Association of Gastroesophageal Factors and Worsening of Forced Vital Capacity in Systemic Sclerosis

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ABSTRACT. ***Objective.*** Interstitial lung disease (ILD) is a common complication of systemic sclerosis (SSc) and causes death. Once lung fibrosis occurs, disease course may become stable or decline. Little is known about risks for progression. We studied SSc–gastroesophageal (GE) involvement in relation to worsening forced vital capacity (FVC) on pulmonary function tests (PFT) to investigate whether it was related to progression. Our objective was to determine whether GE reflux and dysphagia are associated with progressive moderate/severe ILD as measured by PFT over 3 years.

Methods. The Canadian Scleroderma Research Group is a multicenter SSc database that collects data annually. Using indicators of GE involvement and annual PFT, comparisons were made between no/mild ILD, stable moderate/severe ILD, and progressive moderate/severe ILD groups based on changes of FVC. Multivariate analyses determined associations between GE factors and ILD development and progression.

Results. There were 1043 patients with SSc (mean age 55.7 yrs, mean disease duration 10.8 yrs); one-quarter had pulmonary fibrosis on chest radiograph that was related to FVC percentage predicted (Spearman's rho –0.39; p < 0.01). Physician indicators such as esophageal dysmotility (p = 0.009) and postesophageal dilatation (p = 0.041), and patient indicators such as difficulty swallowing (p = 0.016) and waking up choking (p = 0.026) were associated with low FVC. In comparing progressive and stable moderate/severe FVC (< 70% predicted), early satiety (p = 0.018) and a combination term of postdilatation and choking (p = 0.042) increased risk of progression of ILD. Topoisomerase I was not associated with progression over followup.

Conclusion. Symptoms of esophageal dysmotility were associated with worsening FVC in SSc, especially if both need for esophageal dilatation and choking were present. (First Release April 1 2013; J Rheumatol 2013;40:850–8; doi:10.3899/jrheum.120705)

Key Indexing Terms:
SYSTEMIC SCLEROSIS   SCLERODERMA   INTERSTITIAL LUNG DISEASE
PULMONARY FIBROSIS   GASTROESOPHAGEAL REFLUX DISEASE   DYSPHAGIA

Systemic sclerosis (SSc) is a multisystem disease characterized by chronic inflammation, vascular abnormalities, and fibrosis in the skin, kidneys, gastrointestinal (GI) tract, heart and lungs[1,2,3]. There are 2 main subtypes: limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc)[4]. Internal organ involvement (such as pulmonary fibrosis, renal crisis, and cardiomyopathy) is increased in dcSSc; and with earlier and more serious organ involvement[5]. In contrast, Raynaud phenomenon (RP) and GI involvement [gastroesophageal reflux disease (GERD) and esophageal dysmotility] are frequent in both subsets[6,7].

Fibrosis of lung parenchyma results in restrictive interstitial lung disease (SSc-ILD), and is a leading contributor to mortality[8,9,10,11]; about 40% of cases of dcSSc have pulmonary fibrosis on chest radiograph and 17% of lcSSc[12]. Not all patients experience the same disease trajectory for SSc-ILD; some progress to endstage pulmonary fibrosis, others stabilize[3]. Clinical features associated with development of SSc-related ILD include topoisomerase I antibody (topo I or Scl70), dcSSc subset, elevated erythrocyte sedimentation rate (ESR), and digital ulcerations[3,5,12]. Recently, topo I was shown to be predictive of lung function decline in SSc as measured by forced vital capacity (FVC)[13]. Within the first 3 years from disease onset, FVC% predicted was associated with later deterioration[14]. FVC may be related to conditions other than parenchymal disease including respiratory muscle weakness, scleroderma skin involvement of the thorax in the dcSSc subset, and poor performance on pulmonary function testing (PFT).

Esophageal dysmotility and GERD may contribute to the development and exacerbation of SSc-ILD through microaspiration[15,16,17,18,19]. However, not all studies agree[20]. Studying the relationship between esophageal involvement and restriction on PFT is of interest because esophageal involvement is a common manifestation of SSc, affecting 50%–90% of cases, but is not severe in all[21,22,23]. Potential treatments exist to prevent severe reflux and aspiration, so determining whether there is an association between dysphagia and/or GERD and SSc-ILD is important.

The objective of our study was to determine whether GERD and dysphagia are associated with progressive moderate/severe FVC changes as measured over 3 years. This change in FVC could be a surrogate for pulmonary fibrosis (restrictive lung disease), but is not specific for pulmonary fibrosis/ILD because low FVC is nonspecific, particularly in SSc, where other extraparenchymal problems can be present.

MATERIALS AND METHODS

The Canadian Scleroderma Research Group (CSRG) comprises 15 sites that enroll adult patients with SSc (both prevalent and incident). Enrollment requires a diagnosis of SSc by a rheumatologist (about 90% meet the preliminary American College of Rheumatology criteria and some with lcSSc do not)[1,4,24]. All sites have approval of their institutional review board, with written informed consent from all participants. Patients are followed annually with a history (including need for esophageal dilatation, GERD medications, smoking status, and several GI questions), examination [including modified Rodnan skin score (mRSS)], and routine investigations (including annual PFT).

The CSRG has data for 1043 patients. Inclusion criteria for this study required that patients had ≥ 3 consecutive annual visits with available annual PFT for > 3 visits. FVC was used as an indicator of ILD severity or a restrictive defect of pulmonary function, while changes in FVC were used to reflect progression/stability[3]. Patients were organized into 3 groups according to FVC severity: those with no/mild reduction in FVC at baseline and followup (Group 1: FVC% predicted ≥ 70%); those with stable moderate/severe FVC (Group 2: FVC% predicted < 70% with a decrease in lung function of < 5% between any 2 consecutive visits or an overall net decrease of < 3% over the 2 years); and those with progressive moderate/severe FVC (Group 3: FVC% predicted < 70%, with a decrease in lung function ≥ 5% over any 2 consecutive visits and an overall decrease ≥ 3% over the 2 years). If patients satisfied these definitions over > 1 consecutive 3-visit period, the period in which there was the greatest drop in FVC between 3 consecutive visits was chosen.

Because restrictive lung disease is not an either-or condition but exists on a spectrum, we wanted to confirm that there was sufficient contrast between those whom we defined to have PFT restriction and those who did not. We used a cutoff of FVC% predicted above 70% to define the group with no/mild restriction (Group 1) and those with moderate/severe restriction (Groups 2 and 3)[3,14,25,26] to establish contrast between no/mild restriction and moderate/severe restriction for binary comparisons. For progression of ILD, a 5% decrease in FVC% predicted between 2 consecutive visits and/or a 3% overall drop over 3 years was considered important. We chose a decrease of 5% as it represents a relative decrease of 7% for patients with baseline FVC% predicted of 70%, and a 10% change if baseline FVC% predicted was 50%. Within the scleroderma lung study of active ILD, the mean change in placebo in FVC over 1 year was < 3%, so the feasibility of a study with a larger decrease and having an adequate sample size was unlikely[27]. The 5% change for Groups 2 and 3 was greater than the within-patient measurement error for FVC. A net decrease of 3%

between visits 1 and 3 was required to ensure that Groups 2 and 3 represented progressive moderate/severe restriction, so if someone had a decrease in FVC% predicted of 6% at one visit and then increased by 8% at the next visit, they would not be included in the group having progressive moderate/severe ILD.

Several indicators of gastroesophageal (GE) involvement were recorded, including the results of procedures and physician and patient completion of case report forms. Physicians were asked annually to indicate whether the patient experienced esophageal dysmotility (ever at baseline visit; and within the last month on subsequent followup visits), and if an esophageal dilatation had occurred. Esophageal dysmotility in SSc is defined as food sticking in the retrosternal area and/or lack of coordinated swallowing. Patients were asked annually using a standardized questionnaire if they experienced esophageal dysmotility and/or GERD (if ever at baseline visit; and within the last month for followups); if they had difficulty swallowing, had regurgitation of food or acid-tasting liquid into the mouth or nose (food/acid reflux), had burning feeling rising from stomach or lower chest toward the neck on most days (pyrosis), had woken up at night choking, and feeling full shortly after starting a meal on most days (early satiety). The GE variables were divided into dysmotility and indicators of GERD. Dysmotility indicators included esophageal dysmotility from the physician questionnaire forms, and difficulty swallowing and early satiety from the patient forms. GERD was defined from the patient forms giving the answer "yes" to food/acid regurgitation, burning feeling rising from stomach, and/or waking up choking at night from GERD. Esophageal dilatation suggested dysmotility and GERD. This questionnaire was not externally validated but was applied at each annual visit.

The first non-RP SSc symptoms/signs were recorded for each patient, using a standardized questionnaire completed by the physician at the initial CSRG visit. This was included to determine how often the GI symptoms predated the respiratory symptoms.

Statistical analyses. Spearman correlations between FVC and chest radiograph and high-resolution computed tomography (HRCT) evidence of pulmonary fibrosis/ILD were performed for FVC% predicted as a continuous and also a dichotomous variable to determine how consistent FVC was as a surrogate of ILD.

Univariate analyses were first performed for patients in 3 separate groups: no/mild FVC (n = 967) versus stable moderate/severe FVC (n = 56) versus progressive moderate/severe FVC (n = 20); and then in binary groupings: no/mild FVC (n = 967) versus moderate/severe FVC (n = 76) and stable moderate/severe FVC (n = 56) versus progressive moderate/severe FVC (n = 20).

The following demographic and other SSc-related factors were also included in the univariate analysis: age, sex, ethnicity (aboriginal/white), smoking history, disease subtype and disease duration, history of digital ulcers, calcinosis, RP, sclerodactyly, telangiectasia, pulmonary arterial hypertension (PAH; defined by physician), ESR, C-reactive protein (CRP), topo I, anticentromere antibody (ACA), RNA polymerase III, anti-Ro52, anti-La, and anti-PM Scl. Many of these have been associated with either development or protective factors in ILD[3,5,12].

Variables that had a p value < 0.1 in univariate analysis were retained for regression models. Logistic regression models were developed, as follows: esophageal dilatation (Model 1), physician indicated esophageal dysmotility (Model 2), difficulty swallowing (Model 3), choking at night (Model 4), burning feeling rising from stomach on most days (Model 5), food/acid regurgitation on most days (Model 6), and early satiety (Model 7); and with an interaction term composed of dilatation*choking (Model 8) and difficulty swallowing*choking (Model 9). Eighteen models were developed in total, 9 comparing no/mild ILD versus progressive moderate/severe ILD, and 9 comparing stable moderate/severe ILD versus progressive moderate/severe ILD progression. If there were insufficient numbers in each subset of the variables then the regression was not performed. A list of strong covariates was generated through a backward stepwise process. A subset analysis was performed on patients with disease

duration up to 5 years. All statistical analyses were performed using IBM SPSS, version 19.

Exploratory analyses were performed between worsening FVC and other features that developed or worsened (ever or new-onset scleroderma renal crisis, mRSS, and changes in skin score, inflammatory arthritis, and myositis).

RESULTS

Baseline data for the study group (n = 1043) are shown in Table 1: 92.7% represented no/mild FVC (Group 1), 5.4% were stable moderate/severe FVC (Group 2), and 1.9% were progressive moderate/severe FVC (Group 3). With respect to GI symptoms, 84.2% had esophageal dysmotility (physician-reported), 54.5% reported food/acid reflux on most days, and 13.1% had undergone esophageal dilatation (Table 1).

At each annual visit, 22% to 29% of patients had chest radiograph changes compatible with pulmonary fibrosis/ILD with a Spearman correlation of –0.39 comparing radiographic evidence of ILD/pulmonary fibrosis and FVC% predicted as a continuous variable ($p < 0.01$), with

Table 1. Baseline characteristics of patients in the Canadian Scleroderma Research Group (CSRG) cohort, overall and according to categories for forced vital capacity (none, stable, worsening). Discrete variables are presented as absolute counts (percentages of total). Continuous variables are presented as averages ± SD. Disease duration is years since first onset of non-Raynaud symptom to first visit. Early onset of systemic sclerosis (SSc, scleroderma) is ≤ 3 years, late onset is > 3 years.

Covariates	All Patients	± SD (%)	No/Mild FVC Restriction	± SD (%)	Stable Mod/Severe FVC Restriction	± SD (%)	Progressive Mod/Severe FVC Restriction	± SD (%)	p
Total	1043	(100.0)	967	(92.7)	56	(5.4)	20	(1.9)	
Demographics									
Age	55.74	± 11.88	55.75	± 11.69	53.15	± 14.84	62.30	± 9.35	0.012
Sex									
Male	143	(13.7)	834	(13.8)	50	(10.7)	16	(20.0)	
Female	900	(86.3)	133	(86.2)	6	(89.3)	4	(80.0)	0.578
Ethnicity									
Aboriginal	45	(4.5)	39	(4.2)	5	(9.1)	1	(5.3)	0.241
White	906	(93.1)	842	(93.3)	48	(92.3)	16	(84.2)	0.290
Smoking (ever)	643	(63.7)	599	(64.2)	35	(62.5)	9	(45.0)	0.206
Disease duration	10.77	± 9.31	10.73	± 9.37	11.07	± 7.93	12.03	± 10.37	0.808
Classification									
Type of SSc according to physician									
Limited	568	(56.7)	532	(57.5)	25	(45.5)	11	(55.0)	
Diffuse	433	(43.3)	394	(42.5)	30	(54.5)	9	(45.0)	0.216
Early or late onset of scleroderma									
Early	234	(22.8)	221	(23.2)	9	(16.4)	4	(21.1)	
Late	791	(77.2)	730	(76.8)	46	(83.6)	15	(78.9)	0.489
Digital ulcers (ever)	602	(57.7)	569	(58.8)	25	(44.6)	8	(40.0)	0.300
CREST features									
Calcinosis	364	(37.0)	328	(36.1)	25	(44.6)	11	(55.0)	0.105
Raynaud (ever)	959	(97.2)	883	(96.9)	56	(100.0)	20	(100.0)	0.301
Sclerodactyly	922	(93.4)	849	(93.2)	53	(94.6)	20	(100.0)	0.445
Telangiectasia	845	(85.7)	775	(85.2)	54	(96.4)	16	(80.0)	0.050
Pulmonary hypertension	155	(16.3)	135	(87.1)	12	(25.0)	8	(40.0)	0.003
Serum markers[†]									
ESR, mm/h Westergren	21.30	± 20.24	20.69	± 19.56	26.80	± 26.76	34.20	± 24.50	0.001
C-reactive protein, mg/l	8.83	± 19.00	8.38	± 18.19	11.45	± 15.84	22.07	± 44.04	0.004
Antitopoisomerase I	144	(14.8)	127	(14.2)	13	(24.5)	4	(20.0)	0.096
Anticentromere antibody	355	(36.6)	339	(37.8)	10	(19.2)	6	(30.0)	0.021
Variables of interest									
Esophageal dilatation	136	(13.1)	121	(12.6)	9	(16.1)	6	(30.0)	0.058
Esophageal dysmotility	830	(84.2)	757	(83.2)	53	(94.6)	20	(100.0)	0.011
Difficulty swallowing	406	(48.5)	361	(47.4)	31	(56.4)	14	(70.0)	0.066
Food/acid coming up	456	(54.5)	416	(54.6)	26	(47.3)	14	(70.0)	0.212
Choking at night	191	(22.8)	167	(21.9)	17	(30.9)	7	(35.0)	0.130
Burning feeling rising from stomach	246	(29.4)	223	(29.3)	13	(23.6)	10	(50.0)	0.083
Feeling full shortly after meal	317	(37.9)	283	(37.2)	21	(38.2)	13	(65.0)	0.041

[†] There was no statistical difference in other autoantibodies; RNA pol III, Ro52, La, PM-Scl were not significantly different between the groups. FVC: forced vital capacity, normal group is > 70% predicted; pulmonary hypertension: elevated pulmonary artery pressure on echocardiogram (> 40 mm Hg) and physician answering "yes" to "Has the patient ever had pulmonary hypertension?"; ESR: erythrocyte sedimentation rate.

similar significant results using a dichotomous FVC% predicted of ≥ 70% or < 70%. There were only at most 230 patients who had an HRCT scan at any visit, so the numbers were small. In those who had HRCT results, 80% to 90% demonstrated ILD or pulmonary fibrosis. However, we cannot assume that those without HRCT scanning did not have ILD. The correlation between HRCT evidence of pulmonary fibrosis and FVC% predicted at the baseline visit was also significant ($p < 0.01$).

In the cohort, 5.6% had an elevated creatine kinase (CK) above the upper limit of normal; 5.7% had proximal weakness. Only 1.4% had both proximal muscle weakness and elevated CK (defined as CK > 200 U/l in females or > 250 U/l in males). Also, 6.6% had an mRSS of 0 (at cohort entry), which could have been due to skin regression at cohort entry in patients with longstanding disease and less commonly from SSc without skin involvement.

Univariate analysis. No/mild FVC restriction versus stable moderate/severe FVC restriction versus progressive moderate/severe FVC restriction. Initial univariate analysis (at $p < 0.1$) included variables similar to those above (Table 1).

No/mild FVC restriction versus FVC restriction. Subsequent univariate analysis merged the 3 groups in a comparison of no/mild FVC restriction versus the stable or progressive disease groups (Table 2). Differences included esophageal dysmotility ($p = 0.007$), esophageal dilatation ($p = 0.077$), difficulty swallowing ($p = 0.038$), and choking at night from GERD ($p = 0.049$; more in those with FVC% predicted < 70%). Other SSc manifestations of calcinosis, digital ulcers ($p = 0.010$), and PAH ($p = 0.003$) were also significantly associated with low FVC. As expected, ESR ($p = 0.011$), CRP ($p = 0.010$), and topo I ($p = 0.037$) were more common in those with low FVC and ACA was less common ($p = 0.01$). There were no statistically significant associations between other antibodies (RNA polymerase III, anti-Ro52, anti-La, and anti-PM-Scl) and FVC.

Stable versus progressive moderate/severe FVC restriction. Patient-reported food/acid regurgitation ($p = 0.086$), pyrosis (heartburn; $p = 0.032$), and early satiety ($p = 0.043$) were more common in those with progressive moderate/severe FVC restriction. Analysis of other factors revealed that age (increased; $p = 0.002$) and telangiectasia (protective; $p = 0.036$) were significantly different between the 2 groups (Table 2).

Multivariate analysis. No/mild FVC restriction versus FVC% predicted < 70%. The strongest associations with a low FVC in different models were esophageal dilatation ($p = 0.041$), dysmotility ($p = 0.009$), difficulty swallowing ($p = 0.016$), and choking at night ($p = 0.026$), increasing the likelihood of a low FVC < 70% predicted by 2-fold, except for the OR for dysmotility, which was even higher (> 6). Data are shown in Table 3.

Stable versus progressive moderate/severe FVC restriction.

Early satiety was associated with progressive moderate/severe reduction in FVC (OR 4.6, $p = 0.018$), heartburn (OR 2.7, $p = 0.098$), and GERD (OR 3.0, $p = 0.072$) were increased in progressive moderate/severe FVC restriction. Esophageal dilatation and difficulty swallowing were not significant (Table 3). An interaction was studied where the combination of dilatation and choking increased risk of worsening FVC ($p = 0.042$). Table 4 summarizes the associations found between GI signs and symptoms and FVC in SSc.

Table 5 summarizes the first non-RP manifestation at cohort entry. Many patients had > 1 symptom/sign, so the frequency of features is > 100%. Only 7.8% had respiratory symptoms recorded as the first non-RP manifestation, whereas one-quarter had complaints of heartburn or dysphagia.

Exploratory analyses for the association between FVC and worsening organ involvement were limited because of the small numbers of patients in this cohort who had new-onset or worsening other organ involvement over the 3 years of followup in the cohort that had primarily long disease duration. For instance, at enrollment 4.3% had ever had scleroderma renal crisis (SRC) and only about 1% annually had new or recurrent SRC. The skin score was mostly stable over time (median change in mRSS was 0, interquartile range –2 to +3) and the mean change in mRSS was 0.05 to 0.31 in the first 4 years after enrollment. Prevalence of inflammatory arthritis and myositis decreased slightly over followup. Thus analyses between FVC and organ involvement were not performed.

DISCUSSION
In our study, there appears to be a relationship between gastroesophageal severity (need for dilatation and more significant symptoms) and FVC restriction versus no/mild FVC restriction and also with progressive moderate/severe FVC restriction. It is not surprising that choking, esophageal dysmotility, and need for esophageal dilatation were associated with a low FVC and often with progressive moderate/severe FVC restriction, because this has been reported previously with ILD and PFT, but often with small numbers of cases or in cross-sectional studies. Thirteen patients with SSc were assessed using pH monitoring (for GERD severity scores), esophageal endoscopy, and PFT, where GERD scores were correlated with impaired DLCO[18]. By means of manometry in 43 patients, esophageal dysmotility was related to decreased lung volumes and DLCO (i.e., ILD)[16]. In 133 patients with SSc, ILD occurred in more patients with severe esophageal dysmotility[19]. Although no causative association has been established between esophageal and pulmonary involvement[16,19,28], the hypothesis is that tracheobronchial aspiration of gastric secretions over time leads to pulmonary fibrosis[15,18,29]. A rodent model, with recurrent gastric fluid

Table 2. Univariate analysis of the variables associated with normal vs reduced FVC and stable vs worsening FVC. Disease duration is years since first onset of non-Raynaud symptom to first visit. Early onset of SSc is ≤ 3 years, late onset is > 3 years.

| Covariates | No/Mild FVC Restriction (n = 967) vs FVC Restriction (n = 76) | | | Stable Moderate/Severe FVC Restriction (n = 56) vs Progressive Moderate/Severe FVC Restriction (n = 20) | | |
	Difference in Mean	Critical Value/OR	p	Difference in Mean	Critical Value/OR	p
Demographics						
Age	+0.191	4.799	0.909	+3.554	4.678	0.002
Sex		1.053	0.884		0.480	0.299
Ethnicity aboriginal		1.991	0.131		0.556	0.603
Ethnicity white		0.652	0.308		0.444	0.321
Smoking (ever)		0.767	0.273		0.491	0.177
Disease duration, yrs	−0.591	0.311	0.599	+2.289	1.362	0.676
Classification						
Type of SSc according to physician		1.463	0.114		0.682	0.465
Early or late onset of scleroderma		0.704	0.265		1.363	0.644
Digital ulcers (ever)		1.863	0.010		1.210	0.719
Modified Rodnan skin score		2.276	0.064		0.482	0.931
CREST features						
Calcinosis		1.594	0.052		1.516	0.427
Raynaud (ever)		—*	—*		—*	—*
Sclerodactyly		1.777	0.341		—*	—*
Telangiectasias		2.032	0.103		0.148	0.036
Pulmonary hypertension						
Elevated pulmonary artery pressure on echocardiogram (> 40 mm Hg)		2.315	0.003		2.000	0.220
Serum markers†						
Westergren ESR, mm/h	−8.088	12.970	0.011	−7.4	0.015	0.283
C-reactive protein, mg/l	−5.936	3.729	0.010	−10.613	4.509	0.129
Antitopoisomerase I		1.841	0.037		0.769	0.684
Anticentromere antibody		0.470	0.010		1.800	0.329
GI variables of interest						
Esophageal dilatation		1.711	0.077		2.238	0.186
Esophageal dysmotility		4.918	0.007		M	M
Difficulty swallowing		1.666	0.038		1.806	0.290
Food/acid coming up		0.951	0.834		2.603	0.086
Choking at night		1.677	0.049		1.204	0.737
Burning feeling rising from stomach		1.069	0.799		3.231	0.032
Feeling full shortly after meal		1.401	0.167		3.007	0.043

P < 0.05 was considered significant. * Univariate analysis could not be performed. † Other autoantibodies (RNA pol III, Ro52, La, PM-Scl) were not significantly different between the groups. FVC: forced vital capacity; normal group is > 70% predicted; ESR: erythrocyte sedimentation rate; GI: gastrointestinal; SSc: systemic sclerosis.

added to rodent lungs, demonstrated inflammatory cells and cytokines in the lungs, suggesting that GERD and aspiration trigger inflammatory responses leading to pulmonary fibrosis[30].

Comparison of normal FVC to restricted FVC resulted in associations as described previously: PAH, elevated ESR, negative ACA, and digital ulcers. PAH is a known complication of ILD[31]. An elevated ESR may be from inflammatory alveolitis, which can result in pulmonary interstitial fibrosis[3]. A positive ACA was reduced by half in those with low FVC compared to those without low FVC. ACA-positive patients are a different phenotype of SSc[3,5,10].

Perhaps one should treat SSc esophageal involvement more aggressively in cases of progressive moderate/severe FVC. A higher prevalence and degree of ILD changes on HRCT has been associated with more severe dysmotility and decline of DLCO and FVC over 2 years[17]. We found that patient-reported early satiety (gastroparesis) increased the risk of progressive moderate/severe FVC restriction 4-fold. Early satiety shares the same cholinergic neuropathy

Table 3. Logistic regression models for dysphagia and GERD indicators. Comparisons were made between patients with no/mild FVC restriction vs ILD restriction and stable moderate/severe FVC restriction vs progressive moderate/severe FVC restriction. Results are OR (p value). Gastrointestinal (GI) variable of interest is what is studied in each model (listed under each Model). Covariates with $p < 0.1$ from univariate logistic regression were included for each comparison.

Moderate/Severe FVC Restriction vs No/Mild FVC Restriction Covariates	Model 1 Dilatation	Model 2 Dysmotility	Model 3 Difficulty Swallowing	Single Effects				Interaction Effects	
				Model 4 Choking	Model 5 Heartburn	Model 6 Food/Acid	Model 7 Early Satiety	Model 8 Dilatation* Difficulty Swallowing	Model 9 Dilatation* Choking
ESR	1.014 (0.007)	1.016 (0.003)	1.019 (0.001)	1.007 (0.002)	1.019 (0.001)	1.019 (0.001)	1.019 (0.001)	1.019 (0.001)	1.018 (0.002)
ACA	0.497 (0.024)	0.500 (0.026)	0.470 (0.017)	0.480 (0.020)	0.505 (0.029)	0.501 (0.028)	0.485 (0.022)	0.448 (0.012)	0.462 (0.015)
Digital ulcers	1.925 (0.016)	1.843 (0.025)	1.649 (0.072)	1.716 (0.051)	1.742 (0.044)	1.759 (0.41)	1.792 (0.035)	1.649 (0.072)	1.667 (0.067)
Pulmonary hypertension	2.317 (0.005)	2.420 (0.003)	2.436 (0.004)	2.704 (0.001)	2.602 (0.002)	2.538 (0.002)	2.452 (0.003)	2.509 (0.003)	2.658 (0.002)
GI variable of interest	1.937 (0.041)	6.742 (0.009)	1.993 (0.016)	1.962 (0.026)	1.334 (0.327)	1.133 (0.652)	1.538 (0.119)	1.871 (0.476)	0.607 (0.468)
Progressive vs Stable Covariates	Model 1 Dilatation	Model 2 Dysmotility	Model 3 Difficulty Swallowing	Single Effects				Interaction Effects	
				Model 4 Choking	Model 5 Heartburn	Model 6 Food/Acid	Model 7 Early Satiety	Model 8 Dilatation* Difficulty Swallowing	Model 9 Dilatation* Choking
Age	1.066 (0.014)	1.068 (0.011)	1.069 (0.013)	1.067 (0.013)	1.062 (0.021)	1.071 (0.011)	1.072 (0.010)	1.069 (0.012)	1.075 (0.011)
Telangiectasia	0.124 (0.036)	0.126 (0.033)	0.122 (0.028)	0.127 (0.34)	0.138 (0.044)	0.124 (0.040)	0.073 (0.17)	0.142 (0.052)	0.095 (0.028)
GI variable of interest	2.150 (0.263)	—†	2.045 (0.248)	1.325 (0.653)	2.680 (0.098)	3.009 (0.072)	4.573 (0.018)	0.367 (0.677)	29.075 (0.042)

$P < 0.05$ was considered significant. † Multivariate analysis could not be performed. * Indicates interaction term between indicated variables. FVC: forced vital capacity, normal group is > 70% predicted. Pulmonary hypertension: physician answering "yes" to "Has the patient ever had pulmonary hypertension?". ESR: erythrocyte sedimentation rate; ACA: anticentromere antibody positivity; dilatation: esophageal dilatation ever; choking: choking at night; heartburn: burning sensation rising from stomach/pyrosis; food/acid: regurgitation of food/acid; early satiety: feeling full shortly after meal.

as esophageal dysmotility[15,32]. Increased age was slightly associated (OR 1.07) with progressive moderate/severe FVC restriction, whereas it was previously thought not to predict progression of ILD[3]. Telangiectasias were associated less in those with low FVC, as expected, because telangiectasias occur more frequently in cases of lcSSc or the CREST phenotype (calcinosis, RP, esophageal dysmotility, sclerodactyly, telangiectasias)[3,5]; whereas dcSSc has more likelihood of restrictive defects due to ILD and other extrinsic problems including chest wall fibrosis and respiratory muscle weakness.

The dynamic lung compliance in patients who had both impaired peristalsis and esophageal sphincter function was lower than in those with only 1 problem[33]. Combining esophageal dilatation and choking at night yielded the highest association in progressive moderate/severe ILD (OR 29). This seems plausible considering that patients with SSc who undergo esophageal dilatation usually do so to relieve esophageal stricture formation from recurrent GERD and dysmotility. Reduced lower esophageal sphincter tone and esophageal hypomotility result from cholinergic neurotransmission abnormalities[32], prolonging acid clearance[34] and result in severe GERD. However, an esophageal stricture

may reduce GERD symptoms, with worsening postdilatation. Our results agree with previous reports correlating GERD and progression of ILD[16,17,18,19,35,36,37]. In contrast, 2 studies have not shown this association[20,38]. One study showed that a significant drop of FVC (10%–20%) was associated with esophageal manometry only in the dcSSc subset, but that study had only 105 patients. Use of proton pump inhibitors (PPI) may have influenced the effect of GERD on worsening FVC%[20].

Our results must be interpreted with caution because many objective measures for lung and esophageal changes were not routinely performed. CSRG patients have tests that are ordered according to the physicians, except for annual echocardiogram, laboratory investigations, PFT, and chest radiographs. Although PFT are suggestive of ILD, HRCT data could help to support our hypothesis (that a decline in FVC% predicted is associated with GERD and/or dysmotility), but only a quarter of the patients had HRCT scans recorded. Other studies have used FVC below a certain percentage of predicted to measure changes in SSc lung function over time, including the Scleroderma Lung Study of cyclophosphamide versus placebo in SSc patients with ILD[27], but this was only after confirmation of

Table 4. Summary of dysphagia/gastroesophageal reflux disease (GERD) indicators with forced vital capacity (FVC) status.

Indicators	No/Mild FVC Restriction vs FVC Restriction			Stable vs Progressive Moderate/Severe FVC Restriction		
	Association	Baseline %	OR	Association	Baseline %	OR
Dysmotility						
MD: Dysmotility	✓	83 vs 96	6.7	X	95 vs 100	—
PT: Difficulty swallowing	✓	47 vs 60	1.9	X	56 vs 70	2
PT: Early satiety	X	37 vs 45	1.5	✓	38 vs 65	4.6
GERD						
PT: Food/acid regurgitation	X	55 vs 53	1.1	S	47 vs 70	3
PT: Choking at night	✓	22 vs 32	1.9	X	31 vs 32	1.3
PT: Heartburn (pyrosis)	X	29 vs 31	1.3	S	24 vs 50	2.7
Esophageal dilatation						
MD: Esophageal dilatation	✓	13 vs 20	1.9	X	16 vs 30	2.2
Interaction term						
Dilatation*choking				→		29.1

Indicators	No/Mild FVC Restriction vs FVC Restriction		Stable vs Progressive Moderate/Severe FVC Restriction	
Dysmotility				
MD: Dysmotility	→	p = 0.009	↔	—
PT: Difficulty swallowing	→	p = 0.016	↔	p = 0.248
PT: Early satiety	↔	p = 0.119	→	p = 0.018
GERD				
PT: Food/acid regurgitation	↔	p = 0.652	→[†]	p = 0.072
PT: Choking at night	→	p = 0.026	↔	p = 0.653
PT: Heartburn (pyrosis)	↔	p = 0.327	→[†]	p = 0.098
Esophageal dilatation				
MD: Esophageal dilatation	→	p = 0.041	↔	p = 0.263
Interaction term				
Dilation*choking			→	p = 0.042

Gastrointestinal indicators: ✓: significant association, $p < 0.05$; X: no significant association; S: notable trend, but not significant, $p < 0.10$. →/↔ indicate direction of association with regard to FVC status; → indicates association with FVC in No/mild FVC restriction vs FVC restriction, as well as progressive moderate/severe FVC restriction in Stable vs Progressive moderate/severe FVC restriction; ↔ indicates no significant association with any particular FVC group. [†] Multivariate analysis could not be performed because of a 0 value in 1 cell. For FVC, normal group is > 70% predicted; PT: patient; MD: physician.

ILD/pulmonary fibrosis by HRCT scanning. The CSRG study lacks the rigor of a clinical trial where HRCT scanning was not mandatory. We did find a modest correlation between pulmonary fibrosis/ILD on chest imaging (chest radiograph and HRCT) and low FVC. DLCO% predicted was not used in our study because many patients were at risk for PAH and pulmonary hypertension (PH) where the DLCO could decline in PH or ILD. Many patients with SSc do not need manometry because the history is usually sufficient to determine whether esophageal dysmotility is absent, mild, moderate, or severe. Whereas for GI involvement, objective signs were limited in this study to the need for an esophageal dilatation, because the results of upper endoscopy and manometry were not recorded in the database. Because of a lack of rigorous objective measures, there is certainly misclassification of patients as having ILD if only FVC is used as a surrogate for ILD. However, misclassification would bias the results in the negative direction, i.e., with less likelihood of positive results if the complications (GI and/or ILD changes) were not present in some patients who were classified as having organ involvement. Also, the majority of patients were using PPI

for a long time prior to our study, so we could not discern whether the addition of or use of a PPI was protective against progression of ILD. Indeed, use of a PPI especially at high dose was associated with GERD (i.e., more severe GERD received more treatment in general). A study would need to follow an incident SSc cohort to determine whether PPI and other antireflux treatment would potentially reduce progression of ILD. We could not study changes in skin score and PFT changes because this was a mostly prevalent cohort, with long disease duration and stable skin scores. In early dcSSc, one could expect to see worsening ILD and worsening skin changes, but the association likely does not persist in long disease duration SSc and worsening ILD.

The strengths of our study include a large sample size (even though many did not progress; larger than previous studies in progressive moderate/severe restrictive changes on PFT), prospective serial observations including serial PFT over 3 annual visits, very few missing data, and quality control within the database. A weakness is that many had long disease duration, which may not reflect the early progressive moderate/severe FVC changes that occur in the first 5 years, and patients with progressive disease were

Table 5. First non-Raynaud manifestation at cohort entry of CSRG database.

First Non-Raynaud Manifestation	Frequency, % [†]
Puffy extremities	33.1
Skin tightening anywhere	27.1
Stiffness in hands	16.4
Inflammatory arthritis/arthralgia	16.8
Heartburn or dysphagia	25.3
Digital ulcers	12.3
Telangiectasia	10.1
Fatigue	10.2
Respiratory symptoms	7.8
Weight loss	4.8
Erectile dysfunction	1.0
Other*	14.8

[†] Results sum to more than 100% because more than 1 symptom could have occurred simultaneously. * Includes cutaneous: calcinosis cutis (n = 17), hyperpigmentation (8), itching (8), other skin manifestations (11); vascular: arm/leg ulcer (4), digital pitting (3), non-ulcer finger ischemia (1); musculoskeletal: fibromyalgia-like (14), muscle weakness (9), trouble opening jaw (2), lack of hand coordination (1); cardiovascular system: pericarditis (5), chest pain (3), hypertension (1); renal: scleroderma renal crisis (4); gastrointestinal (GI): GAVE (gastric antral vascular ectasia) (2), nausea/vomiting/diarrhea (3), upper GI bleed (1), nonspecific GI (1); nervous system: carpal tunnel syndrome (10), numbness anywhere (10), trigeminal neuropathy (2); serology: positive autoantibody (6); miscellaneous: sicca symptoms (8), parotitis (1), oral ulcer (1), receding gum (1), unspecified (4), CREST symptoms (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias) (2).

uncommon, so a stricter definition of FVC changes lacked power to adjust for all important confounders. Long disease duration gives a survival bias, but many patients who die from SSc-related pulmonary fibrosis do not die until after 5 years of disease even though ILD begins earlier. In SSc lung studies, most do not progress over 1 to 2 years and thus the small proportion of those with rapid progression over 3 annual visits is not unexpected. Topoisomerase I was associated with FVC restriction versus FVC% predicted > 70%, but not with progression over the 3 years of observations. The risks of a low FVC and of further FVC progression are not identical. Multiple testing occurred, but we had predetermined study questions and other secondary analyses, so a Bonferroni correction was not performed. Although the groups had arbitrary definitions, our hypothesis was that progressive moderate/severe FVC restriction would have more significant upper GI involvement, which would predispose to aspiration and hence worsening restrictive pattern on PFT testing, so the analyses were hypothesis-driven. The strongest effect was with both choking/dysphagia and esophageal dilatation, which has face validity for risk of aspiration. Depending on the models the results were similar but not identical. All PFT laboratories were certified but there was no standardization between sites. However, most patients had all sets of PFT performed at the same laboratory, so the within-individual variation should be minimized. The percentage predicted FVC change varied for absolute changes, with more worsening in the lower FVC range. We did not study DLCO changes, because they could reflect PAH. It is unclear whether the association between the severity of esophageal involvement and pulmonary fibrosis is causative[19,39], or if the simultaneous development of esophageal and pulmonary involvement is simply a reflection of more generalized fibrosis[15,16]. An incident SSc study prior to ILD would help answer this question. It would be interesting to investigate whether promotility and gastroprotective medications decrease progression of ILD. The University of California, Los Angeles, Scleroderma Clinical Trial Consortium Gastrointestinal Tract questionnaire[40] was not published at the start of the CSRG study, so it was unavailable. Use of a validated GI questionnaire would presumably find similar results, because the questionnaire our patients completed had similar domains. However, lack of a validated questionnaire for the GI questions and the lack of rigor for performing GI tests may be important limitations.

Esophageal dysmotility and GERD appear to be associated with low FVC in SSc, and some upper GI signs and symptoms occur more frequently in progressive moderate/severe FVC restriction. The presence of both severe dysmotility and GERD was strongly associated with reduction of progressive moderate/severe FVC. Because this was mostly a prevalent cohort, we could not study patients at the initial onset of GI symptoms and then determine whether there were more severe complaints in those who subsequently developed ILD or worsening FVC. However, some GI symptoms are associated with restrictive changes of pulmonary function and worsening FVC.

APPENDIX 1

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