Original Article

# Assessments of Pulmonary Involvement in Patients with Systemic Sclerosis

Keivan Gohari Moghadam MD•[1], Farhad Gharibdoost MD[2], Gilda Parastandechehr MD[3], Pirooz Salehian MD[4]

**Abstract**

**Background:** The lungs are affected in 70 – 90% of cases diagnosed with systemic sclerosis. Pulmonary involvement is associated with increased morbidity and mortality.

**Materials and Methods:** Fifty-five cases of systemic sclerosis underwent plethysmography, diffusion lung capacity for carbon monoxide (DLCO) measurement, high resolution computed tomography scanning, and bronchoalveolar lavage (BAL) to evaluate their diagnostic roles in grading the severity of lung involvement and their relationships to each other.

**Results:** The indices of DLCO% (measured DLCO to predicted ratio) and DLCO value, total lung capacity (TLC) value and TLC% (measured TLC to predicted ratio), forced vital capacity (FVC) and FVC% (measured FVC to predicted FVC) were significantly lower in patients who presented with a severer degree of lung involvement on high resolution computed tomography scan. No meaningful correlation between bronchoalveolar lavage findings and the degree of involvement on high resolution computed tomography scan was noted.

**Conclusion:** Although there is a correlation between imaging and lung capacities in physiologic studies. Bronchoalveolar lavage findings did not correlate with either imaging or physiologic tests. It seems that DLCO, TLC, and FVC are the most valuable measures with which to evaluate disease severity.

**Keywords:** bronchoalveolar lavage, systemic sclerosis fibrosing alveolitis, systemic sclerosis

## Introduction

Systemic sclerosis (SSc) tends to involve the lungs in up to 70 – 90% of cases.[1] Slow disease progression, delayed diagnosis and lack of definitive,[2] standardized and evidence-based therapy present challenges for the physician.

Lung and kidney involvement are the leading causes of morbidity and mortality in these patients.[3] Many studies have been carried out to evaluate lung involvement by physiologic and imaging methods, and cellular components of bronchoalveolar lavage (BAL)[2] of which controversial results were obtained.

This study was carried out in the Rheumatology Research Center and Pulmonary Clinic of Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran to evaluate pulmonary involvement by physiologic, imaging, and BAL studies.

The aim of this study was to compare different methods of imaging, physiologic and BAL findings together and to detect correlations among them in order to enable better judgment for the detection of disease severity and perhaps influence treatment planning.

**Authors' affiliations:** [1]Respiratory Disease Clinic, Shariati Hospital, Tehran University of Medical Sciences, Tehran, [2]Rheumatology Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, [3]Internal Medicine Clinic, Shariati Hospital, Tehran University of Medical Sciences, [4]Department of Pathology, Shahid Hasheminejad Hospital, Tehran University of Medical Sciences, Tehran, Iran.

•**Corresponding author and reprints:** Keivan Gohari Moghadam MD, Pulmonary Ward, Shariati Hospital, Tehran University of Medical Sciences, North Kargar Ave., Tehran, Iran.

E-mail: Kgohari@Sina.tums.ac.ir

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## Patients and Methods

### Patients

This descriptive cross-sectional study was carried out on SSc patients who attended the Rheumatology Research Center at Shariati Hospital, Tehran with the purpose of comparing imaging, physiologic and cellular components to each other. A total of seventy-four cases between January 2005 to September 2007 were considered. Of those, fifty-five patients met the inclusion criteria.

Patients were referred to the Pulmonary Laboratory to perform body plethysmography; from those 74 patients, 19 did not meet the inclusion criteria and were excluded from the study. The main inclusion criteria were: diagnosis of SSc by a rheumatologist, not having taken any cytotoxic drug or no prednisolone more than 10 mg/d within the previous three months. Exclusion criteria were: smoking, history of consumption of any drugs, which induced lung fibrosis, occupations that lead to pulmonary fibrosis and not having two out of the three following tests: body plethysmography, high resolution computed tomography (HRCT) scanning, or BAL during the study. All patients signed an informed consent. Study approved by local Institutional Board of hospital. The questionnaire contained demographic data

**Table 1.** Patient characteristics

| | |
|---|---|
| Number | 55 |
| Male/female | 5/50 |
| Mean age, year (SD, range) | 38.4 (1.3, 17–6 3) |
| Mean time from SSc diagnosis, month (SE, range) | 10.6 (1.7, 1–60) |
| Wheeze and crackle | 38(70%) |
| Dry cough and dyspnea* | 11 (21%) |
| Pyrosis/heartburn | 52(95%) |
| HRCT | |
| Normal | 6 (10.9%) |
| Grade I | 19 (34.5%) |
| Grade II | 11(20.0%) |
| Grade III | 13 (23.6%) |
| Grade IV | 5 (9.1%) |
| Absent | 1 (1.8%) |
| BAL | |
| Normal | 3 (5%) |
| Abnormal | 36 |
| Lymphocytosis | 13 (24%) |
| PMN-eosinophils | 23 (42%) |
| Absent | 16 (29%) |

SD=standard deviation; HRCT=high resolution CT scan; BAL=bronchoalveolar lavage; PMN=polymorphonuclear; *=dry cough

**Table 2.** Mean and 95% CI for FVC, DLCO and TLC

| Lung function test | Mean (SD) | 95% CI |
|---|---|---|
| FVC* | 2.19 (0.65) | 2.01–2.37 |
| FVC% | 68.41 (17.51) | 63.75–73.07 |
| DLCO** | 14.54 (5.45) | 12.76–16.32 |
| DLCO%** | 60.67 (22.26) | 53.40–67.94 |
| TLC | 3.95 (1.02) | 3.68–4.22 |
| TLC% | 81.91 (16.05) | 77.68–86.14 |

FVC=forced vital capacity ; DLCO=diffusion capacity of carbon monoxide; TLC= total lung capacity; *Missing number of FVC: 1, **Missing number of DLCO: 19

**Table 3.** Correlation of HRCT grade and lung function tests

| Lung function tests | R (*P* values) |
|---|---|
| TLC | -0.375 (0.005) |
| TLC% | -0.549 (<0.001) |
| DLCO | -0.513 (0.001) |
| DLCO% | -0.657 (<0.001) |
| FVC | -0.429 (0.001) |
| FVC% | -0.523 (<0.001) |

HTCT=high resolution CT scan; TLC=total lung capacity; DLCO=diffusion limitation of CO; FVC=forced vital capacity

as well as signs and symptoms of disease, time of disease onset and diagnosis, and was completed by a physician.

Body plethysmography and diffusion lung capacity for carbon monoxide (DLCO) measurements (Sensormedics V max 6200) were performed and patients were introduced to the Radiology Department for an HRCT of the thorax in the supine position. In suspicious cases, additional images were taken in the prone position (Siemens spiral plus4). The scans were reconstructed with high resolution (window level -500 to -600 HU; window width 1800 – 2000 HU).

If fiberoptic bronchoscopy was not contraindicated and the patient consented, it (Pentax EB-1970K) was performed at another session, no later than one week after HRCT and body plethysmography. BAL of the segments with intermediate degrees of HRCT involvement was performed after wedging fiberoptic bronchoscope (FOB) by three aliquots of 50 mL of saline solution.[4] The returned BAL fluid was not less than 50 mL (33%) in all cases. BAL fluid was sent to the Pathology Department within one hour following the procedure. After twenty min of centrifuging BAL fluid at 2500 rpm, the supernatant was removed and five slides were prepared from the sedimentation: three for Pap staining, one each for giemsa and Ziehl-Nielson staining. Light microscopic study of Pap staining was used to detect neoplastic cells. In order to differentiate between the cells, a total of 200 cells were counted by giemsa staining. BAL fluid with more than 15% lymphocytes, more than 3% polymorphonuclear, or more than 0.5% eosinophils was considered abnormal.[5]

HRCT grading of the thorax included[6]: O, normal; I,

**Table 4.** Distribution of BAL findings and symptoms according to HRCT results

| | HRCT results | | | | |
|---|---|---|---|---|---|
| **Characteristics** | **0** | **I** | **II** | **III** | **IV** |
| BAL findings | | | | | |
| Normal | 1 (25%) | 1 (8%) | 1 (12.5%) | 0 | 0 |
| Neutrophils | 1 (25%) | 2 (17%) | 6 (75%) | 5 (50%) | 3 (60%) |
| Lymphocytes | 2 (50%) | 6 (50%) | 1 (12.5%) | 3 (30%) | 1 (20%) |
| Eosinophils | 0 | 3 (25%) | 0 | 2 (20%) | 1 (20%) |
| Symptoms | | | | | |
| Dyspnea | 0 | 15 (88%) | 10 (91%) | 9 (82%) | 2 (40%) |
| Cough | 1 (33%) | 1 (6%) | 0 | 0 | 1 (20%) |
| Dyspnea and cough | 2 (67%) | 1 (6%) | 1 (9%) | 2 (18%) | 2 (40%) |

HRCT=high resolution CT scan; BAL=bronchoalveolar lavage

ground glass appearance more than reticular; II, equal ground glass and reticular areas; III, reticular area more than ground glass; and IV, diffuse honeycomb lesions in the upper and central zones. Due to the low numbers of patients in each subgroup, HRCT grades I and II were considered a low grade, and grades III and IV were high grade.

### Statistical analysis

For description of qualitative variables, absolute and relative indices were used. Mean index and standard deviation were used for the description of quantitative variables. Student's *t*-test was used to compare mean values and the ANOVA test for comparison in more than two groups. Mann-Whitney U test and Kruskal-Wallis H tests for non-parametric values were used

Chi-square compared the relation between lymphocytes and HRCT. Statistically meaningful values were 5% and a confidence interval of 95% for pulmonary function test values.

## Results

From Jan 2005 to Sep 2007, 74 SSc patients with or without pulmonary signs and symptoms were enrolled in the study. Nineteen patients were excluded from the study due to smoking, occupational history, consumption of drugs as the etiology of interstitial lung disease (ILD), treatment with cytotoxics or high dose steroids, or lack of performing two of the three necessary study tests. The mean age of patients was 38.4 years (SE: 1.4, range: 17 – 63 years). Only five patients were male. Normal HRCT was seen in six patients (10.9%). whereas Grade I HRCT was the most common presentation in 19 (34.5%) patients. Only three patients (5%) had normal BAL results. Neutrophilic-eosinophilic BAL was more common than lymphocytic BAL. Patients' characteristics are shown in Table 1. Mean total lung capacity (TLC) value was 3.95 l (3.75 – 4.32), the mean DLCO value was 14.54 mL/mm Hg/min (11.1 – 15.23) and mean forced vital capacity (FVC) value was 2.19 litters. Other mean values in addition to the 95% CI of the lung function tests are shown in Table 2. Correlations between DLCO, TLC and FVC values, and their percentiles (compared to normal values after adjusting for sex, race, height, and weight) with HRCT grade findings were noted (Table 3).

There were no correlations between patients' symptoms and HRCT findings. In addition, no correlations were seen between HRCT and BAL results. No normal BAL results were noted in patients with grades III and IV HRCT, whereas normal BAL findings were present in grades 0, I, and II HRCT. BAL neutrophilia was present mainly in grades II to IV HRCT and BAL lymphocytosis was mainly observed in grade II HRCT. Although there were more abnormal BAL and neutrophilic BAL in grades III and IV HRCT, no meaningful correlation between BAL and HRCT grade findings were seen (Table 4).

## Discussion

The main aim of this study was the evaluation and comparison of imaging, physiologic, and cellular components of the inflammatory process of systemic sclerosis fibrosing alveolitis (SSFA). Although pathologic sampling and examination of lung tissue could guide diagnostic and therapeutic strategies, in addition to determining prognosis in these patients, however, it is neither necessary nor possible to do the invasive procedures. Nonspecific interstitial pneumonitis (NSIP) is the dominant pathology of these patients.[7] The different types of inflammatory cells[7] and different nature of disease progression among these patients[2,7] are probably the reason for variations in prognosis and response to treatment. HRCT is suggestive of ILD and in known cases of SSc the diagnosis of fibrosing alveolitis is established by HRCT unless there are unusual patterns in HRCT, which make invasive procedures necessary.

Is HRCT alone sufficient for grading disease severity, degree of involvement, functional impairment and enable treatment planning? According to some studies, discordances between patients' signs and symptoms, pulmonary function test (PFT) indices and HRCT results exist.[2,7–9] In

this regard PAL may be helpful.[9,9,10,11] The decrease in diffusion capacity and FVC values has been correlated with the extent of fibrosis and implied a poor prognosis.[7,12,13] Our study showed a correlation of HRCT findings with PFT indices such as absolute DLCO, TLC and FVC values, and their percentiles. It is not surprising that more severe and extensive lung involvement seen with HRCT shows more decrease in diffusion capacity and lung capacities. On the other hand, some patients with ground glass opacity on HRCT have normal lung capacities.[8] HRCT and PFT may have complementary roles in disease severity, functional impairment, decision to initiate treatment and follow up with patients to determine treatment response. Controversies exist regarding the importance of BAL and BAL findings in studies.

The rational for BAL is that inflammatory cells may play a role in inflammation[8–11] or at least they are markers of disease severity and inflammation.[8] On the other hand, BAL cellularity could be a marker of a "switch " from an inflammatory state to a fibrotic state[14] and could identify a group of patients who warrant continued immunosuppressive therapy.[15] The presence of polymorphomuclears (PMNs) in BAL fluid denotes progressive disease[2,10] and more functional impairment,[2] which requires treatment but is strongly associated with more extensive disease in the lavaged lobe rather than the global extent of disease.[8] Although in a trial of 158 patients, there was no difference in the change in FVC after 12 months in BAL defined alveolitis and normal BAL groups,[16] which did not predict the rate of functional deterioration.[17]

Our study did not show any correlation between BAL, HRCT findings and PFT indices, which may be due to two reasons: the low number of patients in each HRCT group make statistical analysis impossible and BAL analysis reveals the cellular component in the lavaged lobe rather than the global extent of disease severity. It may be partly due to our sampling from involved lobes. In some studies, sampling has been performed from the right middle lobe or lingual, regardless of radiological involvement[2,8,10] thus routine sampling from these lobes regardless of the severity of radiologic involvement may underestimate disease severity,[18] which has shown a significant discordance between ground glass opacity findings in HRCT and BAL neutrophilia or eosinophilia.[18] HRCT and PFT give us a global morphological estimate of disease extent and severity of functional impairment, respectively[19] instead of information about disease extent in the involved lobe by BAL. BAL findings reveal a local milieu of inflammation rather than the global extent of disease.[2] It is believed that a higher percentage of PMNs would be retrieved from more involved lobes, which affects results[20] as applied to some extent in our recent study in which BAL was performed from segments with an intermediate degree of radiologic involvement. It has been proposed that neutrophils may have a key role in fibrosing alveolitis in the early stages of lung disease[9]; a "switch" from inflammatory to fibrotic state[18] and even an influx of neutrophils occurs late in the course of advanced fibrosis.[11] The reduction of DLCO is related to bronchoalveolar lavage fluid (BALF) granulocytosis and DLCO values are considerably lower than BALF lymphocytosis and normal BAL.[2] Our study did not show any correlation between BAL findings and HRCT or PFT results due to the presence of a few patients with normal BALF results and with high percentages of abnormal BAL due to the lavage of affected segments. Although it seems that HRCT can not completely substitute for BAL in assessing inflammatory disease activity,[2] the role of BAL remains a subject of debate in decision making and treatment strategies.[13,15–17] BAL analysis could give important information about active inflammation, particularly in the early stages of SSc for treatment planning.[21] Its role in predicting prognosis is uncertain.[16,21] For example, in a retrospective study, patients with BAL eosinophilia had poor prognoses[7] whereas in a larger prospective study, no association between BAL eosinophilia and poor prognosis was seen.[13] In a prospective study, BAL neutrophilia neither determined the rate of functional and physiologic deterioration, nor the response to treatment.[13] In fact, BAL findings may be an epiphenomenon rather than pathogenically significant.[21] Nevertheless it is common practice to perform BAL in some centers for the identification of SSc patients who may benefit from immunosuppressive therapy.[21–23]

Treatment of SSc lung disease is largely empiric and there is no consensus to answer the questions of when and how to treat.[22] Additionally, due to the heterogenous groups of patients, both prognosis and response to treatment strategies are difficult to determine for each individual patient. It seems that the extensive honeycomb pattern carries a worse prognosis in comparison with other ILDs.[23] Many patients' pathologies are diagnostic of nonspecific interstitial pneumonitis (NSIP),[7] which appears to have a better prognosis than usual interstitial pneumonitis (UIP) when adjusted by age and functional parameters,[7] therefore SSFA has a better prognosis than idiopathic pulmonary fibrosis (cryptogenic alveolitis)[7] when match with age, sex, degree of involvement in HRCT, and PFT abnormality when compared to IPF (UIP pathology).

Our study did not show any correlation between symptoms, signs and HRCT findings. This may be partially due to different perceptions of dyspnea, the insidious nature of the disease and different progression patterns.

PFT indices decreased in parallel to the severity of HRCT grading in our study. HRCT is sensitive in detecting fibrosing alveolitis and is of morphological importance; it seems that with higher grade HRCT (III and IV) the absolute DLCO, TLC and FVC values decrease more than those seen with both normal and lower grade HRCT (I and II). Although these latter imaging and physiologic studies are

parallel and enable decision making, however determination of disease activity in a cross-section of time is impossible. Thus, additional follow up of physiologic and imaging studies may be necessary to assess prognosis and treatment response. The role of BAL may be in the detection of cellular components at a cross-section of time which can give information about the extent of disease and possible disease activity. The exact role of blood cells in the pathogenesis of SSFA is unknown, therefore it is difficult to explain BAL findings and their relationship with other diagnostic tests.

It seems that HRCT is useful for detecting early ILD and diagnosing SSFA, but it is prudent to say that HRCT may reflect some extents of disease severity. Perhaps it is insufficient for assessing severity, progression, course of disease, decision to treat, follow up and response to treatment, per se. For example some areas of ground glass appearance as seen on HRCT may not represent active inflammation and alveolitis, rather they may be established fibrotic areas.[2] It seems that SSFA has active and inactive phases. Thus, follow up of these patients may be completed by the addition of serial BALs instead of a single BAL during their course of disease. The addition and integration of HRCT and PFT enables better judgment for the type of cellular activity during the course of the disease as well as its prognostic and predictive significance.

Therefore HRCT findings should be completed and integrated with physiologic tests, perhaps by BAL results, particularly in instances where infection is a concern.[21]

In conclusion, our study has shown increased impairment of absolute DLCO, TLC, FVC values and their percentiles in cases of more disease severity as seen on HRCT. There is no correlation between radiologic and physiologic tests with BAL findings. It seems that non-invasive radiologic and physiologic tests of lung and diffusion capacities should be integrated and simultaneously interpreted for better decision making and more efficient treatment planning.

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