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Improvement of Lung Function in a Scleroderma Patient Treated for 12 Months with Cyclofenil

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ABSTRACT

A 48 year old male scleroderma patient with typical impairment of respiratory function, including low vital capacity, low static lung compliance and low diffusing capacity for carbon monoxide, was treated with cyclofenil for one year. Assessment of lung function after 3, 6 and 12 months treatment showed marked improvement of vital capacity, increased physical working capacity, less hypoxia at maximum work, increase of static lung compliance and decrease of maximal transpulmonary pressure. Closing capacity decreased, and an increase in diffusing capacity for carbon monoxide was seen.

INTRODUCTION

Scleroderma (progressive systemic sclerosis, PSS) is a complex disorder of connective tissue which may affect any organ or organ system. The annual incidence in USA has been estimated to be 4.5 per million population and women are affected about 3 times as often as men (10). Pulmonary involvement is a frequent manifestation. Piper and Helwig (14) found 1955 lung fibrosis at autopsy in 90 % of cases. The morphological changes in the lung may involve the whole bronchial system as well as the alveoli, alveolar walls and interstitium. Early pathological changes in the respiratory units are local widening, oedema and capillary congestion in and increased cellularity of the alveolar walls. Later, the classical picture includes widespread interstitial fibrosis of the alveolar walls with obliteration of alveoli and alveolar capillaries. There is also bronchiolitis with peribronchial fibrosis, bronchiolectasis and cystic formation as well as varying degrees of vasculitis (1, 2, 4, 6, 9, 13, 15, 17, 18). The main respiratory symtom is dyspnoea, initially on exertion, later at rest. The most common physical finding in the lungs is fine rales over the bases, while chest radiograph may be normal or show varying degrees of pulmonary fibrosis. There is a poor correlation between respiratory function and radiological findings (1). In most cases, respiratory symtoms are preceeded by articular or cutaneous manifestations of the disease, but occasionally they may herald its onset.

CLINICAL DATA

The patient, a 48 year old male non-smoker, had worked as a glazier for many years and thus had had some silica exposure. His previous history included peptic ulcer, and hypothyroidism controlled by substitution therapy. In 1964 he developed disturbing muscle cramps when running and the following year his hands and feet became stiff and swollen. Raynauds phenomenon developed, followed by necrosis and gangrene of two finger tips on the left hand in 1969. Later, he was affected by severe dyspnoea and muscle atrophy. In 1968, he complained of eye irritation, impaired vision, dryness of the mouth and polydipsia, and he was noted to have generalized hair loss, a subnormal temperature, and hepatic and splenic enlargement. Skin biopsy showed evidence of PSS, and LE cells and increased amounts of gammglobulin were seen, while a liver biopsy showed increase in fibrous tissue resembling cirrhosis. The chest radiograph showed marked bilateral interstitial infiltrates. Despite treatment with cortisone, vasoactive drugs and D-penicillamin his condition deteriorated over the subsequent 7 years, with anorexia, weight loss from 84 to 57 kg and the development of marked sun sensitivity and generalized skin pigmentation.

The patient was admitted to this hospital in October 1975. He was very thin, with generalized muscle atrophy, extensive pigment deposition on hands, fingers, neck and chest, and acrocyanosis of ears and fingers. Marked skin stiffness was found around the eyes, on the face and the extremities, especially over the hands. There were telangiectases, mostly on the abdomen. He had severe dyspnoea at rest, chest movement was severely limited and marked crepitations were heard, predominantly over the bases of the lungs.

After clinical investigation, including lung function tests, treatment with cyclofenil (Sexovid ®) was started in a dosage of 200 mg t.i.d. Cyclofenil is a diphenyl ethylene derivative related to stilboestrol, with very low oestrogenicity but with marked effects on connective tissue metabolism (7). After 3 months treatment the skin tissue felt softer with a better circulation and a more normal colour, and after 6 months the gangrenous changes of the left fingers had disappeared. Total muscle mass and strength had increased considerably, chest movement was normal and he had no dyspnoea at rest. Appetite, food intake and swallowing improved and body weight increased from 56 to 64 kg by 12 months, when the liver and spleen were no longer palpable.

INVESTIGATION OF LUNG FUNCTION

Static lung volumes and airway resistance were measured by means of a constant-volume whole-body plethysmograph. Dynamic lung volumes, timed flows and flow-volume curves were determined with a low-resistance waterless spirometer and registered with a fast X-Y recorder with a time marker at 0.5, 1.0 and 3.0 seconds. Static lung compliance and maximal transpulmonary pressure at total

lung capacity was determined with the oesophageal balloon technique (11). Closing volume curves were obtained using the N_2 method (5) taking care that the inspiratory and expiratory vital capacity did not differ more than 5 per cent. The diffusing capacity for carbon monoxide was determined by a single breath technique (12). These two methods were not available in the pre-treatment investigation. Gas exchange was determined in the supine and in the sitting position at rest, and during graded exercise using an electrically braked bicycle ergometer (16). Arterial blood was collected through a short polyvinyl cannula in the brachial artery, while expired air was collected in a Douglas bag. Right-to-left intrapulmonary blood shunting was determined by breathing pure oxygen during supine rest for at least 10 minutes and monitoring the nitrogen washout continuously. The steady state diffusion test for carbon monoxide was performed during exercise at a heart rate of about 120 beats per minute. Maximal physical performance was determined on the bicycle ergometer in the sitting position, recording standard ECG, heart rate, breathing frequency and blood pressure at rest and during and after the exercise periods. After the exercise the patient was asked to assess the subjective degree of work intensity, leg tiredness, breathlessness and chest pain on an arbitrary scale (3).

RESULTS

Before cyclofenil treatment, lung function showed markedly restrictive changes, with low vital capacity (VC) and total lung capacity (TLC), and a high thoracic gas volume (TGV)/TLC ratio, in spite of normal or supranormal air flows and specific airway conductance (SG_{aw}) (tables 1-4). Diffusing capacity for carbon monoxide (TCO_{ss}), closing volume (CV) and static lung compliance were very low, while maximal transpulmonary pressure at TLC was high (table 5). The slope of the alveolar plateau was increased, showing impaired distribution of ventilation. At rest, ventilation and arterial blood gases were normal (table 6), while the arterial oxygen tension ($aB\text{-}pO_2$) breathing pure oxygen was low, indicating an increased right-to-left intrapulmonary shunt. On exercise (25 watts) there was marked arterial hypoxaemia with a high alveolar-arterial oxygen pressure difference ($P(A\text{-}a)O_2$) and carbon dioxide retention, (table 6). TCO_{ss} was very low and dead space ventilation high. Working capacity was only 25 watts, and the limiting symptom was dyspnoea.

After 6 and 12 months treatment with cyclofenil there was a marked improvement in VC, the result of a decrease in residual volume (RV) in the presence of an unchanged TLC (table 1). There was an improvement of TGV/TLC ratio. Static lung compliance increased and maximal transpulmonary pressure at TLC fell (table 4), SG_{aw} being unchanged. There was an increase in peak expiratory flow (PEF) and a decrease in maximal mid-expiratory flow (MMF) (table 3), reflecting changes in VC, muscular strength and compliance. CV increased, the reduction in

CC simultaneously recorded being due to the fall in RV. More even regional ventilation was reflected by a decrease in the slope of the alveolar plateau. The single breath carbon monoxide test showed no definite change during treatment, but no measurements were made before the administration of cyclofenil. At rest, ventilation in relation to oxygen uptake increased as did the dead space-tidal volume ratio and there was also some decrease in arterial carbon dioxide pressure. $P(A-a)O_2$ increased. However, when breathing pure oxygen $aB-pO_2$ was 81 kPa compared to 67 kPa before treatment, a reduction in right-to-left shunt from 11 to 5 per cent. Working capacity was not increased to 50 watts although ventilation and $aB-pO_2$ during exercise was essentially unchanged after treatment. The tendency to carbon dioxide retention noted before treatment was diminished, while a marked increase in TCO_{ss} was seen.

DISCUSSION

This patient with PSS showed the typical respiratory function impairment described by other investigators; restrictive lung changes with low VC, low static lung compliance and low TCO_{ss} (1, 2, 8). The patient had arterial hypoxaemia during exercise but in contrast to earlier findings, he also had a tendency to carbon dioxide retention (2). Measurements of expiratory flow were normal, indicating that obstruction of larger airways was not present. Despite the failure of earlier forms of therapy to modify the patient's diasese, treatment with cyclofenil over a period of 12 months produced significant improvement in his respiratory function with increases in VC, static lung compliance and TCO_{ss}, and reductions in RV and right-to-left shunt. More even distribution of ventilation was also seen. Clinically, the patient's general condition improved considerably and dyspnoea disappeared, his working capacity increased and he was able to start part time work.

Table 1. Lung volume.

	VC		TGV		RV		TLC		TGV/TLC		RV/TLC	
	L	% P	L	% P	L	% P	L	% P	%	% P	%	% P
0	2.1	40	3.0	66	1.9	79	4.0	52	75	54	48	31
II	2.3	44	2.3	52	1.5	64	3.8	50	60	54	39	31
III	2.7	52	2.4	54	1.2	52	3.9	51	61	54	31	31

In all tables: 0 = control before cyclofenil administration, II = control after 6 months' treatment, III = control after 12 months' treatment.

VC = vital capacity, TGV = thoracic gas volume, RV = residual volume, TLC = total lung capacity, P = predicted value. All volumes in litres BTPS.

Table 2. Dynamic spirometry.

	FEV_1		FEV_1/VC		MMF		FET	MVV_{40}		PEF	
	L	% P	%	% P	L/s	% P	s	L/min	% P	L/min	P range
0	1.9	50	89	74	5.9	162	2.2	78	60	525	450-585
II	2.1	54	86	74	5.3	145	3.0	76	58	555	450-585
III	2.1	54	86	74	4.3	110	4.0	80	62	555	450-585

FEV_1 = forced expiratory volume in one second, MMF = maximal midexpiratory flow rate, FEV = forced expiratory time, MVV_{40} = maximal voluntary ventilation of 40 breathing cycles per minute, PEF = peak expiratory flow rate measured with Wright's Peak Flow Meter.

Table 3. Flow-volume.

	$\dot{V}_{max}$		$\dot{V}_{75}$		$\dot{V}_{50}$		$\dot{V}_{25}$		PIF
	L/s	% P	L/s	% P	L/s	% P	L/s	% P	L/s
0	9.3	102	9.3	115	6.5	118	2.0	82	3.2
II	9.3	101	9.3	115	6.3	115	2.9	117	4.9
III	10.1	111	10.0	124	6.2	113	2.2	90	5.0

$\dot{V}_{max}$ = maximal expiratory flow rate, $\dot{V}_{75}$ = maximal expiratory flow rate at 75 % vital capacity, $\dot{V}_{50}$ = maximal expiratory flow rate at 50 % vital capacity, $\dot{V}_{25}$ = maximal expiratory flow rate at 25 % vital capacity, PIF = maximal inspiratory flow rate.

Table 4. Lung mechanics.

	SG_{aw}	$P_{I\ el\ max}$	CR_{max}	C_{st}	SC_{st}
	$cm\ H_2O^{-1} \cdot s^{-1}$	$cm\ H_2O$	$cm\ H_2O \cdot L^{-1}$	$L \cdot cm\ H_2O^{-1}$	$cm\ H_2O^{-1}$
0	0.41	48	12.1	0.07	1.7
II	0.58	40	10.7	0.08	2.0
III	0.40	40	10.6	0.11	2.8
Predicted range	0.12	20-40	2.5-8.6	0.35-0.50	4.5-7

SG_{aw} = specific airway conductance (G_{aw}/TLC), $P_{I\ el\ max}$ = maximal transpulmonary pressure at total lung capacity, CR_{max} = coefficient of retraction (elastance), ($P_{I\ el\ max}$/TLC), C_{st} = static compliance measured between 50-80 % of TLC, SC_{st} = specific static compliance (C_{st}/TLC).

Table 5. Closing volume and diffusion capacity.

	CV		CC		N_2/L		TCO_{SB}	
	%	% P	%	% P	%	% P	ml · min^{-1} · mm Hg^{-1}	% P
0								
I	11	64	57	148	2.5	211	8.28	34
II	18	99	51	132	2.8	239	6.76	28
III	22	126	48	125	2.2	182	8.19	34

I = control after 3 month's treatment, CV = closing volume (phase IV/VC x 100), CC = closing capacity [(phase IV + RV/TLC) x 100], N_2L = slope of alveolar plateau measured between TLC-1 liter and the beginning of phase IV, TCO_{SB} = single breath diffusion capacity for carbon monoxide.

Table 6. Gas exchange during exercise.

	Rest			Work 25 Watts			Work 50 Watts		
	0	II	III	0	II	III	0	II	III
HR	79	85	75	114	105	109		119	123
BF	22	18	25	32	24	33		34	36
$\dot{V}_{O_2}$	229	264	281	674	595	372		847	1008
V_D/V_T	36	58	54	40	52	47		50	51
R	0.76	0.91	0.82	0.92	0.99	0.85		1.07	0.88
$aB\text{-}pO_2$	11.9	11.9	12.8	8.0	8.1	8.4		7.1	8.1
$aB\text{-}pCO_2$	5.5	5.1	4.4	6.0	5.6	4.8		5.2	4.8
$P(A\text{-}a)O_2$	1.5	2.7	2.1	5.9	6.0	6.3		8.0	6.7
TCO_{ss}				4.6	12.8	8.5			

HR = heart rate, BF = breathing frequency, $\dot{V}_{O_2}$ = oxygen uptake, V_D = dead space, V_T = tidal volume, R = respiratory quotient ($\dot{V}O_2/\dot{V}CO_2$), $aB\text{-}pO_2$ = arterial oxygen pressure, $aB\text{-}pCO_2$ = arterial carbon dioxide pressure, $P(A\text{-}a)O_2$ = alveolar-arterial oxygen pressure difference, TCO_{ss} = steady state diffusion capacity for carbon monoxide.

REFERENCES

1. Adhikari, P.K., Bianchi, F.A., Boushy, S.F., Sakamoto, A. & Lewis, B.M.: Pulmonary function in scleroderma: its relation to changes in the roentgenogram and i the skin of the thorax. Am Rev Respir Dis 86:823, 1962.
2. Ashba, J.K. & Ghanen, M.H.: The lung in systemic sclerosis. Dis Chest 47: 52-64, 1965.
3. Borg, G. & Dahlström, H.: Psykofysisk undersökning av arbete på cykelergometer. Nord Med 62: 1383-1386, 1959.(Swe.)
4. Caplan, H.: Honeycomb lungs and malignant pulmonary adenomatosis in scleroderma. Thorax 14: 89-96, 1959.
5. Godfrey, S., Bluestone, R. & Higgs, B.E.: Lungfunction and the response to exercise in systemic sclerosis. Thorax 24: 427-434, 1969.
6. Goetz, R.H. & Berne, M.B.: The pathology of progressive systemic sclerosis (Generalized scleroderma) with special reference to changes in the viscera. Clin Proc 4: 337-392, 1945.
7. Herbai, G.: Separation of growth inhibiting potency from oestrogenicity in different weak oestrogenic drugs of various chemical structure. Acta Endocrinol (Copenh) 68: 249-263, 1971.
8. Laitinen, O., Salorinne, Y. & Poppius, H.: Respiratory function in systemic lupus erythematosus, scleroderma and rheumatoid arthritis. Ann Rheum Dis 32: 531-535, 1973.
9. Maher, P.M., Evans, J.A. & Steinberg, I.: Scleroderma: Relation of pulmonary changes to esophageal disease. Ann Int Med 40: 92-110, 1954.
10. Medsgar, T. & Masi, A.: Epidemiology of systemic sclerosis (Scleroderma). Ann Int Med 74: 714-721, 1971.
11. Milic-Emili, J., Mead, J., Turner, J.M. & Glauser, E.M.: Improved technique for estimating pleura pressure from esophageal ballons. J Appl Physiol 19: 207-211, 1964.
12. Ogilvie, C.M., Forster, R.E., Blakemore, W.S. & Worton, J.W.: A standardized breath holding technique for the clinical measurement of the diffusing capacity of the lung for carbon monoxide. J Clin Invest 36: 1-17, 1957.
13. Pigmentel, J.C.: Tridimentional photographic reconstruction in a study of the pathogenesis of honeycomb lung. Thorax 22: 444-452, 1967.
14. Piper, W.N. & Helwig, E.B. Progressive systemic sclerosis. Visceral manifestations in generalized sceroderma. Arch Dermatol 72: 535-546, 1955.
15. Ritchie, B.: Pulmonary function in scleroderma. Thorax 19: 28-36, 1964.
16. Wahlund, H.: Determination of the physical working capacity. Acta Med Scand Suppl 215, 1948.
17. Weaver, A.L.: The lung in scleroderma. A clinical-pathological study. Thesis. Graduate School, Univ. of Minnesota 1966.
18. Wilson, R.J., Rodnan, G.P. & Robin, E.D.: An early pulmonary physiologic abnormality in progressive systemic sclerosis (diffuse scleroderma). Am J Med 36: 361-369, 1964.

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