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Loss of Peristaltic Reserve, Determined by Multiple Rapid Swallows is the Most Frequent Esophageal Motility Abnormality in Patients with Systemic Sclerosis

Dustin A. Carlson¹, Michael D. Crowell², Jessica N. Kimmel¹, Amit Patel³, C. Prakash Gyawali³, Monique Hinchcliff⁴, W. Leroy Griffing⁵, John E. Pandolfino¹, and Marcelo F. Vela²

¹Department of Medicine, Division of Gastroenterology and Hepatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

²Division of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, Arizona, USA

³Division of Gastroenterology and Hepatology, Washington University School of Medicine, St. Louis, Missouri, USA

⁴Department of Medicine, Division of Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

⁵Division of Rheumatology, Mayo Clinic, Scottsdale, Arizona, USA

Abstract

We assessed peristaltic reserve using multiple rapid swallows (MRS) during esophageal high-resolution manometry (HRM) of 111 patients with systemic sclerosis (89 female; ages 42–64 years). We performed a retrospective analysis of HRM studies that included MRS in patients with systemic sclerosis, performed at 2 tertiary referral centers, and compared data with those from 18 healthy volunteers (controls). HRM findings were analyzed according to the Chicago Classification to provide an esophageal motility diagnosis. Response to MRS was evaluated for presence of contraction and for augmentation, defined as distal contractile integral after MRS greater than the median distal contractile integral of 10 supine swallows. Esophageal motility

Corresponding author: Marcelo Vela, Division of Gastroenterology and Hepatology, Mayo Clinic, 13400 East Shea Blvd., Scottsdale, AZ 85253, vela.marcelo@mayo.edu.

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diagnoses included 41% with absent contractility, 31% with normal motility, 23% with ineffective esophageal motility, and 5% that met the criteria for other esophageal motility disorders. Contraction (37%) and peristaltic augmentation (18%) following MRS were observed less frequently in patients with systemic sclerosis than in controls (83% and 100%, respectively). Impaired peristaltic reserve, as assessed with MRS during HRM, is therefore the most common esophageal motility finding among patients with systemic sclerosis.

Keywords

systemic sclerosis; high-resolution manometry; esophageal motility

Introduction

Systemic sclerosis (SSc) is a multi-system, autoimmune disease that commonly involves the esophagus, with up to 80% of patients reporting symptoms of dysphagia or association with gastro-esophageal reflux disease (GERD) and up to 90% of patients demonstrating some objective evidence of esophageal dysmotility.^{1, 2} Traditionally, the esophageal motility pattern consisting of absent peristalsis and hypotensive lower esophageal sphincter (LES) pressure is considered scleroderma esophagus, however this pattern can also be seen in other systemic diseases (e.g. diabetes, multiple sclerosis).³

Multiple rapid swallows (MRS) during high-resolution manometry (HRM) is a simple provocative measure that has been proposed as a method to assess peristaltic reserve.^{4, 5} During the MRS sequence, neural inhibition leads to esophageal smooth muscle and LES relaxation followed by a robust contraction in the esophageal body; thus, a normal response to MRS requires both intact neural mechanisms to regulate motility and muscular integrity to respond to the MRS stimulation.⁶ Previous studies suggested that MRS may be a useful complement to the standard manometric evaluation with abnormalities in peristaltic reserve potentially contributing to GERD or symptom development.⁶⁻⁸ Thus, an assessment of esophageal neuromuscular integrity using MRS may shed insight into SSc esophageal dysfunction.

The aim of our study was to evaluate responses to MRS during HRM to assess the rate of impaired peristaltic reserve in patients with SSc.

Methods

Patients

Patients from two tertiary referral centers (Mayo Clinic, Arizona and Northwestern University, Chicago) with SSc who had previously undergone HRM studies that included MRS were respectively identified. The Mayo Cohort was identified from a query of a dedicated motility database between January 2012 and September 2014. The Northwestern cohort was identified by billing codes generated between January 2004 and May 2014 using a comprehensive database of electronic health records of Northwestern Memorial Hospital and affiliated clinics. Patients were referred for esophageal manometry often for evaluation of dysphagia and/or reflux-related symptoms. Charts were reviewed to confirm SSc

diagnosis by 2013 American College of Rheumatology SSc criteria.⁹ Presence or absence of symptoms of dysphagia, reflux (heartburn or regurgitation), and chest pain were evaluated by clinical interview (Mayo) and chart review (Northwestern). Patients with previous history of upper GI surgery, such as fundoplication, were excluded from analysis.

A previously described cohort of 18 asymptomatic subjects (controls; ages 18 – 32, 10 female) who underwent HRM with MRS at Washington University in St. Louis was included for comparison.⁴

The study protocol was approved by the Mayo Clinic, Northwestern University, and Washington University Institutional Review Board. A waiver of informed consent was obtained for the retrospective analysis.

High-resolution manometry studies

The HRM studies were completed after at least a six-hour fast using a 4.2-mm outer diameter, solid-state assembly with 36 circumferential pressure sensors spaced 1 cm apart (Medtronic Inc, Shoreview, MN). The HRM protocol included a 5-minute baseline recording, ten 5-ml water swallows at 20-30 second intervals in a supine position, and an MRS sequence involving five 2-ml swallows every 2-3 seconds in the upright position.

The HRM studies were analyzed using Manoview Analysis Software v3.0 (Medtronic) by authors MDC and MFV (Mayo SSc patients), DAC (Northwestern SSc patients), and AP and CPG (controls). Baseline esophageal motility diagnosis was assigned according to the Chicago Classification.¹⁰ Basal esophagogastric junction (EGJ) pressures were measured during the baseline recording period at end-expiration using the isobaric contour; <9 mmHg was considered hypotensive. The MRS sequence was analyzed for intact inhibition and contractile response. Inhibition was designated abnormal if a contraction segment with isobaric contour >20mmHg, >3cm in length, and distal contractile integral (DCI) > 100 mmHg-s-cm was present during the course of the multiple, rapid swallows. The contractile response following the MRS was described by presence or absence of a peristaltic response (DCI > 100 mmHg-s-cm) and the DCI was measured. An augmentation ratio was calculated as the DCI following MRS divided by the median of the non-failed (i.e. DCI > 100), supine swallows. As a normal response after MRS should be an increase in the peristaltic vigor, thus an augmentation <1 was considered abnormal.

Statistical analysis

Comparisons were made among SSc-patients and controls by HRM diagnoses and by MRS-response. Categorical variables were compared using Fisher's exact tests and continuous variables were compared using Mann-Whitney or Kruskal-Wallis tests. Statistical comparisons were made at P<0.05.

Results

Subjects

At total of 111 SSc patients (89 female; age 51 (42 – 64) years; BMI 23.95 (20.98 – 29.08 kg/m²) with HRM including MRS were included for analysis; The Mayo cohort included 63

patients (after exclusion of 32 total patients: 8 did not meet SSc ACR 2013 criteria, one had prior fundoplication, and 23 had technically-limited HRM) and the Northwestern cohort included 48 patients (after exclusion of 49 patients: 37 did not meet SSc ACR 2013 criteria, 6 had prior upper GI surgery, and 6 had technically-limited HRM), which were generally similar with respects to demographic, clinical, and manometric characteristics, though differed regarding SSc subtypes and percentage of patients with reflux symptoms (Table 1).

Esophageal motility characteristics

Absent contractility (41%) was the most frequent Chicago Classification motility diagnosis, followed by normal motility (31%) and ineffective esophageal motility (IEM, 23%). 5% (6/111) of SSc patients had other esophageal motility diagnoses, which included, Jackhammer esophagus (n=3), EGJ outflow obstruction (n=1), distal esophageal spasm (n=1) and type III achalasia (n=1). Hypotensive EGJ pressure was observed in 56% (61/109) of SSc patients, including 64% (29/45) of patients with absent contractility.

Response to MRS

Among all SSc patients, contraction and peristaltic augmentation after MRS was seen in 37% (41/111) and 18% (20/111) of patients; thus, abnormal peristaltic reserve was the most common manometric finding among our SSc cohort (Figure 1A). Contraction ($p < 0.001$) and peristaltic augmentation ($p < 0.001$) following MRS were observed less frequently in SSc patients than in controls. Frequencies differed among SSc patients by esophageal motility diagnoses, (contraction: $p < 0.001$; augmentation: $p = 0.001$), Figure 1B. Impaired inhibition during MRS was observed in 10 (9%) of patients with SSc (3 IEM, 2 Normal motility, 2 Jackhammer, 1 EGJ outflow obstruction, 1 distal esophageal spasm, 1 type III achalasia) and 5 (28%) of controls, $p < 0.001$.

Discussion

By evaluating SSc patients from a multi-centered cohort using HRM with MRS, we observed that abnormal MRS response was the most common motility pattern, not absent contractility or IEM with or without LES hypotension. Additionally, we found that impaired peristaltic reserve was observed in the majority of SSc patients regardless of baseline esophageal motility diagnosis.

Although previous studies assessing the manometric diagnoses of patients with SSc report absent contractility as the most common motility pattern among SSc patients, absent esophageal peristalsis is not a universal finding among patients with SSc; IEM and normal esophageal motility are also observed.¹¹⁻¹³ Another study using HRM to evaluate patients with SSc reported similar frequencies of esophageal motor patterns as our current study: 22/48 (46%) had absent peristalsis, 10/48 (21%) had hypotensive peristalsis and 16/48 (33%) had normal peristalsis.¹²

The manometric response to MRS has not been reported specifically in patients with SSc. A previous study of patients without reported connective-tissue disease presenting with esophageal symptoms reported that almost two-thirds of patients with normal esophageal motility by conventional manometry demonstrated an abnormal peristaltic augmentation

following MRS, suggesting that an abnormality in peristaltic reserve may contribute to symptom generation in a subset of patients.⁶ Further, among patients with IEM, over half were able to generate a normal peristaltic response following MRS. The authors suggested that although integrity of both neural (inhibitory and excitatory) and muscular function is required to generate a normal peristaltic response, IEM may be related to a neuropathy that can be overcome with MRS provocation in patients with intact esophageal musculature.⁶ In our study normal MRS augmentation was observed less frequently: only 32% of SSc-patients with normal motility and 25% with IEM. This lends further support to esophageal dysfunction of SSc being related to myopathy, such as demonstrated by histologic studies of cadaveric esophagi from patients with SSc.^{14, 15} These studies demonstrated that the majority of patients with SSc (70-94%) had esophageal smooth muscle atrophy as the predominant finding (tissue fibrosis, the often suggested cause of esophageal dysfunction in SSc, was not commonly seen).

Applying findings of HRM with MRS may have clinical implications with regards to management of patients with SSc. The use of promotility agents is somewhat limited by side effect profiles (e.g. tardive dyskinesia with metoclopramide) and lack of consistent clinical benefits in SSc patients with esophageal dysmotility. Selection of SSc patients with an ability to augment peristalsis following MRS response may help identify those patients most likely to benefit from promotility therapy; particularly if and/or when novel, efficacious promotility agents become available.^{6, 16} Additionally, although anti-secretory therapy with proton-pump inhibitors is the most effective medical therapy for GERD and is recommended in all patients with SSc, it is associated with a small increased risk of infection (such as *Clostridium difficile* and community-acquire pneumonia), small-intestinal bacterial overgrowth, and possibility osteoporosis, in a dose-dependent fashion.¹⁷⁻²¹ However, lower doses of anti-secretory therapies may be preferable in patients with a normal MRS response that may be less susceptible to GERD.^{7, 8}

In conclusion, we observed that an abnormal response to MRS, i.e. abnormal peristaltic reserve, was the most common manometric pattern in a retrospectively-evaluated, large, multi-centered cohort of patients with SSc. This observation supports myopathy as the primary pathogenesis of esophageal dysfunction associated with SSc and may have implications for clinical management of patients with SSc. However, future studies using HRM with MRS and addressing clinical outcomes after therapeutic intervention are needed to better demonstrate the clinical utility of findings associated with the MRS response on HRM.

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Abbreviations

DCI	distal contractile integral
EGJ	esophagogastric junction
GERD	gastro-esophageal reflux disease
HRM	high-resolution manometry
LES	lower esophageal sphincter
MRS	Multiple rapid swallows
SSc	Systemic sclerosis

Figure 1. Esophageal motility characteristics and peristaltic reserve among patients with systemic sclerosis (SSc)

1A) Frequencies of esophageal motility diagnoses and abnormal multiple rapid swallow (MRS) responses among SSc patients. **1B).** MRS characteristics of controls and SSc patients by esophageal motility diagnoses. None of the SSc patients with absent contractility had contraction or peristaltic augmentation after MRS.

Table 1
Baseline characteristics of systemic sclerosis (SSc) cohorts by study site

	Mayo Clinic	Northwestern	P-value
Age; yrs	56 (42-65)	49 (41-62)	0.110
BMI; kg/m ²	23.71 (20.70-28.40)	26.35 (22.25-29.83)	0.177
Female; n (%)	48 (54)	41 (46)	0.227
Chest Pain; n (%)	18 (29)	11 (23)	0.523
Dysphagia; n (%)	48 (76)	41 (85)	0.337
GERD; n (%)	41 (65)	42 (88)	0.008
SSc Subtypes			<0.001
Limited; n (%)	36 (57)	25 (52)	
Diffuse; n (%)	25 (40)	8 (17)	
Other ¹ ; n (%)	2 (3)	15 (31)	
HRM Motility Diagnosis			0.962
Absent contractility; n (%)	25 (40)	21 (44)	
IEM; n (%)	14 (22)	11 (23)	
Normal motility; n (%)	20 (32)	14 (29)	
Other ² ; n (%)	4 (6)	2 (4)	

All results are median (IQR) unless otherwise specified.

¹Other SSc subtypes included 6 with mixed (2 Mayo; 4 Northwestern); the remainder were from Northwestern: systemic sclerosis sine scleroderma (n = 6), Overlap (n = 5), and unreported (n = 1).

²Other motility diagnoses included 3 with jackhammer (2 Mayo, 1 Northwestern), 1 with EGJ outflow obstruction (Northwestern), 1 distal esophageal spasm (Mayo), and 1 type III achalasia (Mayo).

IEM – ineffective esophageal motility.