Longitudinal Changes in Lung Function and Respiratory Symptoms in Progressive Systemic Sclerosis

Prospective Study

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Most patients with progressive systemic sclerosis (PSS) exhibit lung involvement. However, the natural history of lung disease in PSS remains poorly defined. To evaluate lung function over time in PSS, a battery of lung function tests were prospectively performed serially between 1973 and 1982 in 61 patients with PSS. Functional indexes of restriction (vital capacity and total lung capacity) and diffusion impairment (diffusing capacity) showed greater-than-expected annual rates of change. Male subjects showed a trend toward faster declines in forced vital capacity, forced expired volume in one second, total lung capacity, and functional residual capacity and a more rapid increase in static recoil pressure at 90 percent of total lung capacity than did female subjects. Nonsmokers had greater rates of decline in total lung capacity and static lung compliance (but not in forced vital capacity or diffusing capacity) and a greater rate of increase in static recoil pressure than did current and former smokers. Level of lung function at initial study visit, age, race, and chlorambucil therapy had no significant effect on the annual rates of change in lung function, whereas longer duration of disease prior to study entry was associated with a slower annual decrease in lung volumes. Between the first and last visits (mean interval 3.1 years, maximum nine years), the frequency of abnormality in pulmonary function test results showed significant change only in the diffusing capacity (60 percent increasing to 82 percent) and static lung compliance (40 percent increasing to 54 percent), whereas the frequency of respiratory symptoms showed little change. These findings indicate an overall indolent progression of PSS-related lung disease, with substantial individual variability.

Lung involvement is a major complication of progressive systemic sclerosis (PSS), and, with heart and kidney involvement, is one of the major causes of death in PSS [1–4]. Pulmonary involvement in PSS consists of diffuse interstitial fibrosis (74 [5] to 100 percent [4] of autopsy subjects) and/or pre-capillary pulmonary vascular changes (47 percent) [6] and is found clinically in 40 [3] to 60 percent [4] of patients with PSS. When pulmonary involvement is present (defined by the presence of bilateral basilar interstitial fibrosis, pleuritis, pulmonary hypertension, or a diffusing capacity for carbon monoxide of less than 12 ml/minute/mm Hg), the five-year mortality is approximately 50 to 60 percent [3] and approximately 90 percent when the diffusing capacity for carbon monoxide is less than 40 percent of predicted [7]. Restriction of the chest wall due to hidebound skin of the thorax is rarely severe enough to cause significant effects on lung function [8]. The contribution of respiratory muscle weakness due to PSS-related myositis to the development of ventilatory restriction has not been addressed adequately.

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The natural history of pulmonary involvement in PSS, including the rate of change in lung function over time, and the factors influencing this rate of change, has not been fully characterized. Such information is important for determining prognosis and assessing response to treatment. Previous studies have led to conflicting conclusions concerning the progression of functional pulmonary impairment in PSS: uniform progression [9]; long-term stability after an initial decline [1,10]; little overall progression but marked individual variability; and both early and late deterioration with intermittent periods of improvement [11]. In addition, prognostic factors remain controversial. Several authors have suggested that poor prognostic signs include male gender [3,10,12,13], lung involvement early in the course of disease [8], low diffusing capacity for carbon monoxide [1,14], relatively little initial impairment in forced vital capacity [14], former cigarette use [14], and black race [3]. On the other hand, other investigators have found that initial pulmonary function tests and clinical features do not provide prognostic information [1,11,14]. For example, an isolated abnormality in diffusing capacity for carbon monoxide may revert spontaneously to normal [14], a worse initial diffusing capacity for carbon monoxide has been associated with a smaller rate of decline subsequently, and race, sex, duration of disease, cigarette use, or diffuse interstitial changes on chest radiography have not been found to influence the longitudinal rate of decline in lung function [1,10,11,14]. Earlier studies of the natural history of pulmonary involvement in PSS can be criticized because of the use of only one or two test points over time [9–11,14], retrospective design [10,11], small numbers of subjects, and pre-selection of patients with PSS and known lung involvement [1,9,15]. In the present study, we prospectively analyzed serially collected data obtained on at least three occasions in a large number of unselected patients with PSS participating in a longitudinal clinical trial to determine the annual rate of change in lung function and to assess the influence of several factors, including drug treatment, initial lung function, smoking status, and demographic data, on the subsequent rate of change in lung function and change in respiratory symptoms and chest radiographic findings. Since no benefit accrued to the use of the trial drug [16], these data provide insight into the natural course of pulmonary involvement in PSS.

PATIENTS AND METHODS

Between 1973 and 1982, patients with PSS who were referred to or regularly followed at UCLA were recruited to participate in a prospective randomized placebo-controlled, double-blind clinical trial to evaluate the impact of chlorambucil therapy on the natural course of PSS. Exclusionary criteria included life-threatening disease, an arterial oxygen tension consistently less than 55 mm Hg with the patient breathing room air, blood pressure above 160/100 mm Hg despite antihypertensive medication, creatinine clearance less than 60 ml/minute, serum creatinine value greater than 2 mg/dl, severe intractable malabsorption, chronic debilitation from PSS or another disease, requirement of more than 20 mg per day of prednisone, or a persistent blood dyscrasia. Only two patients were excluded because of severe pulmonary involvement due to PSS associated with severe hypoxemia. A total of 61 patients were enrolled in the study. All gave informed consent. Fifty-two had scleroderma by major criteria (hidebound skin proximal to the metacarpal or metatarsal joints) and seven by minor criteria (at least two of the following three characteristics: sclerodactyly, digital pitted scars, and chronic interstitial changes on chest radiography). Two subjects had CREST syndrome alone (absence of scleroderma by major or minor criteria and at least three of the following five characteristics: calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia). Of the 61 patients entered into the study, 38 were randomly assigned to receive placebo and 23 to receive drug therapy consisting of at least 0.05 mg/kg per day of chlorambucil for a minimum of one year.

Patients were subsequently withdrawn from the study if they were found to be unreliable regarding clinic visits or tablet ingestion or if a persistent oxygen tension less than 50 mm Hg, intractable congestive heart failure, malignant hypertension, creatinine clearance less than 60 ml/minute, a rising serum creatinine level, or proteinuria greater than 1.5 g per day developed. Drug or placebo was decreased in dose or withdrawn if the white blood cell count fell below 3,000/mm^3, the platelet count fell below 100,000/mm^3, or any of the following conditions developed: gastrointestinal intolerance, drug fever, skin hypersensitivity, neurotoxicity with clonic and tonic movements, or pregnancy.

A complete history and physical examination were performed at study initiation and every 12 months thereafter. In addition, a brief clinical evaluation was performed each month. Patients underwent pulmonary function tests on study entry, approximately every six months before 1976, and roughly every 12 months after 1976.

Vital capacity and forced expiratory flow rates were determined at least in triplicate using a 13.5-liter water-sealed spirometer (Warren E. Collins, Inc.). Spirometric indexes were calculated from the best of three satisfactory breaths and compared with published predicted values [17]; values greater than 1.65 SD below the predicted value were considered abnormal. Subdivisions of lung volumes were determined by the helium-dilution method [18]; values greater than 1.65 SD above or below the predicted value [19,20] were considered abnormal. The single-breath diffusing capacity for carbon monoxide was determined in duplicate by the method of Ogilvie et al [21] and was considered abnormal if it was more than 1.65 SD below the predicted value of Cotes [22]. Radial arterial puncture was performed for sampling arterial blood at rest with the subjects inspiring room air; arterial pH, carbon dioxide tension, and oxygen tension were determined in duplicate using a semi-automated blood gas analyzer (Radiometer BMS3MK2; Corning, model 168). Alveolar oxygen tension was calculated assuming a respiratory quotient of 0.8.

Alveolar-arterial oxygen difference was derived and compared with predicted normal values for age [23].

Transpulmonary pressure was measured with the subject in the sitting position, using a latex esophageal balloon that was positioned in the lower third of the esophagus [24] and connected to a differential pressure transducer (Validyne, model MP-45-3, range ± 50 cm H_2O). Expired and inspired volumes and flow were measured using a rolling-seal spirometer. Transpulmonary pressure, volume, and flow were recorded on a multichannel oscilloscopic recorder (Electronics for Medicine, model DR8). Static deflation pressure-volume curves were constructed from the transpulmonary pressure and volume measurements recorded during breathholding intervals during deflation from total lung capacity toward residual volume. Static lung compliance calculated from the deflation pressure-volume curve in the tidal volume range was considered abnormal if it was less than 0.13 liter/cm H_2O, based on data collected in our laboratory. Static recoil pressure at 90 percent of predicted total lung capacity was considered abnormally increased if it was greater than 2 SD above the predicted values of Turner et al [25].

At each visit, subjects were queried regarding symptoms of cough (with or without phlegm production), wheeze, and shortness of breath (at rest and on mild exertion). Posteroanterior and lateral chest radiographs were obtained annually. Chest radiographs were interpreted by a single radiologist unaware of the subjects' treatment and smoking status, pulmonary function tests, or clinical severity. Radiographs were evaluated for the presence of fine or coarse reticular or reticulonodular densities with or without associated volume loss or honeycombing [26]. Assessment of the presence or absence of pulmonary hypertension from posteroanterior and lateral chest radiographs was based on the size of the right descending pulmonary artery [27].

Because of the important effect of cigarette smoking on lung function, the effect of smoking was evaluated separately, with subjects placed in one of three different smoking categories (current, former, or never-smokers). Current smokers demonstrated no significant differences in rate of change in any measured pulmonary function parameter when compared with former smokers ($p > 0.05$; unpaired t tests). Therefore, the former and current smokers (smokers) were combined for comparison of results with never-smokers in all analyses. Linear regression was used to determine the mean annual rate of change for each parameter for each individual subject. In order to minimize the effect of regression to the mean, only patients in whom individual lung function tests were carried out on at least three different occasions were included in the analyses of annual rate of change. Comparison of mean annual rates of changes between patients treated with chlorambucil and those given placebo showed no significant benefit from chlorambucil treatment for any pulmonary function test ($p > 0.05$; unpaired t test and multiple regression). Therefore, the treatment groups were combined for all analyses.

Mean baseline pulmonary function test results of smokers (current and former smokers combined) were compared with those of the never-smokers; t tests were used to compare the results as percent predicted for all tests except static lung compliance, for which the absolute values were compared. The annual rate of change of each pulmonary function test result was compared between the two smoking groups using the Student t test. Similar analyses were performed to compare results in men and women. To determine the effect of several additional factors on the annual rate of change, multiple regression analyses were performed using annual rate of change in lung function as the dependent variable and age, duration of disease, smoking status, treatment group, and baseline pulmonary function as the independent variables. Analysis of variance was used to compare annual rates of change in lung function across race (Caucasian, black, and Hispanic). Prevalence of abnormal symptoms and of abnormality in each lung function test result was determined separately for each smoking group at both the first and last visits. McNemar's test was used to compare prevalence of respiratory symptoms and pulmonary function abnormality between the first and last visit for all subjects and separately for subjects within each smoking category. Chi-square or Fisher's exact test was carried out to determine differences between smokers and nonsmokers at the first visit. Statistical analyses were performed using BMDP programs [28].

TABLE I Demographic and Clinical Characteristics

	Nonsmokers	Smokers*	Total
Age (years; mean ± SEM)	48 ± 2	47 ± 2	47 ± 2
Disease duration (years; mean ± SEM)	12 ± 2	8 ± 2	10 ± 2
Sex (number)			
Male	5	3	8
Female	25	28	53
Race (number)			
Caucasian	21	22	43
Black	4	3	7
Hispanic	4	4	8
Other	1	2	3
Disease classification (number)			
Scleroderma	25	27	52
CREST†	5	4	9
Chlorambucil treatment (number)			
Yes	5	11	16
No	20	18	38
Discontinued	5	2	7

* 19 current smokers and 12 former smokers.
† Includes seven patients with scleroderma by minor criteria alone.

RESULTS

Demographic and clinical characteristics of the study population at the time of entry into the study are indicated in **Table I.** There were 53 female patients and eight male patients, with an average age of 47 ± 12 (SD) years. Most of the subjects were Caucasian. The most common initial symptom attributed to PSS was Raynaud's phenomenon. Symptoms related to Raynaud's phenomenon, cu-

TABLE II Baseline Pulmonary Function (mean ± SEM)

Test*	Nonsmokers	Smokers	Total
FVC	72 ± 3	81 ± 3†	77 ± 2
FEV_1	78 ± 4	86 ± 3	82 ± 3
FEV_1/FVC ratio (percent)	83	80	82
$FEF_{25-75\%}$	86 ± 5	83 ± 6	85 ± 4
TLC	83 ± 4	88 ± 3	86 ± 2
FRC	101 ± 6	106 ± 4	104 ± 3
D_LCO	73 ± 4	59 ± 4†	66 ± 3
C_{Lst}	0.12 ± 0.01	0.15 ± 0.01†	0.13 ± 0.01
Pst at 90 percent TLC (cm H_2O) (expected)	27 ± 2 (14)	28 ± 2 (13)	28 ± 2 (14)
A-aDO_2 (mm Hg) (expected)	21 ± 2 (11)	24 ± 2 (12)	22 ± 1 (12)

* Test values are expressed as percent predicted except as noted in parentheses.
† Significantly different from PSS, nonsmokers ($p < 0.05$).
FVC = forced vital capacity; FEV_1 = forced expired volume in one second; $FEF_{25-75\%}$ = forced expiratory flow over mild-half of FVC; TLC = total lung capacity; FRC = functional residual capacity; D_LCO = diffusing capacity for carbon monoxide; C_{Lst} = static lung compliance; Pst = static recoil pressure; A-aDO_2 = alveolar-arterial oxygen difference.

taneous sclerosis, or inflammatory polyarthritis were the presenting symptoms in more than 90 percent of subjects. The mean duration between the first symptom attributable to PSS and initiation of the study was 10.2 ± 10.2 (SD) years (range, 0 to 40 years). Twenty-eight patients had disease less than five years and 33 greater than five years. Thirty were never-smokers, 12 former smokers, and 19 current smokers.

The mean baseline pulmonary function test results as absolute and percent of predicted values are presented in **Table II** for the entire study sample and for subgroups segregated by smoking status. For the entire group, mean forced vital capacity was reduced below 80 percent of predicted, whereas the ratio of average forced expired volume in one second to forced vital capacity exceeded the predicted value, indicating a restrictive ventilatory abnormality in the group as a whole. In addition, mean diffusing capacity for carbon monoxide was reduced below 75 percent of predicted, whereas mean static recoil pressure at 90 percent of total lung capacity was increased, indicating overall diffusion impairment and increased lung stiffness. On comparison of current or former smokers with never-smokers at study entry, forced vital capacity and static lung compliance were significantly higher, whereas the diffusing capacity for carbon monoxide was significantly lower in the smoking subgroup (Table II).

Table III lists the mean annual rates of change for each pulmonary function parameter for the total group of subjects and by smoking status; also listed are the average expected annual rates of change based on published cross-sectional data [17,19–22,25] obtained in healthy Caucasian nonsmokers. Annual changes in selected indexes of lung function by smoking status are illustrated in **Figure I**. The mean annual rate of decline in forced vital capacity was approximately twice that predicted from cross-sectional studies, whereas the rate of decline in one-second forced expiratory volume was about one and a half times expected. As a result, our subjects with PSS showed an increase in the ratio of one-second forced expiratory volume to forced vital capacity with age rather than the normally expected slight decline. Mean forced expiratory flow over the middle half of the forced vital capacity ($FEF_{25-75\%}$) in our subjects also increased with age in contrast to the normally expected decrease. Total lung capacity declined at a several-fold greater rate than expected, whereas functional residual capacity remained nearly constant in contrast to the expected increase in functional residual capacity with age. Diffusing capacity for carbon monoxide decreased at a markedly accelerated rate compared with expected rate of decline. Static lung compliance decreased whereas static recoil pressure increased with age, as opposed to the increase in

TABLE III Annual Change in Pulmonary Function

Test	Nonsmokers (mean ± SEM)	Smokers (mean ± SEM)	Total (mean ± SEM)	Expected*
FVC (ml)	−42 ± 16	−60 ± 16	−51 ± 12	−24
FEV_1 (ml)	−48 ± 16	−26 ± 13	−37 ± 10	−25
FEV_1/FVC (percent)	0.64 ± 0.46	0.63 ± 0.38	0.64 ± 0.29	−0.18
$FEF_{25-75\%}$ (liters/second)	−0.04 ± 0.04	0.05 ± 0.05	0.01 ± 0.03	−0.03
TLC (ml)	−112 ± 39	−13 ± 32	−66 ± 27	−8
FRC (ml)	−14 ± 28	16 ± 36	0.68 ± 22	16
D_LCO (ml/minute/mm Hg)	−1.35 ± 0.34	−1.24 ± 0.54	−1.29 ± 0.32	−0.16
C_{Lst} (ml/cm H_2O)	−14.4 ± 4.2	−2.1 ± 3.4	−8.8 ± 2.9	↑
Pst at 90 percent TLC (cm H_2O)	2.90 ± 0.87	−0.51 ± 0.63	1.24 ± 0.60	−0.21

* From cross-sectional annual rates of change based on published prediction equations (see text).
↑ = expected annual increase with age.
Abbreviations as in Table II.

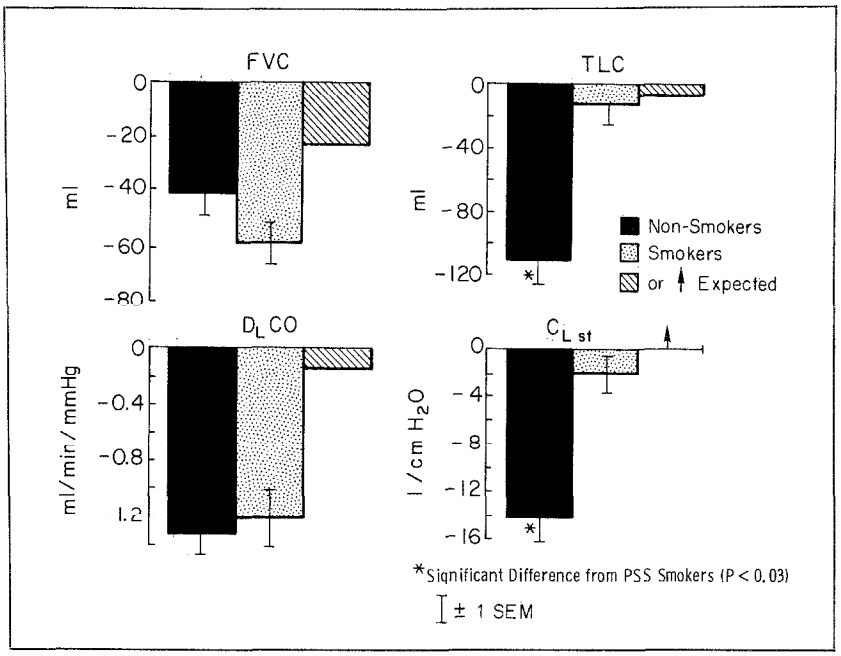

Figure 1. *Annual rates of change in forced vital capacity (FVC), total lung capacity (TLC), diffusing capacity (D_LCO), and static lung compliance (C_{Lst}) in the study sample of patients with progressive systemic sclerosis (PSS) segregated by smoking status. Nonsmokers refer to never-smokers; smokers include current and former smokers. Expected rates of change were determined from published regression equations derived from cross-sectional population studies of healthy nonsmokers (see text).* ↑ = *expected annual increase with age.*

compliance and decrease in recoil pressure that normally occur with aging.

Annual rates of change in lung function were compared across subjects in different smoking categories (current, former, and never-smokers). Current smokers demonstrated no significant differences in the rate of change of any measure of lung function when compared with former smokers. Therefore, results for former and current smokers were combined for comparison of results with never-smokers. Smokers had significantly smaller annual decreases than nonsmokers in static lung compliance (−2.1 versus −14.4 ml/cm H_2O, respectively) and in total lung capacity (−13.1 versus −112.7 ml, respectively) and small annual decreases in the static recoil pressure (0.5 cm H_2O) as opposed to annual increases in static recoil pressure in nonsmokers (2.9 cm H_2O).

No significant influence of sex or race (Caucasian, black, Hispanic) on the annual rate of change of forced vital capacity, one-second forced expiratory volume, total lung capacity, functional residual capacity, diffusing capacity for carbon monoxide, static lung compliance, or static recoil pressure was noted (analysis of variance; $p > 0.05$). The influence of chlorambucil therapy, age, the duration of disease prior to study entry, and baseline lung function at the first visit on the annual rates of change of lung function was also examined by multiple regression. There was no demonstrable beneficial effect of chlorambucil on the rate of change in any index of lung function. Age had no demonstrable effect on the annual change in lung function. On the other hand, a longer duration of disease prior to study entry correlated significantly with a smaller annual decrease in the forced vital capacity, total lung capacity, and functional residual capacity ($p < 0.05$). Aside from a significant correlation between a narrower alveolar-arterial oxygen difference at baseline and a larger subsequent annual widening of the alveolar-arterial oxygen difference, there was no significant influence of the baseline value for any other lung function parameter on subsequent rates of change in lung function.

Smokers had a significantly lower prevalence of abnormal static lung compliance and a significantly higher prevalence of an abnormal alveolar-arterial oxygen difference at study entry (**Table IV**). Smoking had no demonstrable significant effect on any other measured functional parameter in our sample of subjects. There was also no significant relationship between smoking and the presence or absence of respiratory symptoms or chest radiographic evidence of interstitial lung disease or pulmonary hypertension at study entry (**Table V**).

The duration between the first and last visit for each subject ranged from one to nine years with a mean of 3.1 years. On comparison of the prevalence of abnormal lung function between the first and last visit, few patients changed from initially normal to abnormal results and there was very little net increase in the prevalence of significant abnormality for any test of lung function except for the diffusing capacity for carbon monoxide (60 percent abnormal at first visit, 82 percent abnormal at last visit) and static lung compliance (40 percent abnormal initially, 54 percent abnormal at final visit) (Table IV and **Figure 2**). When evaluated by smoking subgroup, these changes were most marked in the never-smokers. No significant change occurred between the initial and final visits in the presence or absence of respiratory symptoms or of evidence of diffuse interstitial changes or pulmonary hypertension on chest radiography (Table V).

TABLE IV Prevalence of Abnormal Pulmonary Function Test Results (percent)

Test	First Visit			Last Visit		
	Nonsmokers	Smokers	Total	Nonsmokers	Smokers	Total
FVC	53	32	43	60	45	52
FEV_1	43	35	39	46	45	46
FEV_1/FVC	4	0	2	7	0	3
$FEF_{25-75\%}$	43	50	47	50	50	50
TLC	4	0	2	0	3	2
FRC	4	0	2	0	7	4
D_LCO	48	71	60	76*	87	82*
C_{Lst}	54†	27	40	73*	35	54
Pst at 90 percent TLC	76	81	78	88	77	82
$A\text{-}aDO_2$ difference	32†	75	55	42	68	56

* Significantly different comparing first and last visits ($p < 0.05$; McNemar's test).
† Significantly different from smokers at first visit ($p < 0.05$; chi-square).
Abbreviations as in Table II.

TABLE V Prevalence of Abnormal Symptoms and Chest Radiographic Changes

	First Visit			Last Visit		
	Nonsmokers	Smokers	Total	Nonsmokers	Smokers	Total
Shortness of breath at rest	33	30	31	33	22	27
Shortness of breath with exercise	33	31	32	25	23	24
Wheeze	21	19	20	25	12	18
Cough	58	41	49	50	41	45
Sputum	25	35	30	33	38	36
Interstitial changes	63	43	53	63	43	53

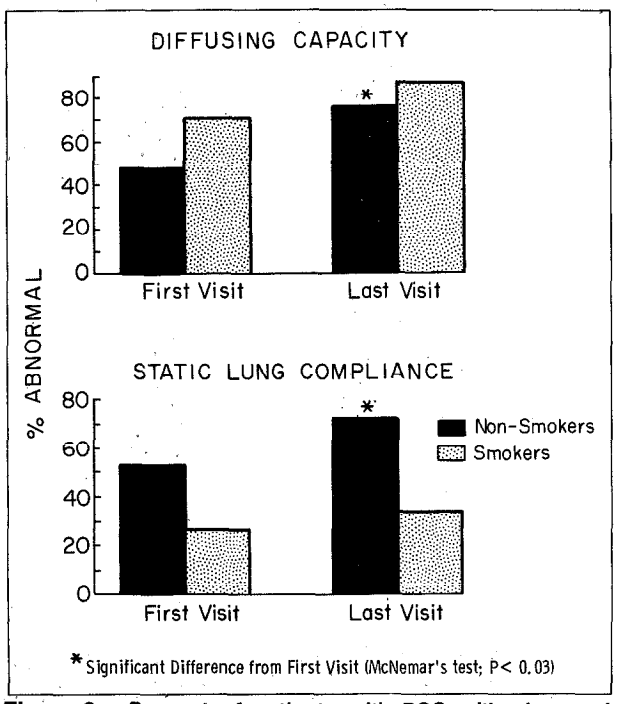

Figure 2. *Percent of patients with PSS with abnormal diffusing capacity or static lung compliance at first visit and last visit for smokers and nonsmokers separately. Nonsmokers refer to never-smokers; smokers include current and former smokers.*

Eleven patients (five never-smokers and six current or former smokers) died during the course of this study. Three (one never-smoker and two current or former smokers) died of pulmonary disease, three of renal involvement, one of esophageal carcinoma, one of a cerebral vascular accident, and two of other causes; one patient committed suicide. There was no significant difference in the rate of change of any measure of lung function on comparison of the 11 patients who died with those who survived when segregated by smoking category. The one never-smoker who died of pulmonary insufficiency exhibited rates of decline in forced vital capacity and total lung capacity that were approximately two- and six-fold greater, respectively, than the average rates of decline in these same indexes among the remaining never-smokers. The two current/former smokers with PSS who died of pulmonary causes had rates of decline in forced vital capacity and compliance that were about two- to three and a half-fold greater, respectively, than the average rates of decline in these indexes among the remaining current/former smokers; moreover, the rate of fall in total lung capacity in the two smokers with a respiratory cause of death was 164 ml per year compared with only 5.1 ml per year among the remaining smokers.

Thirty-eight of the 61 subjects initially involved in the study (including the 11 who died) failed to complete all the visits required by the chlorambucil study protocol. A vari-

ety of reasons accounted for these dropouts, mostly unrelated to pulmonary disease (e.g., renal failure, gastritis, red cell aplasia, leukopenia, herpes zoster, noncompliance with the protocol, perceived inefficacy of the drug, and change of residence). However, 52 patients (i.e., all but nine of the 61 patients initially enrolled in the chlorambucil study) remained in the study long enough to undergo pulmonary function testing on at least three separate occasions, thus permitting assessment of the longitudinal rate of change in their lung function prior to the time of withdrawal from the study. To determine whether there were any differences in the degree of pulmonary involvement that might have predisposed to withdrawal from the study and thus influenced our results, we compared both baseline lung function and annual rate of lung function change between the patients who completed the study and those who withdrew from the study, segregated by smoking status. The only significant differences were as follows: a slightly higher ratio of one-second forced expiratory volume to forced vital capacity and a slightly lower $FEF_{25-75\%}$ at baseline in the patients who withdrew from the study than those who completed the study; and a larger annual decline in total lung capacity in the never-smoking dropouts, as well as a smaller increase in functional residual capacity in the former/current smokers who withdrew from the study, compared with subjects in the same smoking category who completed the study. Despite the baseline differences in one-second forced expiratory volume/forced vital capacity ratio and $FEF_{25-75\%}$ between the dropouts and the patients who remained in the study, the mean one-second forced expiratory volume/forced vital capacity ratio and $FEF_{25-75\%}$ were each normal in both of these groups of subjects.

COMMENTS

Most patients with PSS exhibit lung involvement [4,5,15], which is associated with decreased survival [3]. Previous studies attempting to define symptomatic and physiologic lung changes in PSS have reached inconsistent conclusions regarding the natural history of PSS pulmonary involvement. These discrepancies might be attributable to differences in study design and the number of subjects examined. Hughes and Lee [15] noted a greater-than-expected decline in diffusing capacity for carbon monoxide in eight of 10 patients followed over five years. On the other hand, Colp et al [1] noted progressive reduction in lung volumes and diffusing capacity in only three of 16 subjects over six years and concluded that PSS lung abnormalities occur early and thereafter do not progress significantly. In contrast, Bagg and Hughes [9], who followed nine patients over 12 years, found that lung function changes can occur at any time, with intervening periods of temporary improvement but an overall gradual worsening over time. In 38 patients examined retrospectively, Schneider et al [11] found a greater-than-predicted decrease in forced vital capacity and no change in diffusing capacity for carbon monoxide over five years. In a single-visit follow-up study of 24 of an original group of 76 patients with PSS, Peters-Golden et al [14] noted that the annual change in forced vital capacity, total lung capacity, one-second forced expiratory volume/forced vital capacity ratio, and diffusing capacity for carbon monoxide approximated that of normal subjects. Only a history of former smoking and the presence of severe Raynaud's phenomenon correlated with more rapid pulmonary progression. Recently, Steen et al [10], who reviewed 92 patients with PSS, 44 of whom had received D-penicillamine therapy after a mean period of three and a half years, noted little overall change in forced vital capacity or diffusing capacity for carbon monoxide, although significant individual variability was found. They concluded that progression of pulmonary involvement in PSS was not the rule even when pulmonary disease was initially present. However, the latter study can be criticized because it was retrospective, treatment was nonrandomly assigned, a large number of patients were lost in follow-up, and sicker patients were included in the treated group.

The present study was carried out to evaluate prospectively the natural history of changes in pulmonary status in 61 patients with PSS examined serially during the time period between 1973 and 1982. Because only two subjects had CREST syndrome, the conclusions derived from this study cannot be generalized to the CREST variant. Although some patients were treated with chlorambucil, this agent had no demonstrable beneficial effect on respiratory status. Therefore, the combined data are believed to represent the natural history of changes in the pulmonary manifestations of PSS in our patient population unconfounded by any significant treatment effect.

We compared longitudinal annualized changes in lung function in our patient population with cross-sectional rates of change derived from regression equations generated from data obtained in populations of healthy nonsmokers. Prospectively determined longitudinal rates of change in lung function of healthy persons are not available for most of the parameters of lung function that we measured in our patients with PSS. Although longitudinal changes in forced vital capacity and one-second forced expiratory volume have been measured in some healthy populations, these data are conflicting [29–35] and may actually be lower than the rates of change with age obtained from cross-sectionally derived regression equations [35]. Therefore, the expected rate of change in one-second forced expiratory volume we used for comparison with the longitudinal data obtained in our patients with scleroderma may, if anything, overestimate the true rate of change for healthy persons. Our patients with PSS exhibited a greater-than-expected rate of decline in lung volumes and diffusing capacity. Pressure-volume indexes (lung compliance, and static recoil pressure at 90 percent of total lung capacity) showed evidence of increasing

stiffness rather than the decreasing stiffness expected with increasing age [25]. These results are consistent with an overall progression of diffuse interstitial pulmonary involvement by PSS with time. In contrast, the one-second forced expiratory volume fell to a lesser extent than the forced vital capacity, resulting in an increased ratio of one-second forced expiratory volume to forced vital capacity, consistent with progressive stiffening of the lung [36] and the absence of a significant component of airflow obstruction [26]. Of particular significance is the variability in the individual annual rates of change in lung function. Although the majority of patients showed a greater-than-expected decline in forced vital capacity, diffusing capacity for carbon monoxide, and total lung capacity, from 21 to 37 percent of our subjects exhibited improvement in these indexes.

We failed to demonstrate that race, sex, or age influences the annual rate of lung function change. Although the number of black subjects we studied was small, they did not exhibit more marked pulmonary involvement initially or a greater rate of progression of pulmonary disease than Caucasians, as some authors have suggested [3]. Several investigators have noted a greater rate of progression of PSS lung disease in male subjects [3,10,12,13]. Although we did not observe a significant sex difference, we did note a trend toward greater decreases in forced vital capacity, one-second forced expiratory volume, and total lung capacity, as well as a more rapid increase in static recoil pressure, in male than in female subjects. These differences did not, however, reach statistical significance, possibly because of the small number of male patients in our study. An increased disease duration before study entry resulted in a slower annual decrease in lung volumes (total lung capacity, forced vital capacity, and functional residual capacity). This finding may represent a survival effect or it may be due to a relatively greater decline early in the course of the disease, as has been suggested by some authors [1,10].

Initial lung function results generally had no significant influence on the subsequent rate of change in lung function, i.e., lower initial values of lung function did not presage either a more rapid further worsening or a greater likelihood of improvement. This observation suggests that lung function measured early in the course of PSS cannot be used to predict the future course of pulmonary involvement, and that regardless of the test results upon presentation, lung function can either improve, decline, or remain stable. The only exception to this general observation was the alveolar-arterial oxygen difference, which demonstrated a greater average annual rate of widening in patients with initially better arterial oxygenation.

Unlike previous investigators [9–11,14], we examined rates of change in lung function only in patients with more than two (three to 11) test points over time. Therefore, our results are not likely to be influenced by regression towards the mean. Inspection of individual results in our patients indicates that changes in lung function occur at variable times during the course of the disease: some subjects had early decreases in their diffusing capacity for carbon monoxide, which then stabilized or decreased more gradually, whereas others did not begin having losses in diffusing capacity until years after the initial diagnosis.

Despite the accelerated declines in lung volumes in our patient population compared with normal cross-sectional rates of decline, it is of interest that the frequency of significant abnormality in lung volumes among our patients did not change appreciably over the course of the study. This finding parallels the observation that the frequency of chronic respiratory symptoms also did not increase over time. These results support the concept of an overall indolent course of slowly progressive pulmonary involvement in PSS. On the other hand, the prevalence of an abnormal diffusing capacity and static lung compliance did increase over time, reflecting true progression of parenchymal pulmonary disease involving the microcirculation. Nevertheless, since average symptoms did not appear to progress over the one to nine (mean 3.1) years of follow-up of our patients, the isolated increases in the frequency of abnormality of diffusing capacity and lung compliance over this period of time may have little clinical significance. It is noteworthy, however, that although the average progression of pulmonary involvement was slow, as reflected by the minimal change in the prevalence of abnormality of both symptoms and lung function, lung function in some persons improved dramatically, whereas that in others worsened markedly, resulting in death from pulmonary involvement in three of the 61 patients during the course of the study. We were unable to detect any predictors of those at risk for more rapid progression, except for a tendency for male gender to be associated with greater rates of decline in lung function and for longer disease duration at study entry to be related to a slower decrease in lung volumes.

In comparing smokers with nonsmokers, we combined former smokers with current smokers for two reasons. First, separate analysis showed no significant differences between former and current smokers. Current and former smokers were therefore combined to provide a greater number of subjects for comparison with nonsmokers to increase the probability of identifying a significantly different rate of change in smokers. Secondly, Peters-Golden and co-workers [14] have suggested that smokers with the most severe PSS would be the most likely subjects to stop smoking; therefore, excluding former smokers could yield misleading findings in current smokers by having selected out the worst cases. Smokers did not show statistically different results from never-smokers in the rates of change in forced vital capacity, one-second forced expiratory volume, one-second forced expiratory volume/forced vital capacity ratio, $FEF_{25-75\%}$, static lung compliance, diffusing capacity for carbon monoxide,

functional residual capacity, or alveolar-arterial oxygen difference. Only rates of change in the static recoil pressure, static lung compliance, and total lung capacity were significantly different between smokers and nonsmokers. These differences were in the direction of a lesser rate of increase in lung stiffness in smokers, possibly due to offsetting effects of smoking-related emphysematous changes (decreasing lung stiffness) on the changes related to progressive pulmonary involvement in PSS (increasing lung stiffness). Similarly, the one-second forced expiratory volume might be partially stabilized in smokers with PSS due to counteracting tendencies for the one-second forced expiratory volume to increase in PSS because of increasing lung stiffness related to sclerodermatous pulmonary involvement and to decreases in smokers due to smoking-related airflow obstruction. We do not attribute these lesser rates of change in some indexes of lung function in smokers compared with nonsmokers with PSS to a beneficial effect of smoking in PSS. Rather, these differences are most likely due to the superimposition in smokers of the harmful effects of another disease process, namely emphysema, on the abnormalities related to PSS, as indicated by the lower diffusing capacity for carbon monoxide at entry, followed by the progressive worsening of diffusing capacity for carbon monoxide in our smoking subjects.

Drug therapy resulted in no significant improvement in any parameter of lung function. There remains no clearly beneficial drug therapy for lung disease in PSS. Although some reports have suggested a benefit of D-penicillamine [10,37], these conclusions are tentative and could be affected by both selection bias and the small numbers of patients studied. Moreover, the individual variability in functional pulmonary progression noted in the present study emphasizes the need for appropriately matched control subjects in all studies evaluating drug treatment for PSS lung disease.

It could be argued that selective withdrawal from the study or death prior to study completion could have biased our results toward demonstration of a relatively slower progression of pulmonary disease in PSS than truly might be occurring. However, comparison within each smoking category of the subjects who left the study with those who completed the study revealed no differences at study entry in the frequency of abnormality of lung function, and only slight differences in the annual rate of change in total lung capacity or functional residual capacity. These minor differences do not suggest that the dropouts, as a group, had a greater rate of progression of pulmonary involvement due to PSS compared with those who completed the study. On the other hand, it is noteworthy that nearly 30 percent of the deaths that occurred in our study population were due to pulmonary disease, underscoring the fact that progressive pulmonary involvement secondary to PSS is an important cause of mortality due to this disease.

In summary, our patients with PSS followed for one to nine years (mean 3.1 years) demonstrated abnormal mean rates of change in pulmonary function test results consistent, on the whole, with slowly progressive diffuse interstitial pulmonary fibrosis. However, marked individual variability in the course of pulmonary involvement in PSS was noted: most showed greater-than-expected declines in lung function whereas some patients demonstrated actual improvement in lung function. Prognosis was not related to race, age, chlorambucil therapy, or the presence or degree of lung function impairment on initial testing. On the other hand, a longer duration of disease prior to study entry predicted a significantly slower rate of decline in lung volumes, whereas lung function in male patients showed a tendency to decline faster than that of female patients. Cigarette smoking tended to counteract the restrictive effect of PSS as reflected by significantly smaller annual declines in total lung capacity and static lung compliance and a smaller annual increase in static recoil pressure at 90 percent of total lung capacity observed in smokers compared with nonsmokers. Despite the accelerated rates of change in several measures of lung restriction in patients with PSS, only the static lung compliance and diffusing capacity for carbon monoxide showed a significant increase in the frequency of abnormality over the course of the study, whereas respiratory symptoms were not observed to progress. These findings point, on the average, to an indolent progression of PSS-related pulmonary disease, with significant individual variability. As a reflection of this variability, pulmonary involvement may actually improve in some patients, whereas it can worsen markedly in others, and the outcome can even be fatal.

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