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A Longitudinal Study of Pulmonary Function in Danish Patients with Systemic Sclerosis

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Summary **Objective: To determine the types, prevalence and development of respiratory abnormalities in patients with systemic sclerosis (SSc), and to correlate the results with clinical and serological findings. Methods: 176 patients with SSc observed longitudinally were retrospectively included in the study. The change per year of vital capacity (VC), forced expiratory volume in one second/vital capacity (FEV_1/VC), diffusing capacity (DLco) and diffusing constant (Kco) of carbon monoxide from the first till the latest pulmonary function test were correlated to clinical and serological findings, including anti-centromere, anti-Scl-70, and antinucleolar antibodies. Results: An isolated reduction of DLco was seen in 47% and a restrictive ventilatory pattern in 25% of the patients. Restrictive ventilatory pattern correlated to pulmonary fibrosis, dyspnoea, a low prevalence (13%) of anti-centromere antibodies and a high prevalence of anti-Scl-70 antibodies (36%). Progression of DLco reduction was related to long disease duration, presence of anti-centromere antibodies and absence of treatment with penicillamine. Conclusion: Pulmonary involvement is common in patients with SSc. The occurrence of different serological abnormalities in patients with restrictive disease and in patients with progressive isolated reduction of DLco, suggests that the two types of pulmonary damage may have different pathogeneses rather than being different stages in the progression of pulmonary damage.**

Key words **Systemic Sclerosis, Lung Function.**

INTRODUCTION

Pulmonary involvement is a common manifestation of systemic sclerosis (SSc). It may lead to restrictive as well as obstructive ventilatory defects, even in non-smokers (1,2). An isolated reduction of diffusing capacity without evidence of restrictive or obstructive lung disease is also a common ventilatory defect in SSc (3). Lung disease has become an increasing cause of morbidity and mortality in patients with SSc, since the treatment of renal disease has improved (4). However, previous estimates vary as to the extent to which pulmonary disease contributes to the mortality (5-7).

Clinical and serological abnormalities may be related to different types of ventilatory defects (3,8). The progression of pulmonary disease in SSc may also be influenced by the treatment with penicillamine and other drugs (9,10). Tobacco smoking may worsen the lung function in patients with SSc (1), even though smoking may be only partially responsible for the obstructive component of the pulmonary involvement in SSc (2).

In the present paper serial measurements of pulmonary function in a large group of well defined patients with SSc were compared with a number of clinical and serological findings.

PATIENTS AND METHODS

Patients

Two-hundred and thirty-two patients with SSc who had an initial pulmonary function test (PFT) performed between 1965 and 1992 were identified in the chart records of the participating clinical centres. These centres are responsible for treating SSc on a national basis, primarily in the eastern part of Denmark; the western part is serviced by another centre. All patients met the criteria for

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SSc suggested by the American College of Rheumatology in 1980 (11).

The patients included in the study had to have at least two PFTs performed with an interval of at least one year. 176 patients were included, 150 women and 26 men. The median age at the time of the first SSc symptom was 41 years, ranging from 4 to 74 years. The median duration of disease was 6.2 years at the time of the first PFT. Cutaneous involvement was classified according to a 3-subset model (12): 12 patients (7%) had only digital cutaneous involvement of the skin, 112 patients (63%) had also cutaneous involvement of proximal extremities or face, and 52 patients (29%) had cutaneous involvement of the thorax or abdomen. Onehundred and fifty patients had been treated with penicillamine in doses varying from 250-900 mg per day for a period varying from 1 to 20 years.

Fifty-six patients were excluded from the study since they had only one PFT performed, were followed for less than one year, dropped out or died. The distribution of the PFT patterns obtained for the included and excluded patients are stated in Table I.

Clinical features

Medical history and laboratory findings were entered consecutively into a cumulative database including information about smoking habits, previous tuberculosis, lung surgery, dyspnoea, and treatment with penicillamine. Dyspnoea was defined as chart recorded functional or resting dyspnoea. Disease onset was defined as the time of the first SSc related symptom including Raynaud's phenomenon. Chest radiograms were examined for the presence of pulmonary fibrosis. Pulmonary hypertension was not evaluated by a standardized procedure and consequently not recorded.

Pulmonary function tests

All patients had at least two PFTs performed with an interval of 1 to 28 years (average 8 years). The PFTs were conducted in accordance with standard protocols as follows. The largest of three technically acceptable efforts was used to determine forced expiratory volume in the first second (FEV_1). Slow inspiratory vital capacity (VC), and the ratio between FEV_1/VC were also determined. A single breath helium, CO-dilution technique was performed in 145 patients to determine their diffusing capacity of CO (DLco) and the diffusing constant (Kco), i.e. DLco per litre alveolar volume. PFT results were transformed to standardised values, calculated as percentages of the predicted values with respect to sex, age and height according to Quanjer (13) to minimize any effects of these factors.

VC and DLco were considered abnormal if the values were less than 80% of the predicted values. An FEV_1VC value of less than 70% was considered abnormal. Four mutually exclusive groups of patients were identified by means of the first PFT: patients with a) isolated reduction of DLco ($\leq$80% of predicted) in whom VC and FEV_1/VC were within normal limits, b) restrictive ventilatory pattern (VC$\leq$80% and FEV_1/VC$\geq$70%), c) obstructive ventilatory pattern (FEV_1/VC$<$70%), and d) patients with normal lung function, i.e. all values were within normal limits (3).

The rate of change of the PFT results was expressed as the annual change of the measured/predicted-ratio of VC, FEV_1/VC, DLco, and Kco from time A to B. This method was used to avoid the effect of aging during the observation period, which varied from one to 28 years. The use of two-point estimates has previously been shown to reflect accurately the rate of change of multiple mea-

Table I: *Patterns of pulmonary function test (PFT) results at first examination in 232 patients with systemic sclerosis*

	Isolated reduction of DLco	Restrictive	Obstructive	Normal	All
Patients stratified according follow-up status					
1 PFT or followed < 1 year (%)	16 (29)	19 (34)	6 (11)	15 (27)	56 (100)**
> 1 PFT and followed > 1 year (%)	83 (47)	44 (25)	22 (13)	27 (15)	176 (100)
First time PFT characteristics of patients with repeated tests followed for more than one year					
Mean VC, % of predicted* (SD)	96 (11)	67(9.9)	94 (16)	107 (17)	90 (18)
Mean FEV_1/VC, % of predicted (SD)	101(7.8)	110(9.7)	80(9.7)	101(7.7)	101 (12)
Mean DLco, % of predicted (SD)	61 (14)	63 (16)	69 (21)	92 (14)	68 (18)
Mean Kco, % of predicted (SD)	59 (13)	75 (16)	64 (17)	80 (12)	67 (17)

* Predicted values are calculated on the basis of sex, age and height (13).

** 2×4 Chi square test, p=0.05.

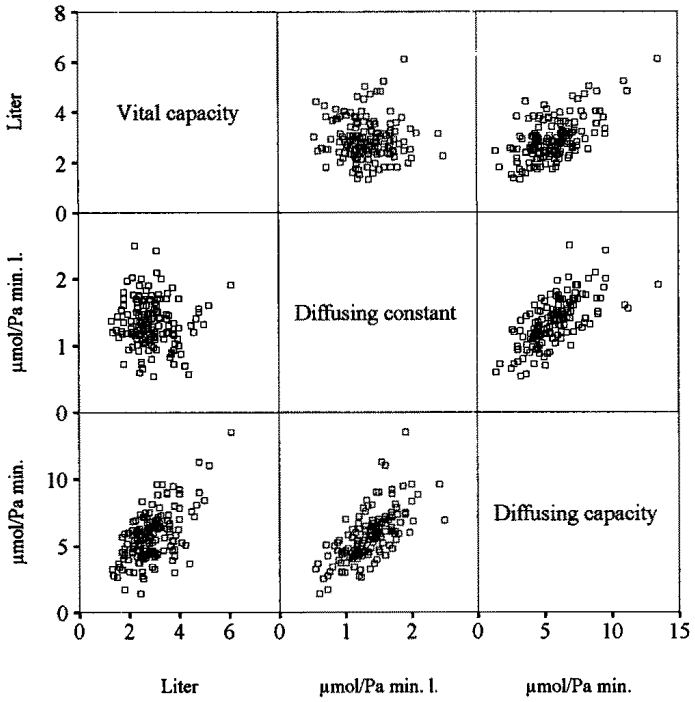

Fig. 1: Matrix correlation plot of VC, DLco and Kco in absolute units obtained at first pulmonary function test.

surements in SSc patients (6). In the following formula, VC is used as an example:

$$\Delta VC/year = \frac{VC_{B,measured}/VC_{B,predicted}) - (VC_{A,measured}/VC_{A,predicted})}{Time_{A-B}}$$

Serological tests

A serum sample was obtained from each patient at the first visit and stored at a minimum of –20°C until use. The serological tests comprised the determination of antinuclear antibodies (ANA) using HEp-2 cells (Immunoconcepts, Sacramento, California) as a substrate. Sera were screened at a dilution of 1:40, and positive reactions were categorized according to the nuclear immunofluorescence pattern (14). Titers were determined by two-fold end point titration. Anti-centromere and antinucleolar antibodies (ab) were reported without further subspecificity testing, whereas a homogenous or fine speckled nuclear pattern was subsequently studied for presence of anti-Scl-70 ab by double immunodiffusion against thymus-spleen extract.

Statistical methods

The pulmonary function data were normally distributed and described by means of arithmetic mean and standard deviation. Parametric analysis of variance was used for continuous variables and the chi-square test for categorical variables when comparing patient subgroups. Median values and quartiles were stated and nonparametric statistics were used for some clinical variables which were not normally distributed. A multiple regression analysis was used to identify factors significantly influencing pulmonary function parameters and their variation over time. A logistic regression analysis was used to identify factors significantly influencing the presence of dyspnoea and radiographic pulmonary fibrosis.

RESULTS

Findings at first examination

The findings at the first PFT are shown in Table I. Fifteen per cent of the patients had a normal PFT at that time. The most common abnormality was an isolated reduction of DLco, which was seen in 47% of the patients. The DLco was also reduced in the group of patients with restrictive lung disease, but after correction for the reduced lung volume the average Kco was found to be higher than in the patients with isolated reduction of DLco. For this reason the relations between VC, DLco and Kco were further investigated and plotted in figure 1. No relationship was found between VC and Kco (r^2=0.4%), whereas significant correlations were found between DLco and VC (r^2=35%), and between DLco and Kco (r^2=46%). A multiple regression analysis showed that 80% of the variation of DLco could be explained by VC and Kco, i.e. DLco is mainly a product of two pulmonary function parameters that relate to different properties of the lung, namely alveolar volume and alveolar gas diffusion.

Table II shows the basic clinical data of the patients related to PFT patterns at the time of the first PFT. Radiographic evidence of pulmonary fibrosis (47%), dyspnoea (42%), and anti-Scl-70 ab (36%) were predominantly found in the group of patients with restrictive lung disease, ant the prevalence of anti-centromere ab (14%) was lowest in this group.

A multiple regression analysis was performed to identify baseline clinical and serological factors related to lung function parameters obtained at first PFT. VC, DLco and Kco were the dependent variables. The presence of anti-centromere ab, anti-Scl70 ab, elevated erythrocyte sedimentation rate (ESR) above 30 mm/h, subsets of skin involvement, and smoking habits were the independent variables. The results in Table III indicate that ESR, skin involvement, disease duration and smoking did not influence the lung function parameters at that time. However, anti-Scl-70 ab was associated with low VC, and anti-centromere ab was associated with high VC and low Kco.

Table II: *Some clinical and serological characteristics of 176 patients with systemic sclerosis stratified according to the pulmonary function test result at first examination*

	Isolated reduction of DLco (n=83)	Restrictive (n=44)	Obstructive (n=22)	Normal (n=27)	P=
Females (%)	92	77	82	81	ns
Median age, years (quartiles)	52 (43-60)	45 (33-58)	59 (55-65)	47 (39-61)	0.001
Median duration, years (quartiles)	6.3 (2.7-11)	5.8 (2.7-12)	6.3 (1.2-19)	5.4 (3.2-16)	ns
Smoking, current and previous (%)	58	40	45	54	ns
Subsets of cutaneous involvement (%)					
Digital only	10	7	24	4	
Proximal extremity	74	81	57	81	ns
Truncal	16	12	19	15	
Anti-nuclear antibodies					
Anti-centromere ab. (%)	33	14	45	41	0.02
Anti-Scl-70 ab. (%)	16	36	9	15	0.01
Anti-nucleolar ab. (%)	13	11	14	15	ns
Dyspnoea (%)	30	42	32	7	0.02
Pulmonary fibrosis, x-ray (%)	13	47	14	4	0.00001

Table III: *Multiple regression analyses of pulmonary function parameters and change over time of these by clinical and paraclinical parameters in 176 patients with systemic sclerosis.*

	First pulmonary function test (PFT)			Change from first to latest PFT per year		
	VC	DLco	Kco	Δ VC/yr	Δ DLco/yr	Δ Kco/yr
Centromere ab	10.06[1]	−0.59	−6.09[2]	−0.22	−2.50[3]	−2.14[3]
Anti-Scl-70 ab	−7.42[2]	−4.27	2.16	0.35	−0.77	−0.03
ESR > 30 mm/h at first PFT	−4.14	−2.14	−1.29	−2.05[1]	−2.45[3]	−1.85[2]
Subsets of skin involvement:						
Digital only	3.66	0.23	−7.37	0.40	−2.33	1.20
Truncal	1.22	−4.03	−5.12	0.13	−1.24	−1.57
Smoking	1.68	−3.58	−2.22	−0.70	−0.92	−1.52[2]
Treated with penicillamine				0.44	2.86[3]	3.84[1]
VC at first PFT				−0.01	–	–
DLco at first PFT				–	−0.10[1]	–
Kco at first PFT				–	–	−0.09[1]
Constant in equation	87.82	72.44	72.09	1.28	5.80	4.39
R square of model	0.13	0.03	0.06	0.08	0.27[1]	0.22[1]

Coefficients (B) of independent variables, constant, and R square for the regression models are given. A negative B indicates a negative influence of an independent variable on the dependent variable and vice versa. Description of coding; Centromere ab, anti-Scl-70 ab, erythrocyte sedimentation rate (ESR) > 30 mm/h, subsets of cutaneous involvement (digital only, truncal), smoking, penicillamine treatment: no=0, yes=1. Pulmonary function parameters: in % of predicted. [2]: $p \leq 0.05$; [3]: $p \leq 0.01$; [1]: $p \leq 0.001$.

The regression models only explained a statistically insignificant part of the variation observed in the pulmonary function parameters.

Changes in pulmonary function

Figure 2 shows the changes of PFT between the first and the latest examination. Sixty per cent of the patients with isolated reduction of DLco at the first PFT had the same abnormality at the latest examination. In 16% of the patients the DLco became normal, 14% developed obstructive lung disease, and 11% developed restrictive lung disease. Sixty-four per cent of the patients who had a restrictive pattern at the first PFT still had restrictive lung disease at the latest examination. Forty-four per cent of the patients with normal lung function at the first examination developed isolated reduction of DLco. The fraction of patients who had normal lung function was 15% at the first examination and 20% at the latest examination.

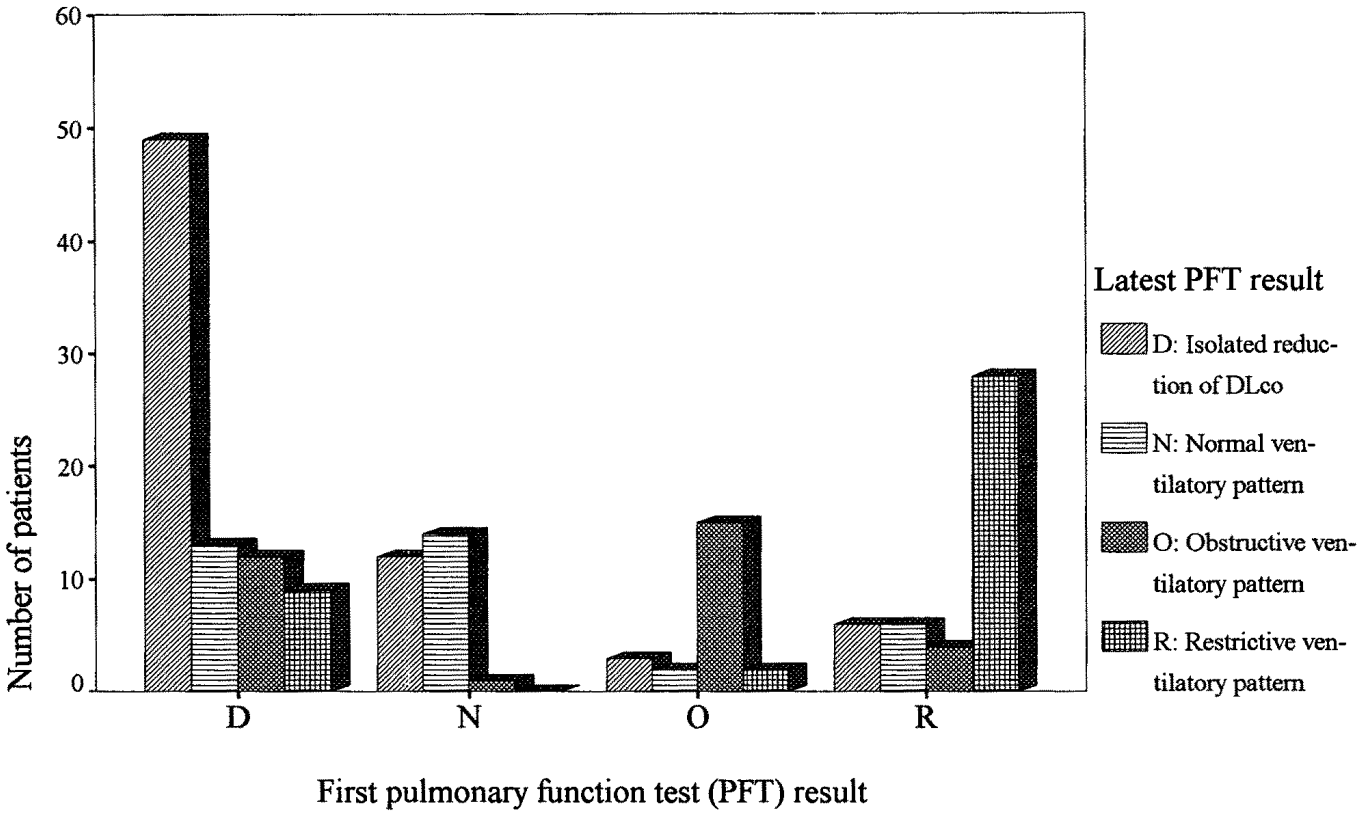

Fig. 2: Changes in pulmonary function test (PFT) patterns from first to latest examination during a mean observation period of 8.1 years.

The change of lung function parameters during the observation period was also analyzed by means of a multiple regression analysis. The changes per year of VC, DLco, and Kco were the dependent variables. The presence of anti-centromere ab, anti-Scl70 ab, elevated erythrocyte sedimentation rate (ESR) above 30 mm/h, subsets of skin involvement, smoking habits and baseline values of the corresponding PFT parameter were the independent variables. High ESR at first PFT was highly associated with a decrease in VC during the observation period. The presence of anti-centromere ab, elevated ESR and smoking were related to a decrease in Kco, whereas Kco was favourably influenced by treatment with penicillamine. Patients with high levels of Kco and DLco at first PFT were most likely to show a decrease in Kco and DLco. Except for smoking, factors that significantly influenced changes in VC and Kco also influenced changes in DLco. The regression models explained between 22 and 27% of the variation in time related changes of pulmonary gas diffusion, which is statistically significant, but probably not enough for clinically meaningful predictive significance in individual cases.

Dyspnoea and radiographic pulmonary fibrosis

Logistic regression analysis showed that dyspnoea was associated with the presence of radiographic pulmonary fibrosis ($p=0.002$) but not to subsets of skin involvement, disease duration, serological findings, ESR, ventilatory pattern, treatment with penicillamine, or smoking. Restrictive lung disease ($p=0.0004$), presence of anti-Scl-70 ab ($p=0.0004$), and high ESR ($p=0.02$) were also associated with radiographic pulmonary fibrosis.

DISCUSSION

The present patient material differs from previous studies (1,15) since the majority of our patients had limited SSc and only 29% had diffuse disease. This distribution is most likely due to a referral pattern which allows the inclusion of mild and limited cases of SSc in the study, but varying definitions of diffuse SSc in the studies may also be of importance. Consequently, the prevalence of anti-centromere ab is relatively high (31%) and the prevalence of anti-Scl-70 ab is relatively low (20%) in this study compared with another patient material in which 52% of the patients had diffuse disease (15). In the same group of patients 40% had restrictive lung disease (16) and 19% had an isolated reduction of DLco (3), in our study these figures were 25% and 47%, respectively. In the present patient material the type of pulmonary damage at the first and the latest PFT was unrelated to the extent of the cutaneous involvement, which has also been

described by other workers (1). On the other hand, according to some papers, an isolated reduction of DLco may be found most often in patients with limited SSc (3,17). According to the latter findings the high prevalence of isolated reduction of DLco in the present patient material may be explained by the high proportion of patients with limited SSc.

The lung function was normal at the first examination in only a small minority of the patients (15%). This fraction of patients was almost unchanged (20%) at the latest examination, about eight years later on the average. During the observation period further deterioration of the lung function was moderate in most patients. These findings agree with previous studies which suggest that the pulmonary damage of patients with SSc may often be a complication with a relatively benign course (6). Possibly, most of the lung damage occurs during the early course of the disease in periods with active alveolitis (18), i.e. before the time of the first PFT performed in the present patient material. Our findings stress the importance of measuring and following lung function parameters in all subsets of SSc patients, since they are all at significant risk of developing or showing progressive pulmonary disease.

Patients treated with penicillamine had the least deterioration of DLco and Kco. Earlier studies also suggest, that penicillamine may favourably influence the progression of DLco but not the VC (9,19). This finding needs confirmation by means of a controlled prospective study. The association between an elevated ESR at first PFT and the following deterioration of all PFT parameters underlines the pathogenetic role of inflammatory mechanisms in SSc lung disease. Smoking had only a modest effect on the lung function. Smoking has previously been found to have a varying effect on the lung function (1,2,5).

In all subgroups of patients with an initially abnormal PFT the lung function became normal in some patients which probably reflects a regression towards the mean. Of the patients with an initially normal lung function 44% subsequently developed an isolated reduction of DLco, but only a few patients with isolated reduction of DLco progressed to restrictive pulmonary disease during the observation period. In this and other materials (3,20), the two types of lung damage were related to different serological findings. In the present material restrictive disease was related to anti-Scl-70 ab and the progression of isolated reduction of DLco was related to anti-centromere ab. Isolated reduction of DLco is associated with pulmonary hypertension without restrictive or obstructive lung disease (isolated pulmonary hypertension). Pulmonary hypertension was not recorded in this study, but other studies have shown that some patients with limited cutaneous involvement have isolated pulmonary hypertension and significant deterioration of diffusing capacity (3,8). Since this group of patients have normal VC, these abnormalities are most likely due to intimal proliferation of pulmonary arterioles (21) leading to an increase of pulmonary vascular resistance and a mismatch between perfusion and ventilation. Our correlation analysis of the various PFT parameters showed that DLco was related to both VC and Kco, i.e. pulmonary gas diffusion is related to both the alveolar volume and to gas transfer. The absent relationship between Kco and VC indicates that these measures reflect different qualities of the lung and that different pathophysiological mechanisms may be operative in the patients. The two main types of pulmonary damage in SSc, i.e. pulmonary fibrosis and primary pulmonary vasculopathy, may have different pathogeneses rather than being different stages in the progression of pulmonary dysfunction.

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