

Lung function in patients with systemic sclerosis

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Scleroderma is a chronic disease of unknown aetiology, usually classified with the collagen diseases. Raynaud's phenomenon occurs in a high proportion of cases. The most obvious manifestations are in the skin, but other organs may be involved, notably the lungs, heart, gastrointestinal tract, and kidneys. The term diffuse or progressive systemic sclerosis has been introduced to describe those cases showing visceral as well as cutaneous manifestations. The essential pathological features are swelling and disintegration of the collagen tissue accompanied by cellular infiltration and fibrosis; the process may also involve the intima of small vessels with fibrinoid necrosis and occlusion.

Lung involvement in systemic sclerosis was first described at the end of the last century (Lewin and Heller, 1894), and there have been several more recent reports (Lloyd and Tonkin, 1948; Shuford, Seaman, and Goldman, 1953; Opie, 1955). The symptoms are usually breathlessness on exertion and cough producing scanty mucoid sputum. Examination may reveal clubbing of the fingers, basal crepitations, and often poor chest expansion, though some patients have no abnormal physical signs. The typical radiological appearance, first described by Murphy, Krainin, and Gerson (1941), is that of diffuse reticular shadowing, usually most pronounced at the bases. Some cases show a cystic appearance, and systemic sclerosis has been included among the causes of 'honeycomb lung' (Spain and Thomas, 1950; Hayman and Hunt, 1952). At necropsy the lungs show diffuse fibrosis involving the alveolar walls with obliteration of capillaries and alveolar spaces. Fibrosis can also involve the bronchial walls and peribronchial tissue. This may even lead to bronchiectatic areas, corresponding to the radiographic cystic appearance. Obliteration of the pulmonary vascular bed may result in pulmonary hypertension. Intercurrent chest infections may complicate the picture, especially in the presence of marked oesophageal involvement resulting in a 'spill-over', whilst involvement of the skin and possibly muscle of the chest wall may restrict movement.

These pathological processes impair lung function in various ways. Deranged lung function in cases of systemic sclerosis has been recognized for some years with an alveolar-capillary block in many instances (Baldwin, Cournand, and Richards, 1949; Austrian, McClement, Renzetti, Donald, Riley, and Cournand, 1951). Very few measurements of the diffusing capacity have been reported, however. This paper presents the findings in 10 patients studied in this laboratory in whom the diffusing capacity was measured by the single breath technique of Ogilvie, Forster, Blakemore, and Morton (1957). Two additional patients studied by Dr. Colin Ogilvie in his unit have been included for comparison.

MATERIAL AND METHODS

Ten patients with systemic sclerosis were studied. The clinical features of their illness are shown in Table I. In several instances Raynaud's phenomenon was the first symptom, often preceding systemic involvement by many years. Pulmonary symptoms were not prominent, and most patients had no abnormal signs in the chest, although chest radiographs were abnormal in six. Two patients (1 and 6) had had previous episodes of chest infection.

Lung function tests were carried out using the following techniques.

Total lung volume and its sub-divisions were measured by the closed-circuit helium dilution method (Bates and Christie, 1950). The trace from this test also measured the minute volume.

Forced vital capacity and F.E.V.% measurements were made with a low resistance Bernstein spirometer (Bernstein, D'Silva, and Mendel, 1952). This instrument was also used for the maximum voluntary ventilation (M.V.V.) test. Wherever possible, this was carried out by asking the patients to breathe as deeply as possible at a rate of 60 breaths per minute over a 15-second test period (M.V.V. 60). Some were unable to achieve this rate and their best efforts are recorded, the figure being marked with an asterisk in Table II.

Diffusing capacity was measured by the single breath, carbon monoxide method of Ogilvie *et al.* (1957). Arterial PCO₂ was measured by the rebreathing method of Campbell and Howell (1960).

TABLE I

CLINICAL DATA

Patient	Sex and Age	Duration of Symptoms (yr.)	Pulmonary Symptoms	Pulmonary Signs	Chest Radiograph	Other Systems Affected
1	F 48	17	15 yr. winter cough with mucoid sputum and Grade 2 dyspnoea on exertion	Poor expansion, bilateral coarse basal crepitations	Increased bilateral basal bronchovascular markings	Joints, oesophagus, and heart (incomplete rt. bundle branch block)
2	F 67	?5	Grade 2 dyspnoea on exertion	Bilateral coarse basal crepitations	Large heart, prominent pulmonary artery and congestive changes	Oesophagus and heart
3	M 71	1½	Dry cough	Nil	Normal	Oesophagus
4	M 55	1½	Grade 2 dyspnoea and retrosternal pain on exertion	Poor chest expansion	Bilateral linear basal atelectasis	Oesophagus and joints
5	F 32	5	Grade 1 dyspnoea on exertion	Nil	Normal	Joints
6	F 61	40	5 yr. rt. sided pneumonia, Grade 1 dyspnoea on exertion, dry cough	Nil	Slight increase in broncho-vascular markings at right base	Oesophagus and joints
7	F 30	4	None	Poor chest expansion	Normal	Oesophagus, joints, and jejunum
8	F 42	16	None	Nil	Normal	Joints
9	F 45	20	Grade 1 dyspnoea on exertion	Nil	Interstitial fibrosis	Joints
10	F 60	8	Grade 1 dyspnoea on exertion	Nil	Normal	Joints and oesophagus
11 ¹	F 42	11	None	Nil	Pleural thickening at both bases with fibrotic shadowing in post-basal segment of left lower lobe	Joints and oesophagus
12 ¹	F 45	5	Grade 1 dyspnoea on exertion	Nil	Normal	Oesophagus

¹ Cases from Dr. Ogilvie's unit

TABLE II

LUNG FUNCTION

Patient	B.S.A. (sq. m.)	Ventilatory Capacity		Residual Volume (ml.)	Total Lung Capacity		R.V./T.L.C. Ratio (%)	F.E.V. ₁ as % of V.C.	M.V.V. ₆₀ (l./min.)	% of Predicted Value	Diffusing Capacity		Minute Volume (l./min.)
		ml.	% of Predicted Value		ml.	% of Predicted Value					ml./mm. Hg/min.	% of Predicted Value	
1	1.60	1,900	73	1,100	3,000	72	37	86	72	80	15	65	8.4
2	1.65	1,350	63	1,050	2,400	55	44	89	54	83	4	17	7.2
3	1.71	3,350	100	2,200	5,500	89	40	73	90 ¹	104	14	54	8.3
4	1.76	2,800	80	1,730	4,530	75	38	78	96	91	14	53	8.0
5	1.60	2,400	93	950	3,350	79	28	76	72	83	8	34	6.0
6	1.59	2,200	89	2,500	4,700	105	53	65	50 ¹	72	14	60	9.9
7	1.48	2,200	71	1,450	3,650	78	40	93	55 ¹	60	17	81	7.2
8	1.64	2,600	88	1,400	4,000	88	35	78	76	92	17.6	73	10.0
9	1.50	1,800	65	1,300	3,100	71	42	89	56	68	14.4	65	8.2
10	1.72	2,200	85	1,000	3,200	76	31	78	100	96	12	43	8.3
11 ²	1.67	2,280	77	2,370	4,650	104	51	90	72	85	19	77	—
12 ²	1.58	2,130	80	990	3,100	71	31	83	70	86	18	80	—
Mean	1.63	2,500	89	1,600	4,100	87	39	86	73	83	14	58	8.2

¹ Best recorded efforts (see text). ² Cases from Dr. Ogilvie's unit

The prediction formulae of Needham, Rogan, and McDonald (1954) were used to calculate the expected values for vital capacity, total lung capacity, and maximum voluntary ventilation. They were used in preference to those of Baldwin *et al.* (1948) because they were derived from a larger number of controls in the sitting position, and a helium dilution method was used for measuring the residual volume, though the M.V.V. was measured by a Douglas bag and valve method. The predicted values for vital capacity and M.V.V., using Needham's formulae, in the present series did not differ greatly from values derived from Baldwin's formulae, but the total lung capacities were constantly higher. The formula described by Ogilvie *et al.* (1957) was used to predict the diffusing capacity.

ILLUSTRATIVE CASE HISTORY

Patient 4, M. S., a 54-year-old man, was admitted to hospital in 1961. In 1935 he had been treated at home for 'pericarditis', and in 1945 he received sulphonamide treatment in hospital for a left-sided pneumonia associated with bilateral pleuritic pain, which persisted for a year subsequently. Since 1955 he had complained of 'tightness in the chest with a feeling of restriction on trying to breathe deeply'. This became worse in 1960, with a recurrence of the pleuritic pain and the development of Raynaud's phenomenon. In the few months preceding admission he developed some difficulty in swallowing and lost a stone in weight. He suffered, too, from recurrent sweating attacks and

TABLE III
SERIAL CHANGES IN LUNG FUNCTION

Patient	Date	Time from Start of Treatment (mth.)	Vital Capacity (ml.)	Residual Volume (ml.)	Total Lung Capacity (ml.)	R.V./T.L.C. Ratio	F.E.V. ₁ as % of V.C.	M.V.V. (l./min.)	Diffusing Capacity (ml./mm. Hg/min.)
4	19.4.61	—	1,900	2,800	4,700	59	82	104	18
	31.7.61	3	1,450	2,550	4,000	64	88	80	14
	4.6.62	13	2,800	1,730	4,530	38	78	96	14
7	20.6.62	—	2,200	1,450	3,650	40	93	55	17
	26.10.62	4	2,200	1,700	3,900	43	95	66	16
10	18.6.57	—	2,600	1,220	3,820	32	—	104	9.6
	13.8.57	2	—	—	—	—	—	—	13
	26.9.62	60	2,200	1,000	3,200	31	78	100	12

became increasingly breathless on exertion and easily fatigued. In addition his elbows had become progressively stiffer over the last three years.

Examination revealed a thin man with sclerodermatous changes of the skin covering the fingers and face, especially round the mouth. Chest expansion was very poor, and the skin was tightly drawn over the chest wall, though not tethered firmly. There were no added sounds in the chest. Movement at the wrist and elbow joints was somewhat limited.

INVESTIGATIONS Hb 68 g./100 ml.; leucocytes 6,700/c.mm. with a normal differential count; sedimentation rate 80 mm. in the first hour (Westergren); total serum proteins 7.5 g./100 ml. (albumin 3.2 g. and globulin 4.3 g., with marked increase in gamma-globulin); blood urea 26 mg./100 ml.; urine normal. An E.C.G. was recorded twice and was similar on both occasions, giving a low-voltage trace: the maximum height of the R wave was 4 mm. in standard lead 2 and 5 mm. in CR 4. No P or T waves exceeded 1 mm. There was no conduction defect and left axis deviation was present without any ventricular preponderance. These changes could be non-specific but would also be compatible with involvement of the heart by a diffuse disease process. Chest radiographs showed linear atelectasis at both bases and a barium swallow revealed dilatation of the oesophagus with delay at the cardia and absent peristalsis. Lung function tests are reported in Table III.

SUBSEQUENT PROGRESS Treatment with steroids, prednisolone, 10 mg. t.d.s., was started in April 1961. This initially produced a good response with a feeling of well-being, increased mobility of the joints and skin, and increased effort tolerance. The patient relapsed, however, when the prednisolone was reduced to 5 mg. a day; he was readmitted and showed a further good response to prednisolone, 5 mg. t.d.s. This dose was later reduced to 5 mg. b.d. when he attended as an out-patient, and he was feeling well and breathing more easily without a feeling of tightness and restriction in the chest wall when his lung function was last tested in June 1962.

RESULTS

From Table II it will be seen that the most constant finding in this series was a reduction of the diffusing capacity. Using their prediction formula, Ogilvie *et al.* (1957) showed that normal subjects had diffusing capacities in the range of 75 to 125% of the predicted value or at the outside 70 to 130%. Nine out of 10 cases tested here had a diffusing capacity of less than 75% of the predicted value, whilst two had very low absolute values (below 10 ml./mm. Hg/min.). This was associated with a minute volume of over 8 litres in seven instances. This hyperventilation was less marked when corrected for body surface area and was not sufficient to reduce the arterial PCO₂, which was within the range of 37 to 45 mm. in the seven patients in whom it was measured. The oxygen saturation of the arterial blood, breathing room air at rest, was 92% in patient 3 and 95% in patient 5.

Ventilatory capacity was good with a reduced F.E.V.₁ in only one instance (patient 6). This woman was the only patient in our series with an R.V./T.L.C. ratio of much over 50% and her total lung capacity was over 100% of the predicted figure, suggesting some degree of emphysema. The maximum voluntary ventilation was also well preserved, being less than 80% of the predicted value in two cases only.

A restrictive pattern with vital capacity and total lung capacity less than 75% of predicted values was shown by three patients (1, 2, and 9) whilst patient 4 had a marked reduction of these volumes before steroid treatment (Table III). These cases were all associated with a diffusion block, however, and only in patients 7 and 12 was there a purely restrictive pattern with a normal diffusion.

All the London Hospital patients received steroid therapy, and in three it was possible

to perform serial studies at intervals of between two months and five years. These results are shown in Table III. In patient 7 there was no change over a four-month period except for an improvement in the M.V.V. Patient 4 showed a striking relief of the restrictive defect over a 10-month period with the vital capacity being virtually doubled. In patient 10 there has been a further restriction over a five-year period. The diffusing capacity initially improved slightly after two months' treatment but has remained constant since, as it has in the other two patients.

Two other cases deserve comment. The patient with the lowest diffusing capacity (patient 2) had cardiac involvement and also pulmonary hypertension, presumably with some degree of occlusion of the pulmonary vascular bed. Patient 7 was a young woman with recent onset of systemic sclerosis and marked scleroderma of the skin over the chest wall. The vital capacity was reduced and there was a reduced M.V.V., whilst the diffusing capacity was within the predicted normal range. Here the disease process was presumably affecting the chest wall rather than the alveolar-capillary membrane.

DISCUSSION

It has been recognized for a number of years that pulmonary scleroderma can cause severe disturbances of lung function. Though an alveolar-capillary block has been described (Baldwin *et al.*, 1949; Austrian *et al.*, 1951), few reports have appeared in which the diffusing capacity has been measured. West, McClement, Carroll, Bliss, Kuschner, Richards, and Courmand (1951) reported a patient whose diffusing capacity for oxygen was 3 ml./mm. Hg/min., whilst a patient described by Marks, Cugell, Cadigan, and Gaensler (1957) had a diffusing capacity of only 2.5 by the steady state carbon monoxide method. Conner and Bashour (1961) measured the diffusing capacity by the single breath CO technique in two cases, obtaining values of 11 and 17 ml./mm. Hg/min., but there has been no other reported series using this technique until that of Catterall and Rowell (this journal, p. 10).

The largest reported series of cases of systemic sclerosis with lung function tests is from the Mayo Clinic (Miller, Fowler, and Helmholz, 1959). This consisted of 22 cases, 14 with pulmonary fibrosis of varying degrees shown radiologically. In all cases the vital capacity and total lung capacity were reduced with a normal R.V./T.L.C. ratio, whilst the F.E.V.% and M.V.V. were well preserved. Though in the group with obvious generalized interstitial fibrosis the changes were

severe (V.C. of less than 63% predicted value and T.L.C. less than 58%), in those with less extensive fibrosis the vital capacity was about 70% and total lung capacity 68 to 93% of the predicted values. This functional picture with reduced volumes but well maintained ventilatory capacity is well recognized in association with the alveolar-capillary block syndrome (*e.g.*, West *et al.*, 1951; Bader and Bader, 1958). Diffusion was not measured.

A different functional pattern was described by Salomon, Appel, Dougherty, Herschfus, and Segal (1955). They described three patients, all of whom had an increased total lung capacity and residual volume whilst two had severe reduction of the vital capacity with increased R.V./T.L.C. ratios. There was also reduction in the M.V.V. in two patients. These changes were more akin to those of emphysema, though the arterial oxygen studies did suggest a possible diffusion block as well, and indeed this pattern was described in the patients with a normal or emphysematous radiograph in the Mayo Clinic series.

Thus two patterns of impaired function in pulmonary scleroderma have been described, one a restrictive pattern with good ventilatory capacity but a diffusion block, and the other with over-inflation of the lungs and impaired ventilation with or without diffusion block. Spain and Thomas (1950) described a case with a 'mixed' pattern, combining features of both, and pointed out how the functional changes in scleroderma could be classified in two ways according to how the process was affecting the lung. On the one hand, a pure interstitial fibrosis will produce the classical alveolar-capillary block syndrome whereas involvement of the skin of the chest wall and possibly the diaphragm would impair ventilation. In addition, in some instances a peribronchial fibrosis could mimic emphysema and give rise to bronchiolar cystic changes. These two factors might produce a ventilatory impairment.

In the present series a diffusion defect was the most common disturbance of function and was present alone in four patients (3, 5, 8, and 10) without abnormal physical signs or radiographic changes. All had rather mild symptoms and normal lung volumes and ventilation. Four patients (1, 2, 4, and 9) also had a restrictive defect. They were more incapacitated and had abnormalities on clinical and radiological examination. The changes here were not as marked as in the Mayo Clinic series, but there was less radiological evidence of fibrosis in our series. It is suggested that involvement of the alveolar-

capillary membrane by fibrosis in systemic sclerosis can occur early in the disease process in some cases. This may be sufficient to cause a diffusion block without prominent abnormalities on clinical and radiological examination. In such cases the demonstration of an impaired diffusing capacity may be sufficient to indicate systemic scleroderma.

In this connexion it is interesting that in some instances pulmonary manifestations of systemic sclerosis have preceded the cutaneous ones (Opie, 1955; Hayman and Hunt, 1952; Shuford *et al.*, 1953). Such cases are analogous to the occasional examples of chronic diffuse interstitial fibrosis preceding rheumatoid arthritis (Bloom and Rubin, 1950; Katz and Auerbach, 1951; Lee and Brain, 1962), and both these collagen diseases should be remembered when investigating chronic diffuse interstitial fibrosis.

Impaired diffusion is not entirely specific in this condition, however, as other patterns of function upset have been described, notably that of emphysema. One of our patients showed this, whilst one of Ogilvie's (patient 11) had an increased residual volume, total lung capacity, and R.V./T.L.C. ratio, and neither had a diffusion block.

The effect of steroid treatment is disappointing as far as lung function is concerned. No improvement was shown in the three patients reported by Salomon *et al.* (1955) or in the patient reported by West *et al.* (1951). In the patients on whom serial lung function tests were performed, the diffusing capacity was not significantly improved by steroids, though the vital capacity was almost doubled in one instance. This may be because steroids improve the cutaneous manifestations by loosening the skin from underlying structures but cannot alter established interstitial fibrosis, whereas once some of the pulmonary arterioles are occluded, recanalization may not be possible.

SUMMARY

Lung function studies made in 12 patients with systemic sclerosis are presented. A combined diffusion block and restrictive defect occurred in four patients, diffusion block alone in four, and restrictive defect alone in two. One patient showed the changes of emphysema, whilst another had the volume changes of emphysema but normal ventilation. Treatment with steroids did not improve the diffusing capacity in the three patients serially tested. In one, the restrictive defect was relieved with a doubling of the vital capacity, but in the other two the lung volumes were unchanged. It is suggested that systemic sclerosis produces a diffusion block by interstitial fibrosis and possibly

pulmonary vascular occlusion. A restrictive defect is produced by involvement of the skin of the chest wall, and the development of emphysema follows peribronchial fibrosis. In the patients studied in this laboratory a diffusion defect was a constant finding and could have diagnostic value in establishing the systemic nature of the disease.

We should like to thank Dr. Colin Ogilvie for permission to include patients 11 and 12 and for helpful criticisms; also Dr. B. H. Bass for the initial studies on patient 4. We are most grateful to Dr. Kenneth Perry for his encouragement and advice and to the physicians of The London Hospital for permission to study their patients. Mrs. Margaret Burnard gave valuable technical assistance.

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ADDENDUM

Since the preparation of this paper we have studied a further patient with systemic sclerosis who also showed a diffusion block, and re-testing of patient 3 nine months after starting steroid therapy showed no change in his lung function. A recent publication (Adhikari, Bianchi, Boushy, Sakamoto, and Lewis, 1962) has reported findings similar to ours. These authors found impaired diffusion in 12 out of 13 cases of systemic sclerosis studied with a mean reduction of the diffusing capacity to 63% of that obtained in comparable controls. These findings are all in accord with those reported here.