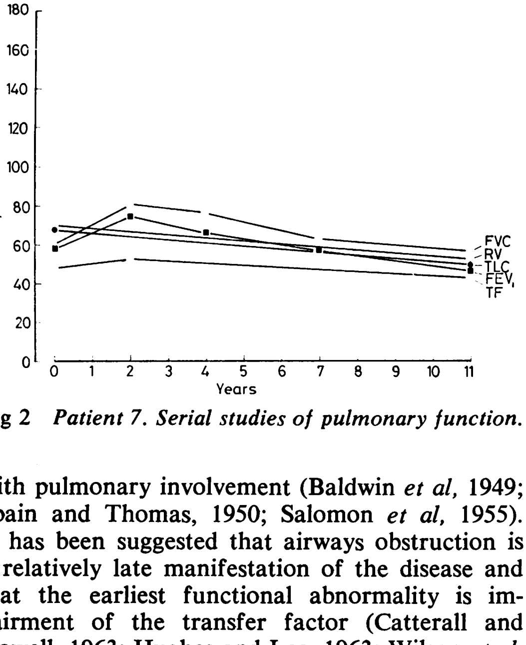

Fig 2 *Patient 7. Serial studies of pulmonary function.*

with pulmonary involvement (Baldwin *et al*, 1949; Spain and Thomas, 1950; Salomon *et al*, 1955). It has been suggested that airways obstruction is a relatively late manifestation of the disease and that the earliest functional abnormality is impairment of the transfer factor (Catterall and Rowell, 1963; Hughes and Lee, 1963; Wilson *et al*, 1964). More recently Guttadauria *et al* (1977) have challenged this view having found in 45 patients with scleroderma that a raised RV and RV/TLC ratio, which they claim reflects small airway obstruction, was seen in more patients, and was more often the sole abnormality than was impairment of the transfer factor.

In our patients impairment of the transfer factor preceded such changes in RV and RV/TLC ratio in each of the four patients in whom the latter developed, being the first abnormality observed in patients 1–5 and falling outside the predicted normal range at initial testing, together with restriction in lung volumes, in patients 6–8. There was a tendency to progressive impairment of the transfer factor in those in whom it was greater than 50% of predicted normal at first testing but to no further deterioration in those in whom it was less than 50%, although transient improvement was seen in several cases. Seasonal fluctuation in transfer factor in patients with systemic sclerosis, significantly higher values being found during the warm months of the year, has been reported (Emmanuel *et al*, 1976) but we did not find this in our patients. Changes in Kco tended to parallel those in transfer factor except in two cases in whom Kco was normal at a time when transfer factor was abnormal. In these the final reduced value of the transfer factor may have been largely due to changes in lung volume.

The functional changes in pulmonary scleroderma are probably related to the presence, in varying degree, of interstitial fibrosis producing restriction, peribronchial fibrosis producing air trapping, and obliteration of the pulmonary vascular bed increasing ventilation-perfusion inequalities (Spain and Thomas, 1950; Wilson *et al*, 1964). Each of these pathological processes may cause impairment of transfer factor, but air trapping will tend to increase RV and TLC while restriction will decrease them. In keeping with this, lung volumes in our patients were relatively well preserved by comparison with transfer factor in all but one case, and changed in a less consistant fashion. A change in the relative predominance of interstitial fibrosis may be reflected in alteration in the pattern of functional impairment from that of air trapping to restriction. During such changes the RV and TLC may return to more normal values, and this may be falsely interpreted as showing some improvement in the underlying disease process. This particularly needs bearing in mind when assessing response to treatment.

Two further factors that need consideration in assessing the changes observed are recurrent inhalation of oesophageal contents in those with oesophageal involvement and the effects of cigarette smoking. The former cannot be discounted as a possible contributory cause of some of the abnormalities in the eight patients with oesophageal involvement, although it has been shown by Mahrer *et al* (1954) that typical lung changes may occur in the absence of such involvement. As to cigarette smoking, of the four patients who developed air trapping, two admitted to the habit and two were life-long non-smokers.

The rate of progress of the disease varies from patient to patient (Siegal, 1977) and this was clearly seen here. One patient, for instance, had no abnormality of pulmonary function 16 years after onset of the first symptom, whereas another had restriction of lung volumes and a transfer factor below 50% of predicted normal after only five years. That such pronounced early involvement of the lungs need not imply a bad prognosis is shown by the latter patient (no 8) who remained free of symptoms referable to the chest and developed comparatively mild airways obstruction as the only additional abnormality over the succeeding 16 years.

In a serial study of pulmonary function reported by Colp *et al* (1973) the abnormalities in most of the patients remained unchanged and in no patients were seen to develop *de novo*. It was therefore postulated that pulmonary changes develop early in the course of the disease and thereafter remain relatively static. In contrast to these findings in our patients there was some deterioration, in at least one of the tests employed, in every case. Furthermore, three patients with normal pulmonary function developed abnormalities during the study, and in two this occurred many years after the onset of the first symptom of the disease.

In conclusion, our results support the view of earlier authors that impairment of the transfer factor is the first abnormality seen in most patients. They also suggest that air trapping, probably associated with obstruction at the level of the small airways, may appear at a relatively early stage in some. Abnormalities of pulmonary function may appear early or late in the course of the disease, and although periods of apparent improvement may occur, the overall trend is for such abnormality to progress gradually.

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