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Associations Between Patterns of Esophageal Dysmotility and Extra-Intestinal Features in Patients With Systemic Sclerosis

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Abstract

Objective.—The gastrointestinal tract is commonly involved in patients with systemic sclerosis (SSc) with varied manifestations. As our understanding of SSc gastrointestinal disease pathogenesis and risk stratification is limited, we sought to investigate whether patterns of esophageal dysfunction associate with specific clinical phenotypes in SSc.

Methods.—Patients enrolled in the Johns Hopkins Scleroderma Center Research Registry who completed high-resolution esophageal manometry (HREM) studies as part of their clinical care between 2011 and 2020 were identified. Associations between esophageal abnormalities on HREM (absent contractility [AC], ineffective esophageal motility [IEM], hypotensive lower esophageal sphincter [hypoLES]) and patient demographic information, clinical characteristics, and autoantibody profiles were examined.

Results.—Ninety-five patients with SSc had HREM data. Sixty-five patients (68.4%) had AC (37 patients with only AC, 28 patients with AC and a hypoLES), 9 patients (9.5%) had IEM, and 11 patients (11.6%) had normal studies. AC was significantly associated with diffuse cutaneous disease (38.5% versus 10.0%; $P < 0.01$), more severe Raynaud's phenomenon, including digital

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. McMahan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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pits, ulcers, or gangrene (56.9% versus 30.0%; $P = 0.02$), and reduced median diffusing capacity of lung for carbon monoxide (50.6% versus 72.2%; $P = 0.03$). AC was observed in most of the patients who died (13 of 14; $P = 0.06$). These findings were not seen in patients with IEM.

Conclusion.—Among patients with SSc, AC is associated with a significantly more severe clinical phenotype. IEM may associate with a milder phenotype. Further studies are needed to evaluate AC, IEM, and their clinical impact relative to the timing of other end-organ complications in SSc.

INTRODUCTION

Systemic sclerosis (SSc) is a complex autoimmune disorder that results in vasculopathy and progressive fibrosis of the skin and internal organs. The gastrointestinal (GI) tract is the most frequently affected internal organ system in SSc (1). Within the SSc GI tract, esophageal dysfunction is common and is observed in up to 90% of patients (2) Clinical manifestations of SSc-esophageal disease can vary, ranging from gastroesophageal reflux disease (GERD), esophagitis, and/or stricture formation to the development of esophageal adenocarcinoma (3–7). These complications are considered a consequence of chronic exposure of esophageal tissue to gastric acid driven in part by esophageal dysfunction (8,9). Furthermore, accumulating data suggest that a subset of SSc patients experience chronic microaspiration, which may exacerbate SSc-related interstitial lung disease (10).

Although esophageal involvement in SSc is common and may significantly impact morbidity and mortality, not all patients with SSc-related esophageal disease experience poor outcomes (11–13). The relationship between different types of esophageal dysfunction and patient outcomes is unclear. Identifying clinical and serologic features associated with high-risk subgroups in SSc patients with esophageal dysfunction may support patient risk stratification, the organization of translational studies around physiologically similar patients, and the development of appropriate treatment algorithms for distinct patient subgroups.

Esophageal motility patterns can be studied using high-resolution esophageal manometry (HREM), which can detect the amplitude of contractile events within the esophagus and its sphincters in relation to time (14–16). Intraluminal esophageal pressure can be measured using esophageal pressure topography, which uses the manometry catheter pressure sensors to determine intraluminal esophageal pressures (14–16). HREM provides information on esophageal contractility and peristalsis patterns, sphincter relaxation in response to bolus, and intrabolus pressure patterns (14–16). Commonly identified patterns of SSc-related esophageal dysmotility include hypotensive lower esophageal sphincter (hypoLES), and/or ineffective esophageal motility (IEM) or absent contractility (AC) (17–19). As a result, HREM can provide insight into the presence and severity of distinct esophageal abnormalities, and inform the selection of specific therapies (19). For instance, buspirone, an 5-hydroxytryptamine 1A receptor agonist, was shown to increase LES resting pressure in up to 80% of SSc patients, but has little to no effect on esophageal motility (20,21). The effects of buspirone on a specific type of esophageal defect suggest that a more targeted approach

to identifying and managing different types of esophageal dysfunction in SSc may benefit patients.

In this study, we aimed to define clinical features associated with different types of esophageal abnormalities in patients with SSc (17,18). We specifically chose to investigate whether clinical characteristics in patients with SSc associate with AC, IEM, and/or hypoLES (defined by the Chicago classification criteria), as the pathophysiology of these areas of dysfunction is different (22,23). Understanding the associations between patterns of esophageal dysfunction and other SSc features may improve our ability to properly phenotype and risk stratify patients with SSc.

PATIENTS AND METHODS

Patients.

Patients in the Johns Hopkins Scleroderma Center (JHSC) Research Registry who were age ≥18 years, met criteria for SSc (2013 American College of Rheumatology [ACR]/EULAR, ACR 1980), at least 3 of 5 features of CREST syndrome criteria (calcinosis, Raynaud's phenomenon [RP], esophageal dysmotility, sclerodactyly, or telangiectasias), or the presence of definite RP, abnormal nailfold capillaries, and an SSc-specific autoantibody, and who completed esophageal manometry studies at Johns Hopkins University (JHU) between 2011 and 2020 were identified through the JHU Precision Medicine Analytics Platform (n = 102) (24,25). Patients were eligible for participation in the study if they had a diagnosis of scleroderma and provided consent to participate in the institutional review board–approved cohort study. Patients diagnosed with or confirmed to have SSc after their clinical visit at JHSC were enrolled in the Johns Hopkins Research Registry at their earliest clinical encounter when consent could be obtained.

Esophageal manometry studies were performed as part of routine clinical care and assessment in patients who had significant symptoms of upper GI dysfunction, including early satiety, nausea, vomiting, reflux, or dysphagia as determined by the treating physician. Of these 102 studies, 7 were excluded as a result of the attempted procedure being aborted due to technical difficulties or patient intolerance, resulting in 95 patients for the present analysis. Data from the manometry reports were downloaded, abstracted, and merged with existing demographic, clinical, and serologic data that had been collected longitudinally from 1991 to 2020 as part of the JHU Center's Research Registry. Written informed consent was obtained from all patients. The present study complied with the Declaration of Helsinki and was approved by the JHU Institutional Review Board.

Clinical phenotyping.

The JHSC database collects demographic and detailed clinical data from patients at their first clinical encounter and every 6 months at subsequent follow-up clinical visits. Disease duration was calculated from the date of the first SSc-associated symptom (RP or non-RP) to the date of the esophageal manometry study. Patients were categorized as having limited or diffuse cutaneous SSc based on the extent and degree of skin tightness (26).

The modified Medsger severity scoring system was used to measure disease involvement and severity in different organ systems, and the maximum score ever recorded during clinical assessment in the Registry for each patient was used to define clinical phenotypes (27). RP severity was scored as: 0 = no involvement; 1 = RP with or without vasodilator requirement; 2 = digital pitting scars; 3 = digital tip ulceration; and 4 = digital gangrene. The Medsger muscle severity score was used to measure the extent of proximal muscle weakness as based on the following scale: 0 = full strength; 1 = ability to lift upper or lower extremities against gravity with some resistance; 2 = ability to lift upper or lower extremities against gravity only; 3 = ability to move upper or lower extremities but not against gravity; and 4 = requiring ambulatory aids to walk (27,28). The presence of a myopathy was determined by the presence of an elevated creatine phosphokinase or aldolase, electromyography consistent with myopathy, magnetic resonance imaging with findings of muscle edema, or a muscle biopsy with pathology consistent with myopathy. GI severity was scored as: 1) score 0 = normal (no GI symptoms); 2) score 1 = GERD requiring medication or an abnormal bowel series; 3) score 2 = GERD requiring maximal dose treatment, or small bacterial overgrowth requiring antibiotics; 4) score 3 = malabsorption syndrome or episodes of pseudo-obstruction; and 5) score 4 = total parenteral nutrition required.

The Medsger cardiac severity was scored as: 0 = normal; 1 = evidence of conduction defect on electrocardiogram or left ventricular ejection fraction (LVEF) of 45–49% on echocardiogram; 2 = evidence of arrhythmia on electrocardiogram, or biventricular enlargement, or LVEF of 40–44%; 3 = LVEF ≤40%; and 4 = clinical heart failure, and/or heart failure or arrhythmia requiring treatment. Pulmonary disease severity was scored as: 0 = normal diffusing capacity of lung for carbon monoxide (DL_{CO}) ≥80% predicted and forced vital capacity (FVC) ≥80% predicted measured by pulmonary function testing, and no evidence of fibrosis on radiographs or rales; 1 = FVC/DL_{CO} 70–80% predicted or rales or fibrosis on radiograph; 2 = FVC/DL_{CO} 50–69% predicted; 3 = FVC/DL_{CO} <50% predicted; and 4 = oxygen required (29). The maximum organ-specific severity score ever recorded was considered significant disease involvement if the score was >1.

To define cardiopulmonary phenotype, the minimum measurement from the FVC and minimum single-breath DL_{CO} measured by pulmonary function testing and maximum measurements of the estimated right ventricular systolic pressure (RVSP; measured by transthoracic echocardiogram) recorded in the Johns Hopkins Scleroderma Research Registry were used for analysis. Sicca symptoms were defined as the presence of at least 1 of the following: dry eyes for >3 months, the sensation of sand or gravel in the eyes, the use of artificial tears 3 times daily, dry mouth for >3 months, swollen salivary glands, and/or the necessity of liquids for swallowing due to dry mouth (30).

Autoantibody profile.

SSc autoantibodies (including anti-Scl-70, anticentromere, antifibrillarin, anti–RNA polymerase III, anti-Ro52, anti-Th/To, anti-PM/Scl, and anti-Ku) were assessed by using banked serum samples. Autoantibody profiles were assessed using the commercially available Euroline immunoblot assay (Systemic Sclerosis Profile, Euroimmun Diagnostics).

Autoantibodies were considered positive if at least 1 of the subunits of the protein assayed was detected and moderate to high titers of the autoantibodies were present, as determined by the manufacturer's thresholds.

Instruments.

All studies were performed at JHU using a standardized clinical protocol. The patients were asked not to use antimotility agents for at least 4 weeks prior to the study, and the patients were instructed to fast at least 6 hours prior to the study. The study was conducted with the patient in the supine position. The HREM catheter was assembled and positioned to record measurements from the upper esophageal sphincter through the esophagus into the stomach following manometric protocol as previously described (31,32). Data were analyzed using Manoview 3.0 (Medtronic) software and classified according to Chicago classification criteria (17,18). The standardized ranges of normal and abnormal motility patterns were described previously (15,32). AC was defined as 100% failed peristalsis with normal integrated relaxation pressure based on Chicago classification criteria (17,18). IEM was defined as ≥50% ineffective swallows or 50% failed swallows with weak distal contractile integral as classified per Chicago classification criteria (17,18). HypoLES was defined as an LES basal pressure <10 mm Hg (normal resting LES pressure 10–45 mm Hg) (31,33).

Statistical analysis.

Our aim was to determine whether distinct esophageal abnormalities identified by HREM (AC, IEM, hypoLES) were associated with specific clinical and serologic characteristics in SSc. We performed chi-square or Fisher's exact tests to evaluate associations between our outcomes of interest and dichotomous clinical and demographic variables when 1 group had a sample size of n <5. Nonparametric Wilcoxon's rank sum tests were used to examine differences between the means of continuous variables between 2 groups (i.e., the presence versus absence of each outcome, AC, IEM, and hypoLES). Univariate logistic regression analyses (model 1) were used to estimate the strength of associations. Multivariable logistic regression models (model 2) were constructed to examine associations after adjusting for clinically relevant covariates and potential confounders. Factors for adjustment in the logistic regression analysis were chosen based on the epidemiology of scleroderma, rather than empirical evidence among this cohort. STATA 15 was used to perform the analyses. A P value of less than 0.05 was considered statistically significant. We did not adjust for multiple comparisons.

RESULTS

Clinical characteristics of the study cohort.

Among the 95 patients with SSc and HREM data, the median age was 57.7 years (interquartile range [IQR] 51.7–62.5 years). Approximately 87.4% were female and 82.1% were White. The median disease duration from first SSc symptom onset (RP or non-RP) was 13.7 years (IQR 6.3–21.9 years). Thirty percent of the patients had diffuse cutaneous disease, and 32.2% of patients had evidence of significant cardiac involvement (score >1). Across the cohort, 65 patients (68.4%) had AC, 9 (9.5%) had IEM, and 11 (11.6%) had

normal studies. Of the patients with AC, 28 patients (43.1%) had both AC and a hypoLES. Seventy-two percent of patients had evidence of significant lung involvement (score >1), with approximately 53.2% of patients having reduced FVC of <80% predicted and 53.2% of patients with reduced DL_{CO} of <60% predicted. Significant GI involvement (score >1) was identified in 85.3% of patients. Muscle involvement was present in 4.3% of patients, and 10.6% had tendon friction rubs. By the time of data set closure, 14 patients (14.7%) had died. Among patients who died (n = 14), the median time from the manometry procedure until the recorded date of death was approximately 3.1 years (IQR 1.4–4.9 years). Of the patients with available serology data, 30 (40.0%) were anticentromere antibody positive, and 18 (24.0%) were antitopoisomerase 1 (anti–Scl-70 antibody) positive. Notably, 16 patients (21.3%) had anti-Ro52 antibodies. Table 1 summarizes the demographic features of the cohort.

Association of AC with distinct clinical features of SSc.

We first sought to determine whether specific clinical features associate with AC. We found no significant associations between the presence of AC and the age or sex of patients. The median disease duration from first SSc symptom to baseline visit in the JHSC was 13.8 years (IQR 6.5–22.6 years) in patients with AC. AC was significantly associated with diffuse cutaneous disease (38.5% versus 10.0%; $P < 0.01$). Patients with AC were also significantly more likely to have experienced severe digital vascular complications, including digital pits, ulcers, or gangrene (56.9% versus 30.0%; $P = 0.02$). Significant pulmonary involvement was not associated with AC, and on cardiopulmonary testing, neither reduced FVC (defined as <80% predicted) nor elevated RVSP (defined as estimated pressure of >40 mm Hg) on echocardiogram was associated with AC. However, a reduced DL_{CO} (defined as <60% predicted) was more commonly observed among patients with AC compared to SSc patients without AC (median percent predicted DL_{CO} 50.6% versus 72.2%; $P = 0.03$). Patients with AC were not significantly more likely to have severe cardiac involvement than patients without AC (38.7% versus 17.9%; $P = 0.06$). Serologically, there were no significant associations between antitopoisomerase-1, anticentromere, antifibrillarin, anti-Th/To, and anti-Ku antibodies and the presence of AC. Table 2 summarizes the comparisons between clinical characteristics among patients with and without AC.

In the collective cohort (n = 95), 14 patients died (14.7%). Of those, 92.9% (13 of 14) had AC. Approximately 20.0% of the patients (13 of 65) with AC died, whereas only 3.3% (1 of 30) without AC died ($P = 0.06$). Notably, 71.4% of the patients who died (10 of 14) also had significant cardiac involvement (score >1), with 46.2% of the AC patients who died having end-stage heart failure (6 of 13, score = 4). All patients with AC who died had evidence of significant lung involvement (score >1), with 61.5% requiring supplemental oxygenation (8 of 13, score = 4). All 13 patients with AC who died also had significant GI involvement on the Medsger severity scale. Interestingly, 53.8% of these AC patients (7 of 13) had concomitant hypoLES on HREM. All 13 patients had RP requiring vasodilation. The cause of death varied among these patients (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25080).

Enrichment of IEM among patients with anticentromere antibodies, a higher DLco, and less severe RP.

We next sought to evaluate whether a distinct clinical phenotype was observed in the IEM group; given our small sample size, we described clinical characteristics rather than statistical comparisons. In the IEM group, the median disease duration from first SSc symptom (RP or non-RP) was 16.5 years (IQR 6.1–19.3 years). Age and disease duration in the SSc patients with IEM were similar when compared to SSc patients without IEM. Interestingly, patients with IEM had a relatively higher (better) median DL_{CO} compared to patients without IEM (85.3% versus 55.7%). In addition, the proportion of patients with IEM were less likely to have severe RP than patients without IEM (11.1% versus 52.3%). Other cardiopulmonary parameters, including measured FVC and measured RVSP, were comparable between groups. Although the sample size of SSc patients with IEM was small, 100% of patients with IEM and measured autoantibodies were anticentromere-antibody positive, compared to only 35.7% in patients without IEM. Diffuse cutaneous disease, which was significantly associated with AC, was less commonly observed in patients with IEM than in those without (11.1% versus 31.4%). The prevalence of cardiac involvement also appeared less common in the IEM group (12.5% versus 34.1%). Although the number of patients in this group was small, and full statistical analyses could not be performed, these findings suggest that the presence of IEM may associate with milder clinical features of SSc. Table 3 summarizes the characteristics of the IEM group as compared to patients without IEM.

Hypotensive LES in combination with AC and severe extra-intestinal SSc disease.

We then sought to evaluate whether including the presence of hypoLES in patients with SSc helped to further define the clinical phenotype (34). Out of concern for a Type 1 error, we focused on descriptive results instead of statistical comparisons in this analysis as well. As almost all patients with hypoLES had concomitant AC (28 of 30), we evaluated patients with both hypoLES and AC in contrast to those with AC alone. The median age of patients with hypoLES and AC was 58.4 years (IQR 53.7–62.6 years), with a median disease duration from first SSc symptom (RP or non-RP) of 12.9 years (IQR 6.8–26.2 years). Approximately 60.7% of patients (17 of 28) with hypoLES and AC had diffuse cutaneous disease relative to 21.6% of patients (8 of 37) with AC alone. Approximately 59.3% of patients (16 of 27) with hypoLES and AC had severe cardiac involvement in contrast to only 21.6% of patients (8 of 37) with AC alone. Of the patients with hypoLES and AC and significant cardiac involvement, 62.5% of patients (10 of 16) had end-stage heart failure (score = 4). Tendon friction rubs were also observed in 25.0% of patients (7 of 28) with hypoLES and AC, whereas tendon friction rubs were seen in only 2.8% of patients (1 of 36) with AC alone. Finally, 71.4% of patients (20 of 28) with hypoLES and AC were noted to have severe RP, in comparison to 45.9% of patients (17 of 37) with AC alone. Patients with hypoLES and AC had a median measured DL_{CO} of 44.7 (IQR 30.2–67.8) versus a median measured DL_{CO} of 54.2 (IQR 35.8–71.9) observed in patients with AC alone. Patients with hypoLES and AC appeared to have a unique clinical phenotype with possible increased cardiac involvement and tendon friction rubs, which was not seen in the AC arm, although additional analysis was limited by the small size sample. Table 4 summarizes the association of characteristics

of the cohort with abnormal HREM and clinical features seen in patients with hypoLES and AC.

Unadjusted and adjusted logistic models.

We then sought to determine whether the associations between clinical variables and abnormal HREM patterns remained after adjusting for relevant covariates and potential confounders. In the unadjusted model (model 1), RP (score >1) was associated with 3-fold odds of having AC (odds ratio [OR] 3.08 [95% confidence interval (95% CI) 1.22–7.75]). In the simple adjusted model (model 2: covariates adjusted for age and disease duration), the strong association between AC and high RP remained (OR 3.79 [95% CI 1.41–10.21]). In addition, patients with AC were 5.63 times as likely to have diffuse cutaneous disease compared to patients with AC in model 1, and 6.07 times as likely to have diffuse cutaneous disease compared to patients with AC adjusting for age and disease duration (model 2). Interestingly, patients with AC were also more likely to have a reduced (worse) DL_{CO} (<60% predicted) compared to patients without AC in bivariate (unadjusted OR 2.69 [95% CI 1.10–6.60]) and adjusted (OR 2.62 [95% CI 1.05–6.54]) models. There was no detectable change in the risk of cardiac disease, lung disease, or muscle disease on the severity scale for those with AC compared to those without. Table 5 shows the statistical models examining the association between AC and the presence of severe SSc-related disease phenotypes. There was no significant increase in the risk of having IEM in association with RP or severe muscle, lung, cardiac, or GI disease, although the sample size was small (see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25080).

DISCUSSION

To our knowledge, our study is the largest cohort study to identify SSc-related features observed with distinct types of abnormal esophageal physiology, including AC, IEM, and hypotensive LES. In this cross-sectional analysis, we found that SSc patients with AC were more likely than SSc patients without AC to have a severe SSc phenotype, including more severe RP, more prevalent diffuse cutaneous disease, and reduced (worse) DL_{CO} on pulmonary function testing, with a suggestion for possible increased severity in cardiac involvement ($P = 0.06$) and prevalence of death ($P = 0.06$). Our study was the first to identify data suggesting that there may be a very strong association with IEM and the presence of anticentromere antibodies, suggesting that the IEM pattern of esophageal dysmotility may be associated with the CREST-associated esophageal dysmotility described in the literature (2). However, confirmatory studies are indicated, given the small sample size of patients with IEM.

Our data suggest that distinct clinical phenotypes may exist based on the presence of either AC or IEM on HREM. First, SSc patients with AC were 6 times more likely to have diffuse cutaneous disease when compared to limited cutaneous disease, even after adjusting for age and disease duration. Furthermore, SSc patients with AC were significantly more likely to have digital ulcers, pits, or gangrene and had a lower (worse) DL_{CO} on cardiopulmonary testing, also consistent with a more severe vascular phenotype (5,35). In contrast to the

AC group, 100% of SSc patients with IEM were positive for anticentromere antibodies, which is typically observed among patients with the limited cutaneous disease (36). In addition, patients with IEM appeared to have less frequent RP and higher (better) DL_{CO} in contrast to patients without IEM (36). Last, patients with IEM were noted to have a median disease duration of 16.5 years (IQR 6.1–19.3 years), whereas patients with AC had a disease duration of 13.8 years (IQR 6.5–22.6 years), suggesting that IEM may be present in SSc patients with a separate, milder clinical phenotype, rather than IEM being a progressive stage toward development of AC. However, longitudinal studies and larger cohort groups are needed to further investigate this hypothesis, as our sample size for IEM was small. Immune-mediated vascular injury and related vascular dysregulation may explain the increased association of severe RP in patients with AC; however, not all data support this hypothesis (5,35,37–39). These novel findings suggest that distinct clinical SSc-related esophageal phenotypes may exist and associate with unique clinical characteristics, rather than being part of a spectrum of disease.

While our data did not reach statistical significance, there was a suggestion for association with the presence of AC on HREM in SSc patients and death ($P = 0.06$), which may have been limited by the small cohort size. Of the patients who died in our cohort, 13 of 14 had AC on HREM. None of the patients with IEM died. These 14 patients who died demonstrated severe disease manifestations, with 100% having severe pulmonary disease, severe GI disease, and severe RP. Within the cohort that died, 50% of patients had end-stage cardiac disease and more than one-half required supplementary oxygen for respiratory support. Although whether AC specifically contributes to increased mortality in these patients remains unclear, AC may potentially serve as a predictor for end-stage disease and a higher risk of mortality in SSc.

Esophageal dysfunction in AC likely predisposes SSc patients to reflux and microaspiration that contributes to pneumonitis and fibrosis (10,19,40–42). While we did not see a significant association with the severity of pulmonary involvement in the general cohort of SSc patients with AC, we did confirm an association with reduced measured DL_{CO} in the AC group compared to patients without AC. This finding is consistent with a prior study evaluating 43 SSc patients, where a faster deterioration of DL_{CO} median values was observed in patients with severe esophageal motor disturbances on manometry. Another study of 79 SSc patients corroborated that the percent predicted DL_{CO} and forced expiratory volume in 1 second were reduced in patients with AC compared to IEM (19,40). Importantly, however, whether AC is an independent biomarker of severity or whether AC contributes to worsening SSc-related pulmonary disease is not yet clear (19). As AC can be heterogenous in its presentation, future studies assessing the degree of esophageal dilatation and the severity of secondary peristalsis may help further differentiate subtypes of AC and predict more severe complications related to reflux and microaspiration (43).

As the basal LES pressure is controlled partially by vagal innervation/the autonomic nervous system, the presence of hypoLES and AC appeared to have a higher prevalence of cardiac involvement. Autonomic nervous system dysregulation has been shown to play a role in SSc-related organ dysfunction and may impact function in both the heart and the GI tract (44). In 1 study of 36 SSc patients, distal esophageal hypocontractility was associated

with autonomic cardiac and pupillary dysfunction (45). Furthermore, SSc GI severity correlated with higher autonomic symptom scores as measured by the validated Composite Autonomic Symptom Score-31 survey (46). In our study, the combination of hypoLES and AC suggested unique SSc-related disease complications, with increased enrichment of cardiac involvement and tendon friction rubs relative to SSc patients with AC alone. One could hypothesize that some types of SSc-related esophageal dysmotility are manifestations of autonomic dysregulation and that other organ systems affected by SSc are impacted through similar mechanisms.

Our study has many strengths. We used a very well-characterized cohort of patients with detailed clinical features and extended autoantibody profiles. Data collection was standardized in the JHSC and strengthened by accrual over a long follow-up period. Some of the limitations of our investigation are secondary to the retrospective nature of the study. The HREM studies were obtained as part of clinical care, and thus while they were protocolized according to the institutional standards, they were not part of a research protocol. While our cohort represents one of the largest studies evaluating clinical features that associate with AC in SSc patients, our subgroup analysis is in part restricted by a small sample size, which limited the extent of multivariable analyses. We also did not have University of California Los Angeles Gastrointestinal Tract Questionnaire 2.0 data available for most patients; therefore patient-reported outcomes were not assessed. Selection bias in our cohort also may limit the generalizability of these results. Finally, these results were obtained as part of a single center assessment; prospective, multicenter studies should be considered to confirm our findings.

Our study demonstrates that the presence of AC in SSc patients in our cohort associates with a severe clinical phenotype; in contrast, our data suggest that IEM may associate with a milder overall clinical phenotype, although further evaluation of this possibility was limited by sample size. Determining the timing of AC onset and whether it precedes other complications of SSc will be an important next step in determining whether esophageal dysfunction can help to identify patients who may be at risk for increased disease morbidity and mortality. Additional prospective studies are needed to evaluate the development and prevalence of AC both early in disease and relative to other disease complications. Helping identify potential therapies that target underlying disease-related esophageal dysfunction will be important for better disease control, reduction in complications, and improved quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE & INNOVATIONS

- Absent contractility (AC) and ineffective esophageal motility may reflect distinct clinical phenotypes, rather than stages along a continuum of esophageal dysfunction.
- AC is associated with more severe systemic manifestations of systemic sclerosis (SSc), such as diffuse cutaneous disease.
- Manometry is an important tool to guide clinical intervention, given the diverse physiologic abnormalities that may exist in the esophagus of patients with SSc.

Table 1.

Characteristics of the 95 SSc patients with esophageal manometry data in the JHSC cohort (n = 95) *

Clinical and demographic features	With manometry (n = 95)
Age at manometry, years	57.7 (51.7–62.5)
Disease duration at manometry from RP, years	13.6 (6.2–21.9)
Disease duration at manometry from first symptom (RP or non-RP), years	13.7 (6.3–21.9)
Race, no./total (%)	
White	78/95 (82.1)
Black	13/95 (13.7)
Other	4/95 (4.2)
Female, no./total (%)	83/95 (87.4)
Diffuse cutaneous disease, no./total (%)	28/95 (29.5)
Myopathy, no./total (%) †	24/95 (25.3)
Muscle involvement (>1), no./total (%)	4/93 (4.3)
Cardiac involvement (>1), no./total (%)	29/90 (32.2)
Gastrointestinal disease (>1), no./total (%)	81/95 (85.3)
Lung involvement (>1), no./total (%)	63/88 (71.6)
Tendon friction rubs, no./total (%)	10/94 (10.6)
Sicca, no./total (%)	81/95 (85.3)
Death, no./total (%)	14/95 (14.7)
Time from manometry to death, years	3.1 (1.4–4.9)
Pulmonary function parameters, no./total (%)	
Low measured FVC (<80% predicted)	50/94 (53.2)
Low measured DL_{CO} (<60% predicted)	50/94 (53.2)
High RVSP by echo (>40 mm Hg) ‡	9/25 (36)
Antibodies, no./total (%)	
Centromere	30/75 (40.0)
Scl-70 (i.e., topoisomerase-1)	18/75 (24.0)
RNA polymerase III	3/75 (4.0)
Ro52	16/75 21.3)
Fibrillarin	1/75 (1.3)
Th/To	1/75 (1.3)
Ku	1/75 (1.3)
PM/Scl	0/75 (0)

* Values are the median (interquartile range) unless indicated otherwise. Severity of organ involvement was determined based on modified Medsger severity scores definitions (refs. 27,28). Definitions for each level of organ-specific severity scale are further characterized in Methods. Autoantibodies that were detectable through the Euroline immunoblot assay (Systemic Sclerosis Profile, Euroimmun Diagnostics) but were not present in this patient cohort were not listed. DL_{CO} = diffusing capacity of lung for carbon monoxide (low measured DL_{CO} defined as <60% predicted value as measured on pulmonary function tests); FVC = forced vital capacity; JHSC = Johns Hopkins Scleroderma Center; RP = Raynaud's phenomenon; RVSP = right ventricular systolic pressure (high RVSP was defined as estimated >40 mm Hg as measured by transthoracic echocardiogram); SSc = systemic sclerosis.

† Eleven of the 24 patients with myopathy were diagnosed by creatine kinase or aldolase elevation alone.

[≠] Elevated RVSP by TTE defined as >40 mm Hg.

Table 2.

Clinical characteristics of the SSc patients in the JHSC cohort with and without AC [*]

Clinical and demographic features	AC (n = 65)	Without AC (n = 30)	*P*
Demographics/physician assessed disease severity measures			
Age at time of manometry	58.3 (51.9–63.6)	54.7 (50.4–59.9)	0.152
Disease duration at manometry from RP, years	13.0 (6.5–22.6)	13.7 (4.1–21.7)	0.458
Disease duration at manometry from first symptom (RP or non-RP), years	13.8 (6.5–22.6)	15.1 (5.2–21.7)	0.707
Female, no./total (%)	54/65 (83.1)	29/30 (96.7)	0.096
SSc type, no./total (%)			
Diffuse cutaneous disease	25/65 (38.5) [†]	3/30 (10.0) [†]	0.007 [†]
Gastrointestinal disease (>1)	58/65 (89.2)	23/30 (76.7)	0.127
Cardiac involvement (>1)	24/62 (38.7)	5/28 (17.9)	0.056
Muscle involvement (>1)	1/64 (1.6)	3/29 (10.3)	0.088
Tendon friction rubs	8/64 (12.5)	2/30 (6.7)	0.494
Dry eyes	20/30 (66.7)	50/65 (76.9)	0.323
Dry mouth	52/65 (80.0)	23/30 (76.7)	0.788
Raynaud's phenomenon (>1)	37/65 (56.9) [†]	9/30 (30.0) [†]	0.017 [†]
Lung involvement (>1)	45/61 (73.8)	18/27 (66.7)	0.609
Death	13/65 (20.0)	1/30 (3.3)	0.058
Cardiopulmonary testing			
Measured FVC % predicted (n = 94)	68.7 (51.5–84.4)	67.8 (49.3–84.5)	0.990 [‡]
Measured DL_{CO} % predicted (n = 94)	50.6 (31.6–69.1) [†]	72.2 (6.9–85.9) [†]	0.026 [§]
Measured RVSP by TTE (n = 25) [¶]	35 (27–48)	28 (25–46)	0.414 [‡]
Autoantibodies, no./total (%)			
Scl-70 (i.e., topoisomerase-1)	15/52 (28.8)	3/23 (13.0)	0.240
Centromere	19/52 (36.5)	11/23 (47.8)	0.445
Fibrillarin	1/52 (1.9)	0/23 (0)	1.000
RNA polymerase III	3/52 (5.8)	0/23 (0)	0.548
Ro52	13/52 (25.0)	3/23 (13.0)	0.362
Th/To	1/52 (1.9)	0/23 (0)	1.000

Clinical and demographic features	AC (n = 65)	Without AC (n = 30)	*P*
Ku	1/52 (1.9)	0/23 (0)	1.000

[*] Values are the median (interquartile range) unless indicated otherwise. Autoantibodies that were detectable through the Euroline immunoblot assay (Systemic Sclerosis Profile, Euroimmun Diagnostics) but were not present in this patient cohort were not listed. Severity of organ involvement was determined based on modified Medsger severity scores definitions (refs. 27,28). Definitions for each level of organ-specific severity scale are further characterized in Methods. Significance was determined by Fisher's exact test unless otherwise indicated. AC = absent contractility; DL_{CO} = diffusing capacity of lung for carbon monoxide percent predicted value; FVC = forced vital capacity percent predicted value (measured by pulmonary function testing); JHSC = Johns Hopkins Scleroderma Center; RP = Raynaud's phenomenon; RVSP = right ventricular systolic pressure; SSc = systemic sclerosis; TTE = transthoracic echocardiogram.

[†] $P < 0.05$.

[‡] Significance determined by Wilcoxon's rank sum test.

[§] $P < 0.05$ determined by Wilcoxon's rank sum test.

[¶] Elevated RVSP by TTE defined as >40 mm Hg.

Table 3.

Clinical characteristics of the SSc patients in the JHSC cohort with and without IEM *

Clinical and demographic features	IEM (n = 9)	Without IEM (n = 86)
Age at time of manometry	57.5 (51.1–59.7)	57.8 (51.7–62.8)
Disease duration at manometry from RP, years	13.8 (3.8–19.3)	13.5 (6.3–22.8)
Disease duration at manometry from first symptom (RP or non-RP), years	16.5 (6.1–19.3)	13.7 (6.5–22.8)
Female, no./total (%)	9/9 (100)	74/86 (86)
SSc type, no./total (%)		
Diffuse cutaneous disease	1/9 (11.1)	27/86 (31.4)
Gastrointestinal disease (>1)	7/9 (77.8)	74/86 (86.0)
Cardiac involvement (>1)	1/8 (12.5)	28/82 (34.1)
Muscle involvement (>1)	1/9 (11.1)	3/84 (3.6)
Tendon friction rubs	1/9 (11.1)	9/85 (10.6)
Dry eyes	4/9 (44.4)	66/86 (76.7)
Dry mouth	6/9 (66.7)	69/86 (80.2)
Raynaud's phenomenon (>1)	1/9 (11.1)	45/86 (52.3)
Lung involvement (>1)	5/8 (62.5)	58/80 (72.5)
Death	0/9 (0)	14/86 (16.3)
Cardiopulmonary testing		
Measured FVC % predicted (n = 94)	83.5 (51.7–101.3)	68.0 (50.4–83.9)
Measured DL_{CO} % predicted (n = 94)	85.3 (73.8–92.7)	55.7 (32.3–71.9)
Measured RVSP by TTE (n = 25) †	30 (25–55)	34 (26–47)
Autoantibodies, no./total (%)		
Scl-70 (i.e., topoisomerase-1)	0/5 (0)	18/70 (25.7)
Centromere	5/5 (100)	25/70 (35.7)
Fibrillarin	0/5 (0)	1/70 (1.4)
RNA polymerase III	0/5 (0)	3/70 (4.3)
Ro52	1/5 (20.0)	15/70 (21.4)
Th/To	0/5 (0)	1/70 (1.4)
Ku	0/5 (0)	1/70 (1.4)

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[*] Values are the median (interquartile range) unless indicated otherwise. Severity of organ involvement was determined based on modified Medsger severity scores definitions (refs. 27,28). Definitions for each level of organ-specific severity scale are further characterized in Methods. Autoantibodies that were detectable through the Euroline immunoblot assay (Systemic Sclerosis Profile, Euroimmun Diagnostics) but were not present in this patient cohort were not listed. DL_{CO} % predicted = diffusing capacity of lung for carbon monoxide percent predicted value (measured by pulmonary function testing); FVC = forced vital capacity; IEM = ineffective esophageal motility; JHSC = Johns Hopkins Scleroderma Center; RP = Raynaud's phenomenon; RVSP = right ventricular systolic pressure; SSc = systemic sclerosis; TTE = transthoracic echocardiogram.

[†] Elevated RVSP by TTE defined as >40 mm Hg.

Table 4.

A comparison of the clinical characteristics of the SSc patients in the JHSC cohort with absent contractility with or without a hypoLES*

Clinical and demographic features	AC + hypoLES (n = 28)	AC alone (n = 37)
Age at time of manometry	58.4 (53.7–62.6)	58.3 (51.8–64.2)
Disease duration at manometry from RP, years	11.8 (7.4–26.4)	13.7 (6.2–21.7)
Disease duration at manometry from first symptom (RP or non-RP), years	12.9 (6.8–26.2)	13.8 (6.5–21.9)
Female, no./total (%)	22/28 (78.6)	32/37 (86.5)
SSc type, no./total (%)		
Diffuse cutaneous disease	17/28 (60.7)	8/37 (21.6)
Gastrointestinal disease (>1)	27/28 (96.4)	31/37 (83.8)
Cardiac involvement (>1)	16/27 (59.3)	8/37 (21.6)
Muscle involvement (>1)	1/27 (3.7)	0/37 (0)
Tendon friction rubs	7/28 (25.0)	1/36 (2.8)
Dry eyes	22/28 (78.6)	28/37 (75.7)
Dry mouth	23/28 (82.1)	29/37 (78.4)
Raynaud's phenomenon (>1)	20/28 (71.4)	17/37 (45.9)
Lung involvement (>1)	21/26 (80.8)	24/35 (68.6)
Death	6/28 (21.4)	7/37 (18.9)
Pulmonary function parameters		
Measured FVC % predicted (n = 64)	64.9 (43.2–79.4)	73.8 (55.2–86.2)
Measured DL_{CO} % predicted (n = 64)	44.7 (30.2–67.8)	54.2 (35.8–71.9)
Measured RVSP by TTE (n = 18)†	35 (34–48)	33 (28–58)
Autoantibodies, no./total (%)		
Scl-70 (i.e., topoisomerase-1)	8/24 (33.3)	7/28 (25.0)
Centromere	7/24 (29.2)	12/28 (42.9)
Fibrillarin	1/24 (4.2)	0/28 (0)
RNA polymerase III	1/24 (4.2)	2/28 (7.1)
Ro52	6/24 (25.0)	7/28 (25.0)
Th/To	1/24 (4.2)	0/28 (0)
Ku	0/24 (0)	1/28 (3.6)

*Values are the median (interquartile range) unless indicated otherwise. Severity of organ involvement was determined based on modified Medsger severity scores definitions (refs. 27,28). Definitions for each level of organ-specific severity scale are further characterized in Methods. Autoantibodies that were detectable through the Euroline immunoblot assay (Systemic Sclerosis Profile, Euroimmun Diagnostics) but were not present in this patient cohort were not listed. AC = absent contractility; DL_{CO} = diffusing capacity of lung for carbon monoxide percent predicted value; FVC = forced vital capacity percent predicted value (measured by pulmonary function testing); hypoLES = hypotensive lower esophageal sphincter; JHSC = Johns Hopkins Scleroderma Center; RP = Raynaud's phenomenon; RVSP = right ventricular systolic pressure; SSc = systemic sclerosis; TTE = transthoracic echocardiogram.

†Elevated RVSP by TTE defined as >40 mm Hg.

Table 5.

Statistical models evaluating the association between AC and the presence of severe SSc-related disease complications[*]

Characteristic	Unadjusted: model 1	Adjusted: model 2[†]
Cardiac disease (>1)[‡]	2.91 (0.97–8.67)	2.81 (0.93–8.45)
Lung disease (>1)[‡]	1.41 (0.53–3.76)	1.42 (0.52–3.85)
Muscle disease (>1)[‡]	0.14 (0.01–1.38)	0.12 (0.01–1.44)
Gastrointestinal disease (>1)[‡]	2.52 (0.80–7.99)	2.46 (0.77–7.84)
Raynaud's phenomenon (>1)[‡]	3.08 (1.22–7.75)[§]	3.79 (1.41–10.21)[§]
Cutaneous subtype, diffuse (based on mRSS)	5.63 (1.54–20.50)[§]	6.07 (1.64–22.5)[§]
Low DL_{CO}	2.69 (1.10–6.60)[§]	2.62 (1.05–6.54)[§]

[*] Values are the odds ratio (95% confidence interval) for having absent contractility (AC) with reference without AC. Low measured diffusing capacity of lung for carbon monoxide (DL_{CO}) defined as <60% predicted value as measured on pulmonary function tests. mRSS = modified Rodnan skin thickness score; SSc = systemic sclerosis.

[†] Logistic regression model adjusted for age and disease duration.

[‡] Modified Medsger severity score >1. Severity of organ involvement was determined based on modified Medsger severity scores definitions (refs. 27,28). Definitions for each level of organ-specific severity scale are further characterized in Methods.

[§] Statistically significant at $P < 0.05$.