Early pulmonary disease in systemic sclerosis: a comparison between carbon monoxide transfer factor and static lung compliance

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Abstract

***Objectives*—Pulmonary disease is responsible for considerable morbidity and mortality in systemic sclerosis (SSc). Static lung compliance (Cst) has been observed to be decreased more often in SSc than the vital capacity, indicating that it is a sensitive measure of lung restriction. In this study Cst was compared with the carbon monoxide transfer factor (T_LCO), a widely used measure of the function of the alveolar capillary unit, and with lung volumes in 59 patients with confirmed or suspected SSc.**

***Methods*—Cst was calculated from the oesophageal pressure at different lung volumes and the T_LCO was measured with the single breath method.**

***Results*—The T_LCO was found to be the earliest sign of pulmonary disease and was already decreased at a disease duration of one year or less. Surprisingly, no relation was found between the T_LCO and smoking habits, nor the degree of peripheral vascular disease. The T_LCO correlated with the Cst and vital capacity.**

***Conclusions*—An early pulmonary lesion can be identified in patients with SSc with decreased T_LCO at a time when no fibrotic changes are manifested.**

(*Ann Rheum Dis* 1993; **52:** 725–729)

Pulmonary disease contributes considerably to morbidity and mortality in patients with systemic sclerosis (SSc).[1] The interstitial disease in SSc has generally been considered as a relatively 'pure' fibrotic disorder, but several studies with bronchoalveolar lavage,[2–6] gallium-67 scanning,[5 7 8] and open lung biopsy[6 8] have shown the presence of alveolitis. A variety of lung function tests have been applied for the detection of pulmonary disease in SSc. Techniques reflecting the mechanics of breathing—for example, measurements of static lung volumes and lung compliance—are commonly used, but also techniques reflecting the functional integrity of the gas exchanging region of the lung, such as the measurement of the carbon monoxide transfer factor (T_LCO). Decreased T_LCO is reported to be an early sign of pulmonary disease in SSc,[9–12] whereas other workers have found that the T_LCO is rarely the only abnormality in SSc.[13 14]

Static lung compliance (Cst) has been reported to be the most sensitive parameter for the detection of abnormal pulmonary mechanics in SSc.[15 16] Few reports[2 13] exist on the relation between lung compliance and T_LCO in SSc.

The purpose of this study was to assess the relation between abnormalities in T_LCO and Cst in patients with SSc with early pulmonary disease and also to relate pulmonary disease to the degree of vascular abnormality, smoking habits, and skin disease.

Patients and methods

Fifty nine patients, 39 consecutive new cases admitted to the department and 20 follow up patients, were investigated for pulmonary disease. Forty eight patients fulfilled the American Rheumatism Association (ARA) criteria for SSc.[17] Seven patients had suspected SSc, with Raynaud's phenomenon and sclerodactyly, but not fulfilling the ARA criteria. Four patients had Raynaud's phenomenon without signs of a systemic connective tissue disease. Of the 48 patients with SSc, 37 had limited cutaneous systemic sclerosis—that is, skin disease restricted to the face, arms and legs,[18]—and 11 had diffuse cutaneous systemic sclerosis with skin changes including the trunk.

The new patients had not been treated with disease modifying drugs but three were receiving glucocorticoids by mouth and one chloroquine. Six of the 20 follow up patients were treated with azathioprine, one with cyclophosphamide, and two with penicillamine. Seventeen patients were smokers; 13 of these had limited SSc, three had suspected SSc, and one had Raynaud's phenomenon only. Four patients, two with limited SSc and two with diffuse SSc, were anaemic with haemoglobin less than 115 g/l.

Vital capacity was measured with a dry spirometer and total lung capacity with body plethysmography. The elastic pulmonary properties were calculated from the oesophageal pressure as measured at different lung volumes.[19] Static elastic recoil pressure was recorded during flow interruptions covering most of the vital capacity. Static lung compliance was measured over the pressure interval 5–15 ml H_2O. Measurement of the transfer factor for carbon monoxide was made with the single breath method; a full vital capacity inhalation of a gas mixture containing

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Accepted for publication 8 June 1993

Table 1 Carbon monoxide transfer factor and pulmonary mechanics (VC, TLC, and Cst) in 59 patients with systemic sclerosis (SSc) investigated for pulmonary disease. Values are median (range)

Diagnosis	*Diffuse SSc (n=11)*	*Limited SSc (n=37)*	*Suspected SSc (n=7)*	*Raynaud's phenomenon (n=4)*
T_LCO				
%p	61 (36–79)**	71 (32–122)****	89 (70–112)	96 (80–107)
Standardised residuals	−2·7 (−4·4 to −1·25)	−1·8 (−4·9–1·3)	−0·75 (−2·2–0·8)	−0·4 (−1·6–0·4)
No of patients below 2SD	9	15	1	0
VC				
%p	76 (73–117)**	90 (46–116)***	107 (93–119)	94 (83–107)
Standardised residuals	−2·0 (−3·0–1·25)	−1·0 (−5·25–1·75)	0·75 (−0·8–1·75)	−0·83 (−1·75–0·5)
No of patients below 2SD	5	9	0	0
TLC				
%p	77 (67–116)**	94 (58–117)**	104 (90–126)	93 (89–119)
Standardised residuals	−2·4 (−3·2–1·4)	−0·6 (−4·6–1·6)	0·4 (−1·0–2·0)	−0·9 (−1·2–1·6)
No of patients below 2SD	6	7	0	0
Cst				
%p	69 (29–138)*	74 (35–129)***	111 (85–119)	83 (74–140)
Standardised residuals	−1·7 (−4·0–2·0)	−1·25 (−3·25–1·7)	0·5 (−0·6–1·0)	−0·88 (−1·3–2·0)
No of patients below 2SD	5	9	0	0
Disease duration (years)	3 (1–22)	5 (0–22)	—	—

Abbreviations: T_LCO=carbon monoxide transfer factor; VC=vital capacity; TLC=total lung capacity; Cst=static lung capacity; %p=% of predicted value; SD=standard deviation.
Levels of significance of difference from predicted values: *p<0·05; **p<0·01; ***p<0·001; and ****p<0·0001.

0·3% carbon monoxide is followed by breath holding for 10 seconds. Alveolar gas is sampled from the following expiration and the concentration of carbon monoxide measured. The amount of gas lost reflects the diffusion of carbon monoxide into the blood. The pulmonary function is expressed for each test as a percentage of the predicted value (%p) and as a standardised residual. Lung volumes were predicted according to Berglund *et al*[20] and Grimby and Söderlund,[21] and the T_LCO according to Quanjer.[22] These predicted values have been tested on groups of normal subjects and have been found to be appropriate. The predicted values of static lung compliance are based on age and sex matched controls established at the department of clinical physiology in Lund.

Statistics

The statistical significance of differences was calculated with the Mann Whitney U test for unpaired observations. The difference from predicted values was calculated with Wilcoxon's test for paired data. Correlation between two variables was calculated with the Spearman's ρ value.

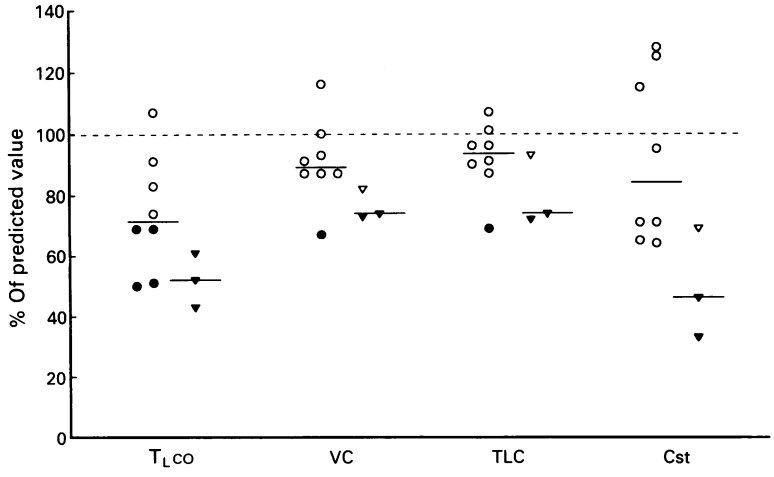

Figure 1 Carbon monoxide transfer factor (T_LCO), vital capacity (VC), total lung capacity (TLC), and static lung compliance (Cst) in eight patients with limited systemic sclerosis (SSc) (○) and three patients with diffuse SSc (▽) and disease duration 0–1 years. Median for the patients marked. Patients below 2SD are marked with closed symbols.

Results

The T_LCO, vital capacity, total lung capacity, and Cst were decreased in the two SSc subgroups compared with predicted values (table 1). No significant decrease was seen in seven patients with suspected SSc and in four patients with Raynaud's phenomenon only compared with the predicted values of vital capacity, total lung capacity, Cst, or T_LCO, though there was a slight decrease in the T_LCO (NS; p=0·09) in patients with suspected SSc.

Eleven of 48 patients with SSc (eight with limited and three with diffuse SSc) had a disease duration of 0–1 year (fig 1). Seven of these 11 had a T_LCO less than two standard deviations (SD), three had a vital capacity and total lung capacity less than 2 SD, and two had a Cst decreased by more than 2 SD. The eight patients with limited SSc had decreased T_LCO (p<0·02) compared with the predicted values, whereas their vital capacity, total lung capacity, and Cst were not significantly low.

Nineteen patients, 12 with limited SSc, five with diffuse SSc, one with suspected SSc, and one with Raynaud's phenomenon only, had serious peripheral circulatory disturbance as manifested by digital ulcers, pitting scars, or acrolysis on radiographic examination. These patients did not differ significantly in their T_LCO (p=0·12), Cst (p=0·20), or disease duration (p=0·08) from patients without such signs of a vascular dysfunction (table 2).

Among patients with limited SSc, 13 smokers and 23 non-smokers had the same median disease duration but, surprisingly, did not differ in T_LCO (p=0·28), lung mechanics, or acute phase proteins (table 3).

In the combined patient groups a correlation was found between T_LCO and Cst (fig 2A) and between T_LCO and vital capacity (fig 2B). No significant correlation was found in 11 patients with a disease duration of one year or less (fig 3A and B).

Table 2 Pulmonary function and acute phase proteins in 59 patients divided according to signs of significant vascular disease

Parameter measured (median (range))	*Significant vascular disease* (n=19)*	*No significant vascular disease* (n=40)*
Disease duration (years)	8 (1–22)	4 (0–14)
T_LCO (%p)†	68 (32–122)	75 (44–112)
VC (%p)	87 (59–109)	91 (46–119)
TLC (%p)	88 (58–119)	94 (63–120)
Cst (%p)	74 (29–140)	80 (35–138)
ESR‡ (mm/h)	13 (4–62)	10 (2–90)
Orosomucoid (g/l)	0·96 (0·62–1·57)	0·91 (0·55–1·70)
Haptoglobulin (g/l)	1·24 (0·44–3·16)	1·20 (0·22–3·73)

*For definition, see text.
†For abbreviations see table 1.
‡ESR=erythrocyte sedimentation rate.

Table 3 Pulmonary function and acute phase proteins in 36 patients with limited systemic sclerosis (SSc) divided according to smoking habits (smoking habits unknown in one of 37 patients with limited SSc)

Parameter measured (median (range))	*Smokers (n=13)*	*Non-smokers (n=23)*
Disease duration (years)	5 (0–12)	5 (1–22)
T_LCO (%p)*	69 (39–86)	76 (32–122)
VC (%p)	91 (67–116)	87 (46–110)
TLC (%p)	100 (69–109)	90 (58–117)
Cst (%p)	77 (50–125)	72 (35–129)
ESR† (mm/h)	11 (2–48)	10 (2–90)
Orosomucoid (g/l)	0·92 (0·76–1·39)	0·82 (0·60–1·50)
Haptoglobulin (g/l)	1·21 (0·91–3·73)	1·18 (0·32–3·11)

*For abbreviations see table 1.
†ESR=erythrocyte sedimentation rate.

The correlation coefficients between T_LCO, vital capacity, total lung capacity, and Cst and acute phase proteins are shown in table 4. The Cst showed a weaker correlation with acute phase proteins than T_LCO.

Discussion

Pulmonary disease in SSc is characterised by a microvascular injury and a fibrosing alveolitis. It is not known whether the alveolitis precedes, accompanies, or follows the derangement of the alveolar wall. Harrison *et al*[6] studied open lung biopsy samples from 12 patients and were unable to find any patient

Table 4 Correlation coefficients (ρ) between pulmonary function abnormalities and acute phase proteins

	*T_LCO (%p)**	*VC (%p)*	*TLC (%p)*	*Cst (%p)*
ESR† (mm/h)	−0·48***	−0·34*	−0·30*	−0·30*
Orosomucoid (g/l)	−0·35**	−0·26*	−0·30*	−0·18^{NS}
Haptoglobulin (g/l)	−0·30*	−0·31*	−0·45***	−0·16^{NS}

Abbreviations: see table 1. ESR=erythrocyte sedimentation rate.
Levels of significance of correlation between two variables: *p<0·05; **p<0·01; ***p<0·001; NS=not significant.

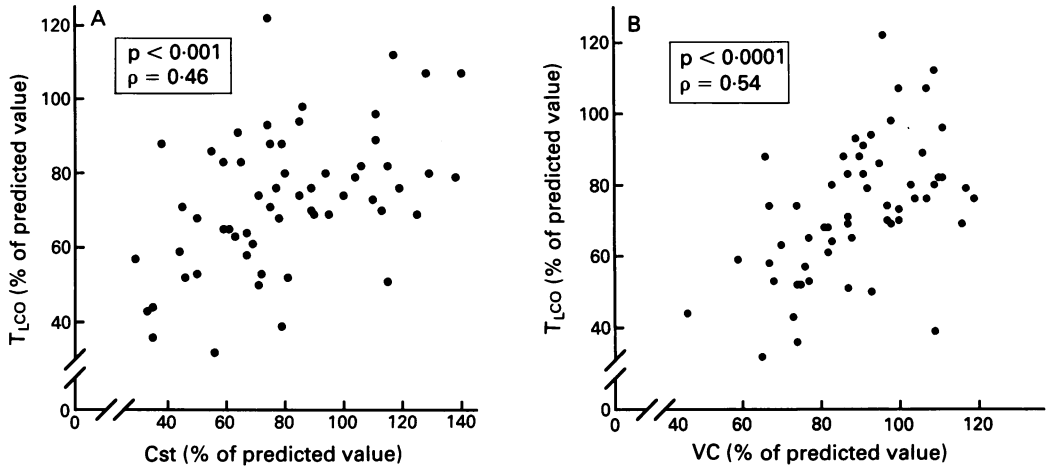

Figure 2 Relation between carbon monoxide transfer factor (T_LCO) and static lung compliance (Cst) (A) and between T_LCO and vital capacity (VC) (B) in 59 patients with systemic sclerosis investigated for pulmonary disease in scleroderma.

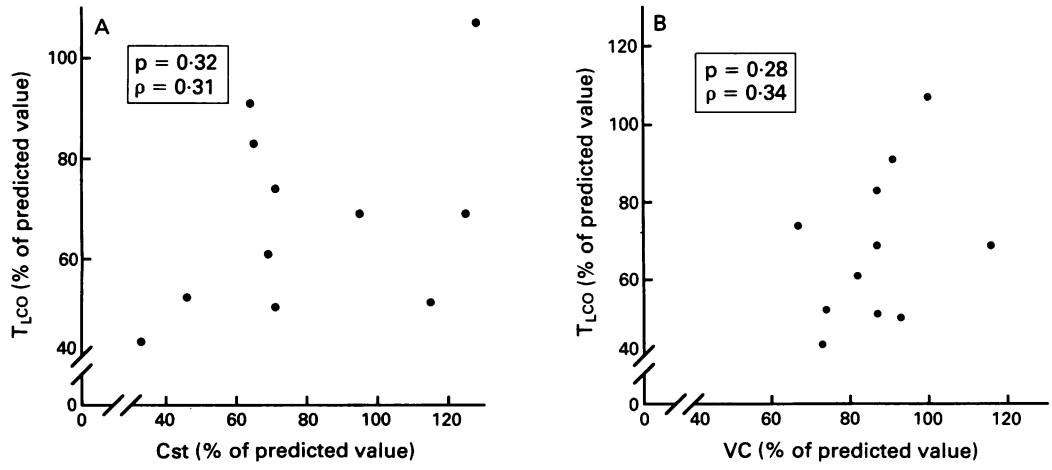

Figure 3 Relation between carbon monoxide transfer factor (T_LCO) and static lung compliance (Cst) (A) and between T_LCO and vital capacity (VC) (B) in 11 patients with systemic sclerosis with a disease duration of 0–1 year.

with inflammatory change not accompanied by fibrosis. They suggested that a concomitant fibroblastic proliferation and an inflammatory reaction proceed from the earliest histologically identifiable stages.

The lung function tests applied in the evaluation of patients with SSc reflect different aspects of the disease process. Measurement of static lung compliance is considered to give the most specific information about the mechanical properties of the lung tissue. Compliance is reduced by interstitial fibrosis, but also by oedema and cellular infiltration. Total lung capacity and vital capacity depend to a large extent on the mechanical properties of the lung, but also on the chest wall mechanics, the function of inspiratory muscles and the mechanical properties of the airways. The main determining factors for the T_LCO are considered to be the available alveolar diffusion area, the diffusion path length (that is, the thickness of the alveolar–capillary barrier) and the available binding sites (depending on the haemoglobin concentration and the pulmonary capillary blood volume). The T_LCO reflecting the function of the alveolar–capillary unit seems to be influenced by alveolitis[3 5] and microvascular disease,[12] and markedly decreased T_LCO values are found in patients with pulmonary hypertension.[23 24] Steen *et al*[25] found lower T_LCO values in smokers than non-smokers.

Although Cst is reported to be the most reliable method to determine lung mechanics in SSc,[15 16] only a few workers have used this method.[2 13 15 16]

In patients with limited SSc and a disease duration of one year or less, we found a lower T_LCO than predicted values, whereas the vital capacity, total lung capacity, and Cst were not decreased. In patients not yet fulfilling the ARA criteria for SSc there was a tendency to decreased T_LCO compared with predicted values. The findings may indicate that functionally significant abnormalities in the alveolar–capillary unit precede interstitial abnormalities in the pathogenesis of SSc. Patients with marked peripheral vascular disease did not have any more disturbed T_LCO than patients without such signs. This finding is in contrast with that of Manoussakis *et al.*[26] We could not find any major effect of smoking habit on the T_LCO as has been reported by Steen *et al.*[25] We did not perform any bronchoalveolar lavage in this study as this investigation is unpleasant for the patients and may cause complications.[2]

In the combined patient group we found a correlation between the T_LCO and the vital capacity similar to that previously reported by Lewis *et al.*[27] In severe pulmonary disease of SSc lung compliance, and thereby lung volumes, are greatly reduced. In such patients the reduction of diffusion area can be expected to affect the T_LCO, thus explaining the correlation. In patients with short disease duration we found no correlation between the T_LCO and the vital capacity or Cst. In this instance the reduction in T_LCO may be attributed more to an increased diffusion path length or decreased pulmonary capillary blood volume, or both. The result of this study supports an alveolitis or a microvascular disease, or both, preceding the restrictive lung disease in SSc.

Treatment with cyclophosphamide has been suggested to be effective in ameliorating pulmonary disease in SSc by Silver *et al*[28] and by our group.[29] This study emphasises the need for a trial of early aggressive therapeutic intervention in SSc at a time when there is not yet any sign of a restrictive lung disease.

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Ann Rheum Dis 1993 52: 725-729
doi: 10.1136/ard.52.10.725

Notes