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Spectrum of esophageal dysmotility in systemic sclerosis on high-resolution esophageal manometry as defined by Chicago classification

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SUMMARY. **The classic manometric findings in systemic sclerosis are aperistalsis of the esophageal body with hypotensive lower esophageal sphincter. These changes contribute to gastroesophageal reflux disease in these patients. With widespread use of high-resolution esophageal manometry, diverse abnormalities are seen. The aim of this study is to characterize esophageal dysmotility in patients with systemic sclerosis undergoing high-resolution esophageal manometry and compare demographic features and diagnostic test results among patients with varying degrees of esophageal dysmotility. Patients with systemic sclerosis who underwent high-resolution esophageal manometry between January 2008 and October 2014 at our institution were identified. High-resolution esophageal manometry studies were reinterpreted using the Chicago Classification, v3.0 criteria. We also reviewed the patient charts for demographic data, indications for manometry, esophagogastroduodenoscopy findings, pH studies, medication use, and autoantibody panel. The cohort consisted of 122 patients with a mean age of 53.3 ± 15.3 years. High-resolution esophageal manometry was normal in 23, showed ineffective esophageal motility in 22, absent contractility in 73, and one case each of type II achalasia, esophagogastric junction outflow obstruction, hypercontractile esophagus, and distal esophageal spasm. Patients with absent contractility were younger and more likely to have erosive esophagitis, hiatal hernia, and esophageal strictures than patients with ineffective esophageal motility or normal manometry. There were no statistically significant differences in the groups based on autoantibodies or indications for manometry. Diverse esophageal motility abnormalities were noted in systemic sclerosis with ineffective esophageal motility or absent contractility observed in over three-fourth of the patients. Patients with absent contractility were younger and had more severe reflux. The severity of gastroesophageal reflux disease related endoscopic findings correlated with the degree of esophageal dysmotility on high-resolution esophageal manometry.**

KEY WORDS: **esophageal motility, gastroesophageal reflux, scleroderma.**

INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease characterized by abnormal deposition of collagen in extracellular matrix leading to skin changes and internal organ dysfunction. It affects women three times more often than men and presents between the ages of 20–40 years.[1] The most common extracutaneous site of involvement in SSc is the gastrointestinal tract, especially the esophagus, affecting up to 90% of patients.[2] The classic esophageal finding is aperistalsis of the esophageal body associated with hypotonic lower esophageal sphincter (LES). These changes lead to severe gastroesophageal reflux disease (GERD), which may be complicated by erosive esophagitis, Barrett's esophagus, strictures, and rarely adenocarcinoma.[3]

The pathophysiologic mechanisms underlying esophageal dysmotility are probably due to complex interplay of vascular, immune and neural systems.[3] The postulated mechanisms include vascular damage with resulting ischemia and hypoxia and dysregulated fibroblast activation leading to excess collagen deposition.[4] These factors, in addition to antineuronal

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antibodies inhibiting muscarinic neurotransmission, may lead to development of neuropathy.[5] The altered cellular and humoral immunity can also lead to production of inflammatory cytokines, which have a direct effect on esophageal function.[3] The variable contributions of these pathogenic factors may lead to heterogeneity in the clinical phenotype of the disease. Since the pathophysiology of motor dysfunction is varied, we wanted to see if there were any manometric abnormalities not previously reported.

The availability of high-resolution esophageal manometry (HREM) with esophageal pressure topography (EPT) has recently allowed for dramatic improvements in diagnosis and management of esophageal motility disorders.[6] HREM, using closely spaced sensors, allows for comprehensive assessment of peristalsis along the entire length of esophagus and sphincter function. In addition to the ease of acquisition and image interpretation, HREM can diagnose subtle functionally significant manometric abnormalities, which are not identified by conventional manometry.[6] There are limited data regarding HREM findings in SSc at the time of initiation of this study. One study of 51 patients from France reported increased contractile velocity in proximal esophagus, reduced amplitude of mid-segment but not distal segment in SSc patients with esophageal dysmotility.[7] In another study of 28 patients with SSc, only those with classic manometric diagnosis of SSc i.e. 100% aperistalsis were studied.[8] Therefore, the aim of this study is to characterize esophageal motility abnormalities on HREM studies in patients with SSc using the Chicago Classification, v3.0.[9] We also sought to compare demographic and endoscopic features and other diagnostic test results in patients with varying degrees of esophageal dysmotility.

MATERIALS AND METHODS

All adult patients with diagnosis of SSc who underwent HREM between January 1, 2008 and October 31, 2014 at our institution were included in the study. The diagnosis of SSc was based on criteria from American College of Rheumatology.[10] Age, gender, race, medication use, alcohol, and smoking history as well as indications for HREM were obtained by electronic medical record search. This study design was approved by our Institutional Review Board.

High-resolution esophageal manometry

All patients underwent HREM using a 36-sensor solid-state catheter (Sierra Scientific Instruments Inc., Los Angeles, CA, USA). Analysis was performed using the Sierra Manoscan software version 3.0.1. All HREM studies were reinterpreted using the Chicago Classification of esophageal motility disorders, v3.0 criteria.[9]

Other diagnostic testing

Patients with SSc underwent additional testing as part of clinical evaluation for symptoms such as heartburn, dysphagia, or prior to lung transplant evaluation. Upper endoscopy reports were reviewed for the presence of hiatal hernia, reflux esophagitis, strictures, dilated esophageal lumen, esophageal diverticula, Barrett's esophagus, food in the esophagus or stomach, candida esophagitis, and gastric findings. PH testing was performed using a 24-hour transnasal catheter or 48-hour wireless Bravo monitoring capsule placed endoscopically. None of the patients had impedance testing. PH testing was considered abnormal if the time spent in reflux (pH < 4) was more than 5.5% of total time or 8.2% in upright or 3% in supine position. Solid-phase gastric emptying test was performed with a standard test meal of egg sandwich labeled with technetium-99m sulfur colloid. It was considered delayed if T1/2 was greater than 90 minutes or if there was more than 10% retention at 4 hours. The presence or absence of the following autoantibodies was also reviewed: anti-Smith (Sm), anti-Ribonucleic Protein (RNP), anti-Ro (SSA), anti-La (SSB), anti-centromere, anti-Scl70, anti-Jo1, and anti-chromatin.

Statistical analysis

Data are presented as mean ± standard deviation, median [25th, 75th percentiles] or frequency (percent). A univariable analysis was performed to assess differences between patients with different manometric patterns; analysis of variance or Kruskal–Wallis tests was used for continuous and ordinal factors and Pearson's chi-square tests or Fisher's exact tests were used for categorical variables. Post-hoc comparisons were done using a Bonferroni correction at a significance level of 0.017 (0.05/3). A $p < 0.05$ was considered statistically significant. SAS version 9.4 (the SAS Institute, Cary, NC) was used to perform all analyses.

RESULTS

A total of 122 patients met the inclusion criteria of which 92 (75%) were women and 30 (25%) were men. The mean age was 53.3 ± 15.3 years. The racial distribution of this cohort was 97 (80.8%) Caucasian, 18 (15%) african-american, 5 (4.1%) others, and unknown in 2 patients. Seventy two patients (59.5%) reported alcohol use, 4 (3.3%) were active smokers, 50 (41.3%) were ex-smokers, and 67(55.4%) denied smoking. Proton pump inhibitor (PPI) use was reported in 102 patients (84%), opiates in

67(55%), benzodiazepines in 42(34%), antidepressants 40 (33%), histamine receptor antagonists in 31 (25%), phosphodiesterase inhibitors in 32 (27%), and immunosuppressants in 82 (69%) of this group. The indication for the manometric evaluation was dysphagia in 62 (52%) patients, heartburn in 74 (63%), and preoperative evaluation for lung transplant in 47 (40%) of patients. Of the 47 lung transplant patients, 13 were asymptomatic at time of HREM and 34 reported reflux, dysphagia, or both.

HREM findings

The HREM diagnoses were as follows: normal motility in 23 (19%), ineffective esophageal motility (IEM) in 22 (18%), absent contractility (AC) in 73 (60%), Type II achalasia in 1, esophagogastric junction (EGJ) outflow obstruction in 1, hypercontractile esophagus in 1, and distal esophageal spasm in 1 patient. The median basal LES pressure was 17.1mm Hg with interquartile range (IQR) of 8.1 to 27.0 mm Hg and the median IRP was 3.4 mm Hg (IQR1.2, 6.3 mm Hg).

We compared the demographic and clinical data between patients with normal contractility, IEM and AC (Table 1). Patients with AC were younger than other two groups, with a mean age of 51 years compared to 55 and 60 years in normal motility and IEM respectively. There was higher prevalence of antidepressant medication use in patients with normal motility (47.8% vs. 40.9% in IEM and 21.9% in AC, $p = 0.031$).

There were no differences in gender, race, tobacco, alcohol use, and medication use among the three groups of patients (Table 1). As expected, the basal mean LES pressure was lowest in AC (Table 2). There were no statistically significant differences in indications, autoantibodies, or medication use among the three groups. In patients with normal HREM diagnosis, 90% of individual swallows were normal and the rest of the swallows were accompanied by weak peristalsis, fragmented peristalsis, premature contractions, or hypercontractile contractions. In IEM group, only 10% of swallows were characterized as normal and 60% of swallows were associated with failed peristalsis and 30% were accompanied by weak peristalsis.

Atypical findings on HREM

Unusual manometric patterns were observed in four patients. First patient was a 55-year-old woman with SSc diagnosed by skin biopsy at age 33. Two years prior to presentation, she had heartburn and acid

Table 1 Patient characteristics of systemic sclerosis cohort

	Normal ($N = 23$)	IEM ($N = 22$)	AC ($N = 73$)	p-value
Age (years)	55.5 ± 11.5	60.1 ± 12.5†	50.6 ± 16.6‡	0.029*
Gender				0.55**
Male	5(21.7)	4(18.2)	21(28.8)	
Female	18(78.3)	18(81.8)	52(71.2)	
Race				0.92***
Caucasian	19(86.4)	17(77.3)	57(79.2)	
African American	2(9.1)	4(18.2)	12(16.7)	
Tobacco use				0.12**
Current smoker	2(9.1)	0(0.0)	1(1.4)	
Never smoker	14(63.6)	10(45.5)	41(56.2)	
Quit	6(27.3)	12(54.5)	31(42.5)	
Alcohol use				0.88**
Yes	8(36.4)	9(40.9)	31(42.5)	
No	14(63.6)	13(59.1)	42(57.5)	
Medications				
Proton pump inhibitors	19(82.6)	16(72.7)	64(87.7)	0.24**
Antidepressants	11(47.8)†	9(40.9)	16(21.9)§	0.031**
Benzodiazepines	11(47.8)	9(40.9)	21(28.8)	0.20**
Opiates	15(65.2)	11(50.0)	39(53.4)	0.53**
H2 blockers	6(26.1)	6(27.3)	18(24.7)	0.97**
Prokinetics	6(26.1)	3(13.6)	18(24.7)	0.51**
Aspirin	7(30.4)	6(27.3)	12(16.4)	0.27**
NSAIDs	5(21.7)	4(18.2)	6(8.2)	0.16**
PDEIs	3(13.0)	6(27.3)	23(31.5)	0.22**
Immunosuppressants	17(73.9)	17(77.3)	48(65.8)	0.52**
Indications				
Reflux	16(69.6)	15(68.2)	53(72.6)	0.91**
Dysphagia	13(56.5)	10(45.5)	39(53.4)	0.74**
Preoperative	5(22.7)	8(36.4)	34(46.6)	0.12**

Values presented as mean ± SD or N (column %); p-values: *ANOVA; **Pearson' chi-square test; d, Fisher's Exact test; †Significantly different from AC; §Significantly different from normal motility; ‡Significantly different from IEM, A significance level of 0.017 was used for pairwise ad-hoc comparisons. AC, absent contractility; IEM, ineffective esophageal motility; NSAIDS, Nonsteroidal anti-inflammatory drugs; PDEIs, phosphodiesterase inhibitors.

Table 2 High-resolution esophageal manometry findings in subgroups of systemic sclerosis

	Normal ($N = 23$)	IEM ($N = 22$)	AC ($N = 73$)	P-value
Mean basal LES pressure	25.0 [20.6,35.6] †	18.5 [7.6,31.6]	14.0 [7.4,20.9]‡	<0.001*
Mean LES-IRP	4.7 [2.2,7.6]	4.0 [1.2,6.8]	2.7 [0.90,5.1]	0.21*
% Failed contractions	0 [0.00,10.0]§,†	60.0 [18.0,70.0]‡,†	100.0 [100.0100.0]§,‡	<0.001*
% Weak contractions	10.0 [0.00,20.0] §,†	30.0[20.0,60.0]‡,†	0.00[0.00,0.00]§,‡	<0.001*
% Normal contractions	90.0 [80.0,100.0]§,†	10.0 [8.3,20.0]‡,†	0.00 [0.00,0.00]‡,‡	<0.001*
% Fragmented contractions	3.3 ± 5.8	0.00	–	–
% Premature contractions	3.3 ± 5.8	0.00	–	–
% Hypercontractile contractions	3.3 ± 5.8	0.00	–	–

Values presented as mean ± SD or median [P25, P75]. P-values: *Kruskal–Wallis test; ‡Significantly different from Normal; §Significantly different from IEM; †Significantly different from AC; A significance level of 0.017 was used for pairwise ad-hoc comparisons. AC, absent contractility; IEM, ineffective esophageal motility; IRP, integrated residual pressure.

Table 3 Diagnostic testing in systemic sclerosis

	Normal motility ($N = 23$)	IEM ($N = 22$)	AC ($N = 73$)	P-value
Endoscopy	17	17	48	0.66*
Hiatal hernia	4(23.5)†	9(52.9)	35(72.9)‡	0.002**
Erosive esophagitis	2(11.8)†	6(35.3)	23(47.9)‡	0.030**
				0.92*
Grade A	0(0.0)	2(40.0)	8(44.4)	
Grade B	2(100.0)	2(40.0)	4(22.2)	
Grade C	0(0.0)	1(20.0)	4(22.2)	
Grade D	0(0.0)	0(0.0)	2(11.1)	
Esophageal stricture	3(17.6)	0(0.0)†	15(31.3)§	0.025**
Dilated esophagus	0(0.0)	3(17.6)	11(22.9)	0.097**
Barrett's esophagus	1(5.9)	2(11.8)	6(12.5)	0.75**
Food in esophagus	1(5.9)	2(11.8)	10(20.8)	0.31**
Candidal esophagitis	0(0.0)	2(11.8)	2(4.2)	0.37***
Food in stomach	1(5.9)	2(11.8)	6(12.5)	0.75**
Gastric ulcer	1(5.9)	1(5.9)	5(10.4)	0.99***
Gastric erosions	2(11.8)	1(5.9)	7(14.6)	0.64**
GAVE	1(5.9)	1(5.9)	2(4.2)	0.99***
Duodenal erosions	0(0.0)	1(5.9)	1(2.1)	0.66***
Abnormal pH test	5/7(71.4)	6/10(60.0)	19/30(63.3)	0.99***
Delayed gastric emptying	10/13(76.9)	7/14(50)	30/43(69.8)	0.28**

Values presented as N (column %). P-values: *Kruskal-Wallis test, **Pearson's chi-square test, ***Fisher's Exact test. ‡Significantly different from Normal; §Significantly different from IEM; †Significantly different from AC; A significance level of 0.017 was used for pairwise ad-hoc comparisons. AC, absent contractility; GAVE, gastric antral vascular ectasia; IEM, ineffective esophageal motility.

regurgitation for which she started on PPIs with good symptom relief. Upper endoscopy showed a 1 cm hiatal hernia but was otherwise normal. Shortly thereafter, she started having solid food dysphagia. HREM showed jackhammer esophagus. Second patient was a 62-year-old woman presenting with Raynaud's phenomenon and dysphagia to solids and liquids. Her endoscopy showed esophageal peptic stricture which improved after dilation. HREM showed EGJ outflow obstruction. Third patient was a 39-year-old woman with Sjorgen's syndrome, digital ischemic ulcers, and toxic goiter s/p radiation therapy presenting with dysphagia and heartburn. Endoscopy showed a patulous LES and moderate gastric antral vascular ectasia (GAVE). HREM showed distal esophageal spasm. Patient was on PPIs and treated by empiric dilation with a 48 French Savary dilator. The final case is a type II Achalasia diagnosed in a 75-year-old woman with SSc presenting with longstanding dysphagia to solids. Endoscopy showed a hypertonic LES but was otherwise normal. She was treated successfully by per oral endoscopic myotomy. Of note, none of these patients were on opiates at the time of HREM.

Endoscopic findings

Eighty six of the 122 (70%) patients underwent an upper endoscopy and 80 (93%) patients had abnormal endoscopic findings (Table 3). The most common esophageal findings were hiatal hernia in 49 (57%), erosive esophagitis in 31 (39%), decreased peristalsis in 21 (24%), peptic stricture in 18 (21%), and dilated esophageal lumen in 14 (16%) patients. Twenty eight out of 31 patients with erosive esophagitis were on PPIs at time of endoscopy. Erosive esophagitis, hiatal hernia, and esophageal strictures were more commonly found in AC than in the other two groups. There were no statistically significant differences in other endoscopic findings in all three groups. In 18 patients with esophageal stricture, 14 patients had an endoscopy on the same day but prior to HREM. Nine patients did not have a stricture and five patients

had a stricture which was dilated prior to HREM. Four patients were diagnosed with a stricture several days after HREM. In 31 patients with erosive esophagitis, 16 patients had healing confirmed by endoscopy on the day of HREM. Eleven patients had esophagitis diagnosed on same day or within one month of HREM and four patients were diagnosed with esophagitis 3 months or later.

Additional diagnostic testing

Forty seven of the 122 patients (39%) underwent pH testing, of which 30 (64%) had abnormal results. pH testing was performed on PPIs in 10 patients. Abnormal supine reflux was seen in 27 (57%) patients, abnormal upright reflux in 19 (40%), and abnormal total reflux in 27(57%). There were no significant differences between the pH test results of the three groups. Of the 72 patients who underwent gastric emptying testing, 49 (68%) had delayed gastric emptying and 4(5.6%) had rapid emptying. There were no significant differences between the gastric emptying test results of the three groups.

DISCUSSION

As per the traditional thinking, the characteristic finding on esophageal manometry in SSc patients is AC. However, this was seen in only 60% of SSc patients in this cohort. This study highlights two important points: (1) normal motility as well as atypical manometric findings seen in these patients point to the heterogeneity of pathological processes and (2) lack of typical manometric pattern should not preclude a diagnosis of SSc. Occurrence of rare esophageal spastic abnormalities has also been reported in recent studies. In a study of 79 patients with SSc reported by Northwestern university group, two patients had achalasia type-I, two had EGJ outflow obstruction and one had jackhammer esophagus.[11] In another study of 200 patients from Mayo, jackhammer esophagus (9%), distal esophageal spasm (2%), EGJ outflow obstruction (3%), and achalasia (3%) were reported.[12] Whether these rare abnormalities are due to SSc or an independent pathological process is uncertain. The findings of hypercontractile esophagus and distal esophageal spasm may be due to associated GERD or direct SSc related pathological process.

This study corroborates previous research showing hypotensive LES and failed or weak peristalsis in patients with SSc as well as a dissociation between symptoms and HREM findings. The prevalence of esophageal dysmotility in SSc ranges from 53% to 90%.[2,13–18] A recent study utilizing HREM in SSc reported esophageal dysmotility in 67.3% and hypotensive LES in 55.1%.[7] Diffuse skin involvement was associated with esophageal involvement. In 87.5% of patients, esophageal symptoms were not predictive of esophageal dysmotility.[7] A large Algerian study of 194 patients with SSc found decreased LES pressure in 61% of patients, aperistalsis in 61% of cases, and IEM in a further 19%.[19]

These data confirm the findings of Kimmel *et al.* that there is no association between the presence of autoantibodies and esophageal involvement.[11] However, in another study esophageal involvement in scleroderma was associated with the presence of anti-Scl70 antibody.[7] These differences may be due to a type II error in our study as autoantibody data were not available in 42% of patients. Furthermore, the laboratory criteria for ELISA testing of autoantibodies used a higher cutoff value of >1.0 compared to Roman *et al.*,[7] which might have decreased the sensitivity in evaluating cases with low level autoantibodies.

These data support the well-established fact that esophageal dysmotility contributes to severe GERD in these patients. Patients with AC were more likely to have severe GERD as manifested by erosive esophagitis, hiatal hernia, and strictures. Esophageal motility abnormalities are more prevalent with increasing severity of reflux disease, from nonerosive reflux disease to erosive reflux disease and Barrett's esophagus.[20] Previous series have identified variable degree of GERD related inflammation ranging from 3.2% to 60% depending on the severity of the underlying SSc.[17,19,21–23] In GERD patients, IEM is the most prevalent motility abnormality in those with respiratory symptoms as it is associated with delayed esophageal acid clearance.[24] The prevalence of erosive esophagitis in our study was 39% and lies within the range of previous studies.

This is one of the large cohorts reporting HREM findings in SSc patients. One of the main strengths of this study is the use of Chicago classification criteria for defining esophageal motility abnormalities found in SSc patients. Furthermore, all the HREM-EPT plots were reviewed again for the study purposes. One of the limitations of this study is that esophageal motility was assessed only in a subset of SSc patients who were referred for dysphagia or reflux or as part of evaluation for lung transplant candidacy. In addition, a significant proportion of patients were on benzodiazepines, opiates, and antidepressants, which were known to have varying effects on the esophageal motility and may have affected the motility patterns observed in the study.[25–29] Of note, 42 out of 47 patients with SSc interstitial lung disease referred for preoperative evaluation had esophageal dysmotility. Uncontrolled GERD in this population can adversely affect the lung graft function. So, we recommend routine pH testing and HREM in SSc patients with lung disease. Based on this study, we cannot infer the prevalence of motility abnormalities in other asymptomatic

SSc patients and even if found, no effective prokinetic therapy exists. So the role of HREM and pH testing in management of SSc patients without esophageal symptoms or lung disease needs to be determined.

In conclusion, although IEM or AC was the most common findings, HREM identified other rare spastic motility abnormalities in SSc. Patients with AC were of younger age and had more severe GERD. Esophageal dysmotility correlated with severity of GERD-related endoscopic findings. Future studies are needed to evaluate the pathophysiology of esophageal disease utilizing HREM.

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