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# The disconnect between visual assessment of air trapping and lung physiology for assessment of small airway disease in scleroderma-related interstitial lung disease: An observation from the Scleroderma Lung Study II Cohort

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## Abstract

**Objective:** To explore the presence of small airway disease (SAD) and emphysema in scleroderma-related interstitial lung disease (SSc-ILD) and to evaluate the physiologic and clinical correlates of SAD in SSc-ILD.

**Methods:** Thoracic high-resolution computed tomography (HRCT) images obtained from the Scleroderma Lung Study II (SLSII) participants were reviewed by a group of thoracic radiologists. The presence of SAD was assessed by visual assessment for air trapping. HRCT scans were also evaluated for the presence of emphysema. The association of the presence of air trapping and emphysema with physiological measures of airway disease and clinical variables was evaluated.

**Results:** A total of 155 baseline HRCT scans were reviewed. For assessment of air trapping, images needed to be adequate end-expiratory examinations, leaving 123 scans. Air trapping was seen in 13/123 (10.6%) of the SSc-ILD cohort and was independent of smoking history, asthma or the presence of gastroesophageal reflux. Air trapping on HRCT was not associated with physiologic evidence of SAD. We also identified 8/155 (5.2%) patients with emphysema on HRCT, which was independent of SAD and found mostly in prior smokers.

**Conclusion:** We report the first study of air trapping on standardized, high-quality HRCT images as a reflection of SAD in a relatively large, well characterized SSc-ILD cohort. The presence of SAD in non-smoking SSc-ILD patients supports that SSc may cause not only restrictive lung disease (SSc-ILD), but also, to a lesser extent, obstructive disease. Physiologic measures alone may be inadequate to detect airway disease in patients with SSc-ILD.

## Keywords

Scleroderma, interstitial lung disease, small airway disease, emphysema, air trapping, systemic sclerosis

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## Introduction

Interstitial lung disease (ILD) is a leading cause of morbidity and mortality in systemic sclerosis (SSc) patients.[1] Airway involvement in SSc-related ILD (SSc-ILD) was suggested by widespread bronchiolectasis and peribronchial fibrosis in early autopsy studies.[2,3] However, reports are conflicting on the prevalence of large and small airway abnormalities in SSc-ILD, with little information regarding their clinical significance.[4–6]

High-resolution computed tomography (HRCT) is an important modality in characterizing SSc-ILD.[7,8] Antoniou showed 333 SSc-ILD patients, of which 12.3% had emphysema on HRCT.[9] While emphysema was present more often in current/former smokers (19.7%), it was also present in 7.5% of lifelong non-smokers. Similarly, Champtiaux reported emphysema in 7.6% of 131 SSc-ILD patients; 14% with concomitant emphysema were never smokers.[10] Finding emphysema in SSc-ILD, particularly among non-smokers, supports the long-standing suspicion that SSc-ILD may represent a restrictive parenchymal process but may also be associated with, albeit to a lesser extent, obstructive pulmonary disease. Parenchymal destruction causing emphysema is closely associated with, and often preceded by, intrinsic disease of the small airways in chronic obstructive pulmonary disease (COPD).[11,12] These studies raise important questions regarding obstructive pulmonary disease in SSc-ILD, including the presence of small airway disease (SAD). Further assessment of the prevalence of emphysematous changes on HRCT in never smokers with SSc-ILD is needed to account for the role of smoking in the development of emphysema in those patients with combined ILD and emphysema.

Scleroderma Lung Study II (SLS II) was a large multicenter clinical trial in patients with symptomatic SSc-ILD,[13] in which participants obtained volumetric thoracic HRCT scans at baseline. The aims of the current study were (1) to explore the presence of SAD and emphysema in SSc-ILD by systematic visual assessment of baseline HRCT scans of the SLS II participants and (2) to evaluate the physiologic and clinical correlates of SAD in SSc-ILD.

## Methods

### Patient selection

SLSII was a randomized, double-blind control trial of oral cyclophosphamide versus mycophenolate in patients from 14 U.S. medical centers with symptomatic SSc-ILD. The protocol was approved by a Data and Safety Monitoring Board, and by the institutional review boards at each participating site (UCLA IRB #11-002659, ethics review board approval information of 13 additional sites are included in supplementary file), and a written consent was obtained from all participants.[13] Inclusion required fulfillment of established criteria for limited or diffuse SSc,[14,15] dyspnea (Mahler Baseline Dyspnea Index (BDI) grade 2,[16] restrictive ventilatory impairment (forced vital capacity; FVC < 80%predicted), any ground glass opacity with or without associated reticulations (fibrosis), and the onset of the patient's first non-Raynaud's symptom of systemic sclerosis within the past 7 years.[13] Patients were excluded if they exhibited severe restriction (FVC < 45%predicted), severe impairment of diffusing capacity (DLCO < 40%predicted, or 30%–40%predicted in the absence of clinically significant pulmonary hypertension), substantial airflow obstruction (forced expiratory volume in 1 s ($FEV_1$) to FVC ratio < 65%), smoking within 6 months, significant abnormalities on HRCT not attributable to SSc, and scans not deemed technically acceptable (see below). We included acceptable screening HRCT studies from 13 subjects who were not randomized into the trial for the following reasons: absent/minimal ground glass opacities (n = 4), presence of pulmonary nodule(s) (n = 3), cardiomegaly (n = 1), and other reasons not HRCT-related (n = 5).

### HRCT scan protocol

All sites performed standardized thin section (< 1.25 mm) reduced dose (80–100 mAs) volumetric non-contrast HRCT scans at both suspended full inspiration and end-expiration in either prone or supine position. Images were acquired from 12 different credentialed multi-detector CT scanners from two manufacturers (GE medical system, Milwaukee, WI and Siemens, Erlangen, Germany) under strict quality control guidelines.

### HRCT image analysis

HRCT scans were reviewed by three thoracic radiologists (L.P., J.G., and F.A.). Scans not meeting the scan protocol specified above were excluded. Technical adequacy of expiratory scans was determined by inward bulging of the posterior tracheal wall and overall reduction in lung volumes and density. Scans with proximal airway disease evidenced by lobar and segmental air trapping with narrowed large airways were excluded.

The presence of SAD was assessed visually for the presence of air trapping by consensus of at least two radiologists. Scans were determined to have air trapping when they fulfilled the following criteria: (1) one or more regions of low attenuation in three adjacent lobules in expiratory images[17] and (2) persistent lucency and lack of volume reduction of the lobule when comparing an expiratory to an inspiratory image.[18]

To differentiate mosaic attenuation attributable to SAD, expiratory images are required. In SAD, air cannot readily escape in the regions where the small airways are obstructed and the attenuation of the involved segments remains relatively unchanged when compared to inspiratory images, making the difference in attenuation between the normal and abnormal areas more pronounced. In

patients without SAD, expiratory scans should show a relatively diffuse increase in attenuation and appear grayer.[19] Additional finding such as air space consolidation, pulmonary nodules, lung cysts, and large airway abnormalities were also assessed for.

We did not use quantitative CT scores for emphysema because the results were confounded by the coexistence of ILD and therefore not reliable. Instead, HRCT scans were visually evaluated for the presence of emphysema on the end-inspiratory exam. CT findings of emphysema are areas of decreased lung attenuation typically without visible walls. Centrilobular emphysema is characterized by destroyed centrilobular alveolar walls and enlargement of respiratory bronchioles and associated alveoli. Paraseptal emphysema has a peripheral distribution and is located adjacent to the pleura and septal lines.

### *Quantitative CT image analysis*

Quantitative scoring by texture-based computer-assisted diagnosis (CAD) system was used to report the extent of interstitial lung involvement on inspiratory HRCT images.[20] Scores were expressed as a percentage of whole lung and included scores for lung fibrosis (QLF), ground glass (QGG), and honeycombing (QHC). Quantitative interstitial lung disease (QILD) scores represent the total ILD pattern as the sum of all three scores (i.e. QLF + QGG + QHC). The CAD score has correlated with visual scoring systems[20] and predicts a decline in FVC in patients with SSc-ILD.[21]

### *Physiological assessment of small airway disease*

Pulmonary function test (PFT) equipment and procedures conformed to the standards of the ATS/ERS Task Force.[22–24] Gender and race-specific predicted spirometric values were calculated using the regression equations of Hankinson.[25] For assessment of SAD, the forced expiratory flow between 25% and 75% of the FVC ($FEF_{25\%–75\%}$) is commonly used.[26] An elevated residual volume (RV) at the end of expiration on body plethysmography also provides a sensitive measure of gas trapping,[5,27] a physiologic feature of SAD. Gender-specific predicted values for RV were calculated using regression equations of Crapo[28] with adjustments for African-Americans.[29] The RV to total lung capacity (RV/TLC) ratio is also a marker of gas trapping.[27] Predicted values were calculated using equations and adjustments recommended by Stocks.[30]

### *Clinical data*

While current smokers were excluded from SLSII, former smokers who quit >6 months before screening were included. Patients with substantial airflow obstruction (FEV1/FVC < 65% predicted) were excluded from the study, while patients with asthma with preserved FEV1/FVC were included.

Questionnaires included the following: (1) St. George's Respiratory Questionnaire (SGRQ) for defining significant cough (cough on several/most days of the week);[31] (2) Mahler's BDI for assessment of dyspnea;[32] and (3) the validated UCLA Scleroderma Clinical Trial Consortium gastrointestinal tract instrument 2.0 (GIT 2.0) for assessment of reflux (the presence of which correlates with endoscopy proven esophagitis and manometric abnormalities).[33,34]

### *Statistical analysis*

Baseline characteristics were compared between patients with or without visual air trapping and with or without emphysema using Wilcoxon rank sum tests for continuous variables and Chi-square tests or Fisher's exact tests for categorical variables. Associations between visual air trapping, physiologic SAD measures, and clinical variables were performed using Chi-square tests or Fisher's exact tests. Spearman rank correlations examined correlations between physiological measurements, quantitative radiological measures, and GIT 2.0 Reflux scores. Two-sided $p < 0.05$ was deemed significant. All statistical analyses were performed using STATA (v14.2, College Station, Texas).

## Results

Baseline HRCT scans from 155 patients were reviewed. Mean age was 53 (SD 10.1) years, 71% were female, mean disease duration was 2.4 years, and 65% had diffuse SSc (Table 1). All 155 scans were reviewed for emphysema using the end-inspiratory images (Figure 1). Of these 155, 32 were not assessed for air trapping for the following reasons: no end-expiratory exams performed (n = 5), not thin section volumetric scans (n = 2), end-expiratory exam was suboptimal (n = 22), and evidence of proximal airway disease (n = 3). Consequently, a total of 123 end-expiratory scans were assessed for air trapping (Figure 1).

### *Presence of obstructive airway disease*

SAD assessed by air trapping on HRCT was seen in 13/123 patients (10.6%; Figure 2). None of these cases demonstrated centrilobular nodularity (finding of hypersensitivity pneumonitis) or tree in bud nodularity (finding of bronchiolitis) to suggest an alternative etiology for air-trapping. Traction bronchiectasis/bronchiolectasis of segmental and subsegmental bronchi were seen in 133/152 patients (89.6%), as a manifestation of architectural distortion that accompanies fibrotic reticulation.

**Table 1.** Baseline characteristics of SSc-ILD cohort.

| Variables | Total (n = 155) | Visual Air trapping (N = 123) | | Emphysema (N = 155) | |
|---|---|---|---|---|---|
| | | Present (n = 13) | Absent (n = 110) | Present (n = 8) | Absent (n = 147) |
| Age, years† | 53.0 (10.1) | 60.7(11.6)* | 51.7(9.4) | 52.6(12.5) | 53.0(10.0) |
| Sex, N(%) | | | | | |
| Male | 42(27.1) | 2(15.4) | 34(30.9) | 5(62.5)** | 37(25.2) |
| Female | 110(71.0) | 11(84.6) | 74(67.3) | 3(37.5) | 107(72.8) |
| Missing | 3(1.9) | 0(0) | 2(1.8) | 0(0) | 3(2.0) |
| Duration of scleroderma, years | 2.4(1.7) | 3.0(2.0) | 2.2(1.6) | 3.1(1.5) | 2.3(1.7) |
| Scleroderma type | | | | | |
| Limited | 57(36.8) | 6(46.2) | 37(33.6) | 1(12.5) | 56(38.1) |
| Diffuse | 95(61.3) | 7(53.9) | 71(64.6) | 7(87.5) | 88(59.9) |
| Missing | 3(1.9) | 0(0) | 2(1.8) | 0(0) | 3(2.0) |
| Smoking, Ever | | | | | |
| Yes | 51(32.9) | 3(23.1) | 38(34.5) | 7(87.5)** | 44(29.9) |
| No | 101(65.2) | 10(76.9) | 70(63.6) | 1(12.5) | 100(68.0) |
| Missing | 3(1.9) | 0(0) | 2(1.8) | 0(0) | 3(2.0) |
| Pack-years | 10.4(15.0) | 0.9(0.8) | 12.0(16.5) | 24.4(21.6)** | 8.4(13.0) |
| Asthma, N(%) | | | | | |
| Yes | 11(7.1) | 1(7.7) | 9(8.2) | 0(0) | 11(7.5) |
| No | 144(92.9) | 12(92.3) | 101(91.8) | 8(100.0) | 136(92.5) |
| BDI (0–12)† | 7.17(2.2) | 7.6(1.7) | 7.0(2.2) | 5.7(3.3) | 7.2(2.1) |
| Cough, N(%) | | | | | |
| Yes | 131(84.5) | 10(76.9) | 93(84.6) | 5(62.5) | 126(85.7) |
| No | 5(3.2) | 1(7.7) | 4(3.6) | 0(0) | 5(3.4) |
| Missing | 19(12.3) | 2(15.4) | 13(11.8) | 3(37.5) | 16(10.9) |
| PFT‡ | | | | | |
| FVC %pred | 66.7(10.6) | 68.9(5.8) | 66.5(11.4) | 61.5(12.7) | 67.0(10.4) |
| FEV1 %pred | 70.2(11.4) | 73.8(7.3) | 69.7(12.0) | 63.9(10.7) | 70.5(11.3) |
| FEV1/FVC % | 83.2(5.6) | 82.8(4.0) | 83.0(6.1) | 82.5(9.5) | 83.2(5.8) |
| $FEF_{25\%–75\%}$, L/s | 2.4(1.0) | 2.5(0.5) | 2.4(1.0) | 2.2(1.0) | 2.4(1.0) |
| $FEF_{25\%–75\%}$ %pred | 86.1(36.5) | 109.0(36.5)* | 85.5(38.1) | 83.7(27.9) | 86.2(36.9) |
| $FEF_{25\%–75\%}$ % pred/TLC % pred | 133.6(64.4) | 156.3(60.5) | 134.6(68.0) | 131.0(42.0) | 133.7(65.2) |
| N(%) $FEF_{25\%–75\%} < LLN$ζ | 20(12.9) | 0(0) | 18(16.4) | 1(12.5) | 19(12.9) |
| TLC, L | 3.6(0.9) | 3.8(1.0) | 3.6(0.9) | 3.5(0.6) | 3.6(0.9) |
| TLC% pred | 66.4(11.5) | 71.1(6.9) | 65.5(11.4) | 64.1(9.6) | 66.5(11.5) |
| RV, L | 1.2(0.5) | 1.3(0.6) | 1.2(0.5) | 1.1(0.3) | 1.2(0.5) |
| RV/TLC, % | 32.9(9.2) | 34.2(7.8) | 32.2(8.9) | 32.3(3.9) | 32.9(9.3) |
| RV % pred | 63.6(23.8) | 65.0(19.1) | 62.3(22.3) | 59.4(13.1) | 63.7(24.0) |
| RV/TLC % pred | 90.81(24.1) | 87.1(15.0) | 90.2(23.6) | 92.7(12.1) | 90.7(24.4) |
| RV %pred/TLC % pred§ | 93.9(25.1) | 90.5(18.1) | 93.5(24.8) | 96.0(13.3) | 93.9(25.4) |
| DLCO % pred | 54.1(14.0) | 59.0(15.4) | 53.8(14.0) | 51.7(17.5) | 54.2(13.9) |
| HRCT visual assessment | | | | | |
| Ground Glass | | | | | |
| Present | 148(95.5) | 11(84.6) | 106(96.4) | 8(100.0) | 140(95.2) |
| Absent | 7(4.5) | 2(15.4) | 4(3.6) | 0(0) | 7(4.8) |
| Fibrosis | | | | | |
| Present | 146(94.2) | 11(84.6) | 103(93.6) | 7(87.5) | 139(94.6) |
| Absent | 9(5.8) | 2(15.4) | 7(6.4) | 1(12.5) | 8(5.4) |
| Honeycombing | | | | | |
| Present | 5(3.2) | 1(7.7) | 2(1.8) | 8(100.0) | 5(3.4) |
| Absent | 150(96.8) | 12(92.3) | 108(98.2) | 0(0) | 142(96.6) |
| Architectural distortion/traction bronchiolectasis | | | | | |
| Present | 133(85.8) | 9(69.2) | 95(86.4) | 6(75.0) | 127(86.4) |
| Absent | 22(14.2) | 4(30.7) | 15(13.6) | 2(25.0) | 20(13.6) |

*(Continued)*

**Table 1.** (Continued)

| Variables | Total (n = 155) | Visual Air trapping (N = 123) | | Emphysema (N = 155) | |
|---|---|---|---|---|---|
| | | Present (n = 13) | Absent (n = 110) | Present (n = 8) | Absent (n = 147) |
| Emphysema | | | | – | – |
| Present | 8(5.2) | 0(0) | 7(6.4) | – | – |
| Absent | 147(94.8) | 13(100.0) | 103(93.6) | – | – |
| CAD quantitative score, % whole lung¶ | | | | | |
| Ground Glass | 19.3(8.6) | 20.4(9.1) | 19.1(8.3) | 13.9(9.0) | 19.4(8.6) |
| Fibrosis | 8.2(7.0) | 8.7(11.6) | 7.7(6.4) | 12.3(10.9) | 8.1(7.0) |
| Honeycomb | 0.1(0.6) | 0.3(0.7)* | 0.0(0.0) | 0.0(0.0) | 0.1(0.6) |
| QILD | 27.5(13.3) | 29.3(19.8) | 26.8(12.5) | 26.3(20.0) | 27.6(13.2) |
| Medications | | | | | |
| Inhaled bronchodilators | 7(4.5) | 1(7.7) | 4(3.6) | 0(0) | 7(4.8) |
| Inhaled steroids | 8(5.2) | 0(0) | 7(6.4) | 0(0) | 8(5.4) |
| Systemic steroids | 41(26.5) | 3(23.1) | 30(27.3) | 1(12.5) | 40(27.2) |
| Immunomodulatory drugs | 23(14.8) | 2(15.4) | 18(16.4) | 1(12.5) | 22(15.0) |
| Mycophenolate | 1(0.7) | 0(0) | 1(0.9) | 0(0) | 1(0.7) |
| Azathioprine | 2(1.3) | 0(0) | 2(1.8) | 0(0) | 2(1.4) |
| Methotrexate | 7(4.5) | 1(7.7) | 5(4.6) | 1(12.5) | 6(4.1) |
| Other | 13(8.4) | 1(7.7) | 10(9.1) | 0(0) | 13(8.8) |

Values reported as Mean (SD) or N(%) unless specified.
*$p < 0.05$ between visual air trapping present vs absent.
†.N = 132.
‡N = 135 for FEF2575, RV, N = 136 for TLC.
ζLLN of $FEF_{25\%–75\%}$ calculated using the global lung function initiative equation.[47]
§Predicted values for RV and TLC using equation presented in Stocks and Quanjer.[30]
¶N = 95.
Abbreviations: BDI, baseline dyspnea index; TLC, total lung capacity; RV, residual volume; %pred, % predicted; $FEF_{25\%–75\%}$, forced expiratory volume 25% to 75%; LLN, lower limit of normal; CAD, computer-aided diagnosis; QILD, quantitative ILD score.

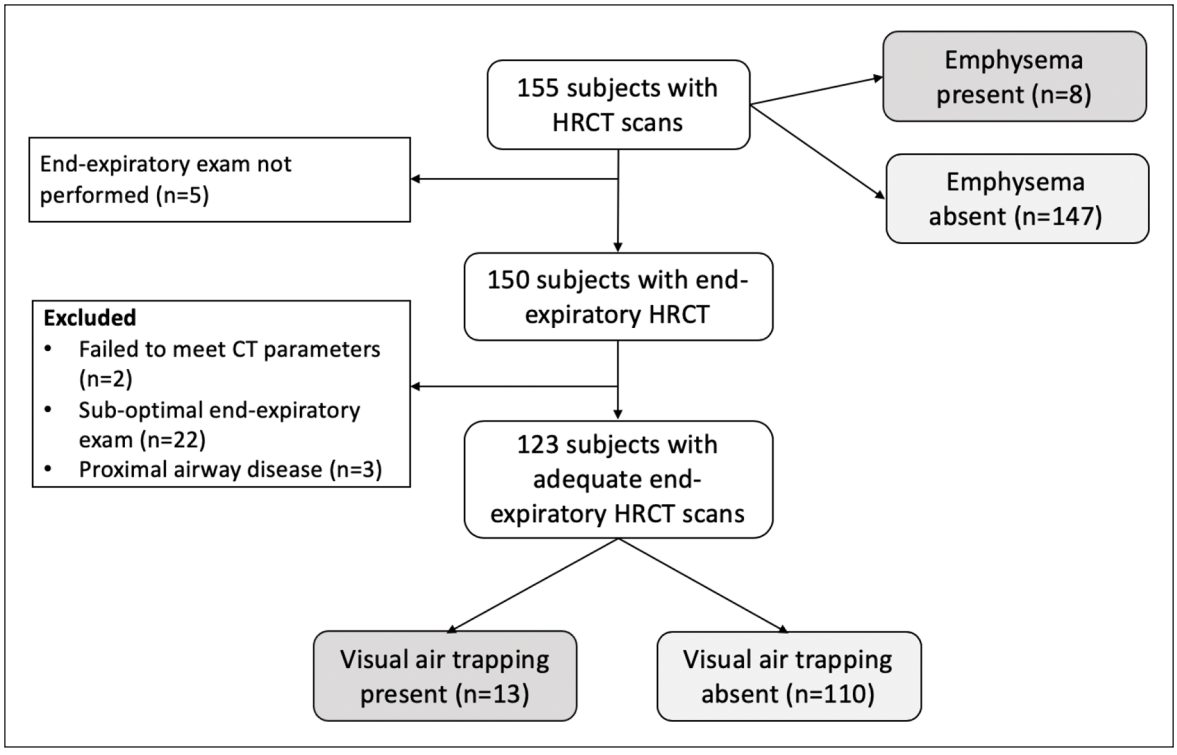


**Figure 1.** Flowchart of subjects.
Flowchart of selected HRCT scans assessed for visual air trapping and emphysema.

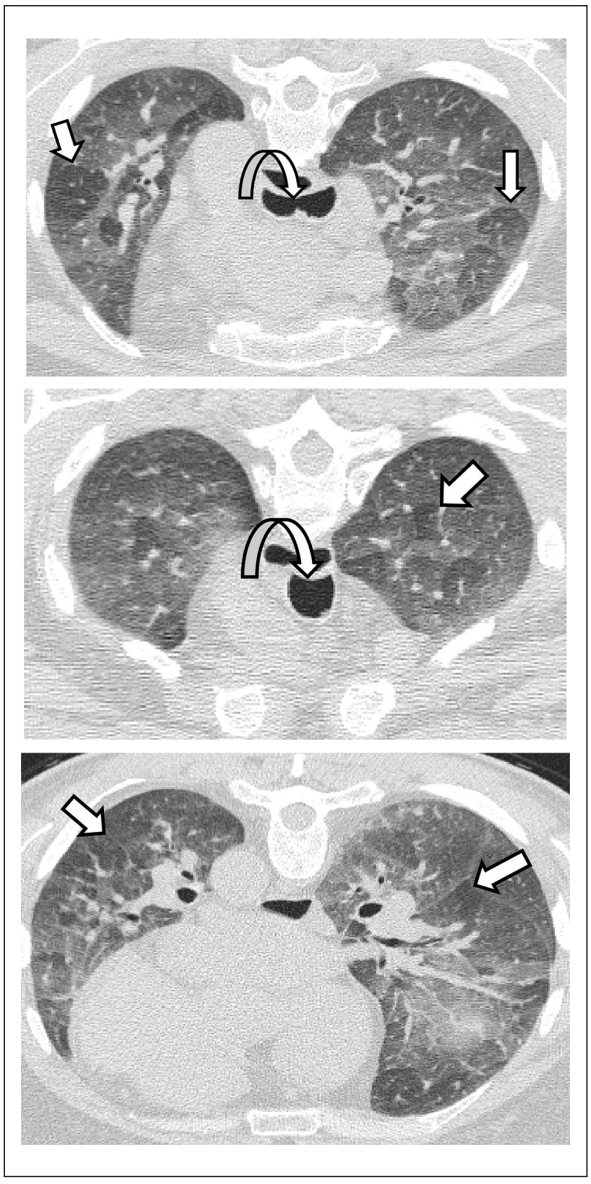

**Figure 2.** Example of visual air trapping on HRCT in an SLS II subject.
CT scan obtained at maximal expiration shows inward bulging of the posterior tracheal wall (curved arrows) with extensive areas of air trapping (straight arrows). Air trapping was seen in 10.6% of cases (13 of 123 patients).

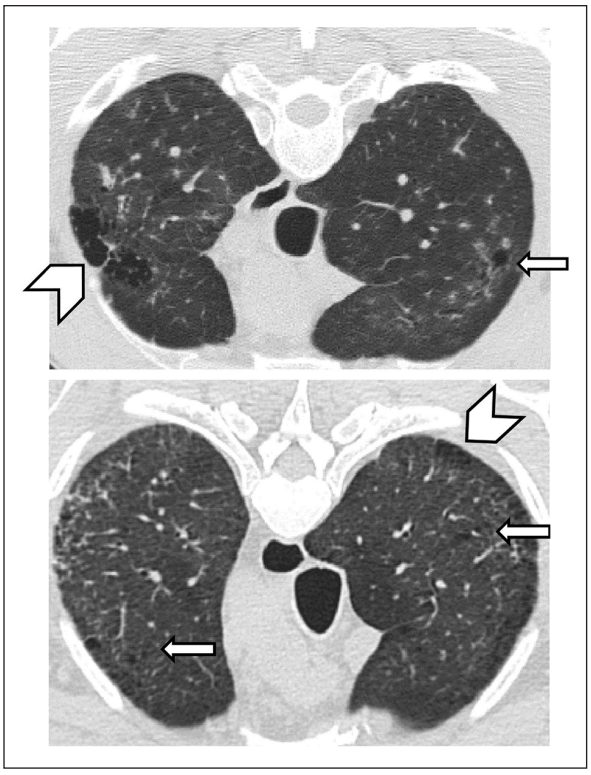

**Figure 3.** Example of emphysema on end-expiratory HRCT scan in an SLS II subject.
Emphysema was seen in 5.2% of cases (8 of 155 patients). Axial CT images of upper lung demonstrate areas of paraseptal emphysema (chevron) and centrilobular emphysema (arrow).

At baseline, patients with air trapping were significantly older ($p=0.004$), had a paradoxically higher $FEF_{25\%–75\%}$ and had a slightly higher QHC score compared to the 110 patients without air trapping. Both groups were similar in all other baseline characteristics, including quantitative HRCT-ILD scores and FVC% predicted (Table 1). Concurrent asthma was similar between the two groups as was use of bronchodilators and inhaled and systemic corticosteroids. Among the patients with air trapping, 10/13 (77%) were lifelong nonsmokers, and there was no association between smoking history and air trapping. HRCT demonstrated that most patients with air trapping had architectural distortion with traction bronchiectasis (69%) and fibrosis (85%) but minimal honeycombing (8%; Table 1). None of the patients with visual air trapping had concurrent emphysema.

Quantitative CAD scores for ILD did not separate those *with* from those *without* visual air trapping. Although quantitative honeycombing scores were statistically higher in the group with visual air trapping ($p=0.02$), the scores were very low in both groups.

## *Presence and extent of emphysema*

Eight of 155 patients (5.2%) had emphysema by visual assessment. Emphysema was trace to mild (<5% of lung parenchyma) and predominantly involved the upper lung zones. Emphysema was paraseptal in 6/8 patients, centrilobular in 1/8, and both paraseptal and centrilobular in 1/8 patients (Figure 3). No differences were seen in demographics or scleroderma duration or subtype (limited or diffuse) between patients with and without emphysema. All but one of the patients with emphysema had a smoking history and none had a history of asthma. Quantitative CAD scores showed no significant difference between patients with and without emphysema ($p=$NS for all; Table 1).

**Table 2.** Association between visual air trapping on HRCT and physiologic measures of small airway disease.

| | RV% predicted | | | RV/TLC% predicted | | | FEF25%–75% predicted | | |
|---|---|---|---|---|---|---|---|---|---|
| | >120% (n=0) | Normal (n=107) | p | >120% (n=9) | Normal (n=98) | p | <80% (n=53) | Normal (n=53) | p |
| Visual air trapping | | | | | | | | | |
| Present | 0(0) | 11(10.3) | – | 0(0) | 11(11.2) | 0.70 | 2(3.8) | 9(17.0) | 0.05 |
| Absent | 0(0) | 96(89.7) | | 9(100.0) | 87(88.8) | | 51(96.2) | 44(83.0) | |

Among a total of 123 patients assessed for visual air trapping on HRCT, PFTs with RV, RV/TLC, and $FEF_{25\%–75\%}$ were available in 107, 106, and 106 patients, respectively.

### *Effect of air trapping on lung physiology*

We explored three physiologic indices commonly used to reflect small airway function: $FEF_{25\%–75\%}$, RV, and RV/TLC. Among 135 patients with PFTs available, those with visual air trapping had a significantly (and paradoxically) higher mean $FEF_{25\%–75\%}$ ($p=0.01$), a numerically higher mean RV, and a lower RV/TLC (p=NS for both) versus those without visual air trapping (Table 1). Patients with visual air trapping had a higher TLC, contributing to their lower RV/TLC.

To assess the proportion of patients who had both PFTs consistent with SAD and visual evidence of air trapping, we dichotomized the PFTs using the following thresholds for abnormality: RV > 120% predicted, RV/TLC > 120% predicted, and $FEF_{25\%–75\%}$ <80% predicted (Table 2). We identified no patients with an elevated RV, 9 patients (8.4%) with an elevated RV/TLC, and 53 patients (50%) with decreased $FEF_{25\%–75\%}$. No patients with SAD by PFT were concordant with patients with visual air trapping on HRCT (Table 2). Given the existing restrictive disease, we have also performed the analysis using a lower RV threshold of >100% predicted which produced similar results (data not included).

When we compared clinical characteristics between patients with PFT-assessed SAD to those without SAD, there were no significant differences in smoking history, emphysema on HRCT, history of asthma, or the extent of ILD by quantitative HRCT scores (Table 3).

### *Association of visual air trapping on HRCT with clinical symptoms*

We examined the relationship of visual air trapping with patient reported measures for cough (on SGRQ) and dyspnea (Mahler BDI) at baseline. Neither cough nor degree of dyspnea were different, comparing patients with or without visual air trapping on HRCT (Table 3). Furthermore, given the suspected association of gastroesophageal reflux with fibrotic lung damage,[35,36] we also explored reflux scores in patients with and without SAD, and again no differences were found. Higher reflux scores correlated with worse dyspnea ($r=-0.3$, $p=0.001$), suggesting that severe reflux may contribute to breathlessness, but neither dyspnea nor reflux scores correlated with air trapping on HRCT. None of the patient with PFTs consistent with SAD showed significant differences in cough, BDI or reflux when compared to those without SAD-associated PFTs (Table 3).

## Discussion

Inflammation and fibrosis of the large and small airways has been noted in early autopsy studies of patients with SSc,[3,37] and obstructive ventilatory defects, either alone or in combination with restrictive ventilatory impairment, have been seen in small SSc cohorts.[38,39] A few recent studies described emphysema on HRCT in SSc-ILD,[9,10] as well as in surgical biopsies (prevalence: 7.6%–76%).[40] Although smoking is typically the major cause of emphysema, the aforementioned studies characterized 7%–48% of SSc patients with emphysema as lifelong nonsmokers. The latter findings support the long-standing suspicion that SSc-ILD may cause not only restrictive, but also obstructive pulmonary disease, independent of smoking.

We investigated the presence of air-trapping and emphysema on HRCT scans of 123 and 155 participants, respectively, from the SLSII trial. We found 13/123 (10.6%) patients with visual air trapping consistent with SAD and 8/155 (5.2%) patients with visual evidence of emphysema. SAD was not attributable to smoking, asthma, or reflux. In fact, patients with visual air trapping were mostly (10/13) never smokers. Thus, it possible that SSc-ILD may be a risk factor for intrinsic SAD even in the absence of prior or current smoking. However, 7/8 patients with visual evidence of emphysema were prior smokers. Moreover, none of the patients with emphysema had a history of asthma, another recognized risk factor for the subsequent development of emphysema.[41]

Prior studies that investigated the presence of SAD in SSc using physiologic measures report conflicting results. Guttaduria et al.[5] reported PFT results in 45 SSc patients and found that 42% of their patients had evidence of SAD as suggested by an isolated elevated RV > 120%, without either restrictive (reduced TLC and VC < 80%) or large airways obstruction (FEV1/FVC < 70%). In contrast to our population, the latter study included patients with obstructive

**Table 3.** Clinical characteristics by measures of small airway disease.

| | Visual air trapping | | RV% predicted | | RV/TLC% predicted | | $FEF_{25\%–75\%}$ predicted | |
|---|---|---|---|---|---|---|---|---|
| | Present (n = 13) | Absent (n = 110) | >120% (n = 0) | Normal (n = 107) | >120% (n = 9) | Normal (n = 98) | <80% (n = 53) | Normal (n = 53) |
| Smoking | | | | | | | | |
| Ever | 3(23.1) | 38(35.2) | 0(0) | 37(34.6) | 2(22.2) | 35(35.7) | 18(34.0) | 19(35.8) |
| Never | 10(76.9) | 70(64.8) | 0(0) | 70(64.4) | 7(77.8) | 63(64.3) | 35(66.0) | 34(64.2) |
| Missing | 0(0) | 2(1.8) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) |
| Emphysema | | | | | | | | |
| Present | 0(0) | 7(6.4) | 0(0) | 4(3.7) | 0(0) | 4(4.1) | 2(3.8) | 2(3.8) |
| Absent | 13(100.0) | 103(93.6) | 0(0) | 103(96.3) | 9(100.0) | 94(95.9) | 51(96.2) | 51(96.2) |
| History of asthma | | | | | | | | |
| Yes | 1(7.7) | 9(8.2) | 0(0) | 9(8.4) | 1(11.1) | 8(8.2) | 8(15.1) | 1(1.9) |
| No | 12(92.3) | 101(91.8) | 0(0) | 98(91.6) | 8(88.9) | 90(91.8) | 45(84.9) | 52(98.1) |
| CAD quantitative score, % Whole lung† | | | | | | | | |
| QLF | 8.7(11.6) | 7.7(6.4) | – | 7.8(7.0) | 7.5(5.6) | 7.9(7.1) | 7.1(6.3) | 8.5(7.6) |
| QILD | 29.3(19.8) | 26.3(12.5) | – | 27.1(13.2) | 27.3(10.3) | 27.0(13.5) | 25.1(12.4) | 29.5(14.1) |
| Cough | | | | | | | | |
| Present | 10(76.9) | 93(84.6) | 0(0) | 103(96.3) | 8(88.9) | 95(96.9) | 51(96.2) | 51(96.2) |
| Absent | 1(7.7) | 4(3.6) | 0(0) | 4(3.7) | 1(11.1) | 3(3.1) | 2(3.8) | 2(3.8) |
| Missing | 2(15.4) | 13(11.8) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) |
| BDI‡ | 7.6(1.7) | 7.0(2.2) | – | 7.0(2.2) | 7.3(1.4) | 7.0(2.3) | 7.0(2.4) | 7.1(2.0) |
| Reflux, GIT 2.0¶ | | | | | | | | |
| Normal to mild | 6(46.2) | 37(33.6) | 0(0) | 43(40.2) | 2(22.2) | 41(44.1) | 20(37.7) | 23(43.4) |
| Moderate to severe | 5(38.5) | 55(50.0) | 0(0) | 59(55.1) | 7(77.8) | 52(55.9) | 31(58.5) | 27(50.9) |
| Missing | 2(15.4) | 18(16.4) | 0(0) | 0(0) | 0(0) | 5(5.1) | 2(3.8) | 3(5.7) |

Values reported as mean (SD) or N(%) unless specified.
p value = NS for all.
†N = 95.
‡N = 132.
¶GIT score normal to mild (0.00–0.48) and moderate to severe 0.50–3.00.
Abbreviations: BDI, basic dyspnea index; GIT 2.0, UCLA scleroderma clinical trial consortium gastrointestinal tract instrument 2.

disease (3 patients with FEV1/FVC < 65%) and smokers (31%) and found the prevalence of smoking to be numerically higher in SAD patients when compared to patients with restrictive or obstructive disease. The authors proposed that the elevated RV was an early marker of SSc pulmonary involvement due to intrinsic SAD. In contrast, Bjerke et al. evaluated several physiologic indices of SAD, including $FEF_{25\%–75\%}$, single-breath nitrogen washout, closing volume, closing capacity, and delta maximal expiratory flow at 50% of the FVC between air and helium-oxygen maximal expiratory flow-volume curves in 39 SSc patients. The study of Bjerke et al. included younger patients (mean age 47 vs 53 years in current study) of whom 44% were smokers, and none had substantial obstructive disease. They found that smokers frequently had abnormalities in multiple physiologic measures of SAD while non-smokers most often had normal results. They concluded that SSc itself generally does not lead to functional evidence of SAD, and that the presence of SAD that was found was usually attributable to smoking.[4]

In our current study, we investigated PFT parameters traditionally used to evaluate SAD, including $FEF_{25\%–75\%}$, RV, and RV/TLC, and found that physiologic evidence of SAD was generally lacking in our SSc-ILD patients, even when there was visual evidence of air trapping on imaging. It is important to note that the two aforementioned studies[4,5] were conducted before HRCT imaging was readily available and also included SSc patients without obvious spirometric or chest roentgenographic evidence of interstitial involvement in the population assessed. Therefore, the current study provides more direct assessment of SAD specifically in SSc-ILD.

The absence of physiologic evidence of SAD in the current SSc-ILD cohort may be due to the fact that physiologic measures of SAD can be influenced by the presence of concurrent restrictive lung disease. For example, $FEF_{25\%–75\%}$ is highly volume dependent so that this measurement in patients with restrictive ventilatory disorders may be spuriously reduced simply due to the reduced vital capacity. Other sensitive measures of small airways involvement, such as instantaneous maximum expiratory flow at 50% or 75% of expired volume (not assessed in the current study), would be expected to be similarly affected by the presence of restrictive ventilatory impairment. However, the presence of ILD is associated with reduced

lung compliance that can lead to tethering of the small airways by the surrounding lung parenchyma, thereby increasing their patency and potentially elevating the $FEF_{25\%–75\%}$, as well as other volume-dependent spirometric measures of SAD. This was previously demonstrated for another measure of airflow obstruction, the FEV1/FVC ratio, which is often elevated in SSc-ILD. Thus, while a decreased $FEF_{25\%–75\%}$ typically indicates obstruction of the small airways, it may not be a reliable physiologic indicator of SAD in ILD. The reduced lung volume and lung compliance from fibrosis also has a confounding effect on the plethysmographic assessments of lung volumes (RV, RV/TLC). While an elevated RV and RV/TLC ratio is suggestive of air trapping in obstructive lung disease, reduced lung compliance can lower the RV. However, an elevated RV could be due to causes other than air-trapping from SAD, such as submaximal expiratory effort, expiratory muscle weakness, and/or decreased chest wall compliance due to strapping of the chest by thickened skin. Finally, TLC is generally low in SSc-ILD, potentially contributing to a spuriously elevated RV/TLC ratio. Despite our attempts to adjust the PFT results to account for the reduced lung volume, the results remained discordant with the findings on HRCT.

In contrast to the physiologic measures of SAD, visual air trapping assessed on HRCT images would not be masked by restrictive lung disease and therefore is a useful tool to assess SAD in SSc-ILD. In contrast to normal or non-pathologic air trapping, which is typically confined to a few lobules and most marked in dependent lung areas, air trapping from SAD affects multiple lobules, frequently extending beyond the lung bases, and is always more prominent in expiratory scans.[42]

We identified emphysema on HRCT in 8/155 patients (5.2%), none of whom had HRCT evidence of SAD. Emphysema in our current study was mostly paraseptal, involving the upper lobes. Combined pulmonary fibrosis and emphysema (CPFE), defined as the association of significant (usually moderate to severe) emphysema in upper lung zones and pulmonary fibrosis in lower lobes, has been described in connective tissue diseases, including SSc,[9,10,43] as well as related to smoking and idiopathic pulmonary fibrosis.[44] The prevalence of CPFE in SSc-ILD has been reported as 8%–12% depending on the definition of "significant" emphysema (reported mean extent was 5.5%–15% of lung surface).[9,10] In contrast, another recent observational cohort of 170 SSc-ILD patients reported the prevalence of emphysema that involved >10% of the total lung surface as only 1%.[45,46] Our current report revealed a somewhat lower prevalence of emphysema (5.2%) compared to initial studies, and the extent of emphysema was mild on visual assessment (<5% of lung surface). The lower prevalence and milder extent of emphysema and lack of centrilobular emphysema in our current study may be explained by the SLSII trial design which excluded recent/current smokers, or patients with overt obstructive lung disease (FEV1/FVC < 65%). The trial also excluded patients with severe diffusion impairment, which is frequently a hallmark of CPFE.

Unlike patients with SAD, most patients with emphysema in our study had a prior history of smoking, suggesting that emphysema likely has a stronger association with smoking history than SSc-ILD. It is important to note that the current study excluded patients with obvious obstructive lung disease which may have led to the exclusion of patients with emphysema on HRCT. However, there is some evidence to suggest that emphysema in SSc-ILD, particularly among never smokers, may be a distinct pulmonary manifestation. A study examining surgical biopsy specimens of SSc-ILD identified 16/21 patients (6 smokers, 10 lifelong non-smokers) with pathological emphysematous changes.[40] Emphysematous SSc-ILD was histologically different from the usual smoking-related form, presenting mainly destruction of fibrously thickened alveolar walls, resulting in abnormal dilatation of the alveolar lumina and alveolar ducts, unlike smoking-related emphysema which presents as destructive holes in secondary lobules. Further studies are warranted to assess the possible association between emphysema and SSc-ILD in non-smokers.

The presence of SAD and emphysema in our SSc-ILD cohort had minimal impact on clinical symptoms. These patients did not have worse cough, dyspnea, or reflux compared to patients without SAD or emphysema. In contrast, a recent report of SSc patients demonstrated patients with CPFE were more symptomatic with increased dyspnea and hypoxemia compared to SSc-ILD patients without emphysema.[10] The dissimilarity of our findings may be explained by the fact that the magnitude of SAD and emphysema was relatively small in our study which may be related to the exclusion of current/recent smokers and those with significantly reduced $FEV_1$/FVC.

Our current work has certain limitations. The cohort analyzed was from a randomized clinical trial which limited the sample population to patients who met the inclusion and exclusion criteria. Although this trial design allowed for separation of the effects of current smoking from SAD (by the exclusion of current smokers or patients with overt obstructive disease), it also likely impacted the prevalence of air trapping and emphysema (especially centrilobular emphysema). Exclusion of patients with obvious obstructive ventilatory impairment makes the data insufficient to describe the association of SSc-ILD with peripheral obstructive ventilatory impairment due to emphysema or asthma. Also, patients with severe diffusion impairment, which can be seen in severe ILD as well as in CPFE, were excluded. Thus, our patients may not be entirely representative of the general population of patients with SSc-ILD and further studies in SSc-ILD cohorts without the aforementioned exclusion criteria may be warranted.

Notable strengths of the present study include the use of a relatively large, well characterized SSc-ILD cohort, with standardized high-quality imaging studies and uniform PFT measurements. The exclusion of smoking, while a limitation with respect to representativeness, is also a strength as it allows some ability to separate the effects of smoking from that of SSc on SAD. The SLSII cohort was recruited from multiple SSc centers of excellence located throughout the United States and thus is geographically representative of SSc patients in the United States.

In conclusion, the current study is the first report to identify evidence of air trapping on HRCT as a reflection of SAD in a relatively large cohort of SSc-ILD patients. The prevalence of air trapping was modest (10.6%), independent of smoking or gastroesophageal reflux, and was not associated with physiologic evidence of SAD or worse clinical symptoms. Therefore, physiologic measures alone may not be adequate to evaluate intrinsic airway disease in SSc-ILD patients. We also identified 5.2% of patients with visual evidence of emphysema, which was independent of air trapping and, unlike SAD, was almost exclusively in prior smokers. While future studies are warranted to further evaluate the presence of airway disease and its clinical implications in SSc, our study supports a minimal impact of SAD in SSc-ILD when patients do not smoke. It continues to support encouraging smoking cessation in SSc-ILD patients who smoke.

## Authors' note

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## Supplemenal material

Supplemental material for this article is available online.

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