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Original Article

# Esophageal Involvement and Determinants of Perception of Esophageal Symptoms Among South Koreans With Systemic Sclerosis

**Joon Seong Lee,[1] Hyun-Sook Kim,[2] Jung Rock Moon,[1] Tom Ryu,[1] Su Jin Hong,[3] Young Sin Cho,[4] Junseok Park,[1] and Tae Hee Lee[1]***

*[1]Institute for Digestive Research, Digestive Disease Center, Soonchunhyang University College of Medicine, Seoul, Korea; [2]Department of Rheumatology, Soonchunhyang University College of Medicine, Seoul, Korea; [3]Department of Internal Medicine, Soonchunhyang University College of Medicine, Bucheon, Gyeonggi-do, Korea; and [4]Division of Gastroenterology, Cheonan Hospital, Soonchunhyang University College of Medicine, Cheonan, Chungcheongnam-do, Korea*

## Background/Aims
Our study aims to characterize esophageal motor function; evaluate the relationships among esophagogastroduodenoscopy (EGD), high-resolution manometry (HRM), and 24-hour esophageal multichannel intraluminal impedance monitoring combined with pH-metry (MII-pH); and elucidate the determinants of esophageal symptom perception in South Koreans with systemic sclerosis (SSc).

## Methods
We reviewed prospectively collected HRM (n = 46), EGD (n = 41), and MII-pH (n = 37) data from 46 consecutive patients with SSc (42 females; mean age 50.1 years) who underwent esophageal tests between June 2013 and September 2018.

## Results
The most common HRM diagnosis was normal (39.1%), followed by ineffective esophageal motility (23.9%) and absent contractility (21.7%). Erosive esophagitis was observed in 12.2% of total SSc patients, with a higher frequency in patients with absent contractility than those with normal motility (44.5% vs 0.0%, $P = 0.01$). Pathologic acid exposure was observed in 6 patients (20.0%) and positive symptom association in 18 patients (60.0%) in MII-pH tests of symptomatic patients. The proportion of SSc patients with esophageal symptoms not explained by reflux or mucosal or motor esophageal abnormalities was 33.0%.

## Conclusions
Esophageal involvement among South Koreans with SSc was characterized by heterogeneous motility patterns, with a higher prevalence of normal motility and lower prevalence of erosive esophagitis. Reflux hypersensitivity or functional heartburn might be partly attributed to the perception of esophageal symptoms in SSc patients who have neither gastroesophageal reflux disease nor esophageal dysmotility.
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## Key Words
Diagnosis; Esophageal motility disorders; Esophagus; Manometry; Scleroderma

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*Correspondence: Tae Hee Lee, MD, PhD
Institute for Digestive Research, Digestive Disease Center, Soonchunhyang University College of Medicine, 59, Daesagwan-ro, Hannam-Dong, Yongsan-Gu, Seoul 140-743, Korea
Tel: +82-2-710-3084, Fax: +82-2-709-9696, E-mail: iman0825@schmc.ac.kr
Joon Seong Lee and Hyun-Sook Kim contributed equally to this work.

## Introduction

The prevalence of systemic sclerosis (SSc) has been reported to be race specific,[1] with a lower prevalence in the white (224.7/million) than the black (315/million) population. In a survey based on the public health system database, a lower prevalence (53/million) was observed in the Japanese population.[2] A recent Korean nationwide population-based study indicated that the prevalence was 77.7/million population.[3] A single-center, predominantly white, SSc cohort in Canada reported ethnic variation in certain clinical features such as esophageal dysmotility and calcinosis.[4] Specifically, East Asians had esophageal dysmotility (69.0%) less frequently compared with the white population (88.0%).[4]

Esophageal manometry is the gold standard to evaluate esophageal dysmotility. The classic sclerosis esophagus is defined when SSc patients have no peristalsis in the distal esophagus and hypotensive lower esophageal sphincter (LES) pressure on manometric examination. Recently, high-resolution manometry (HRM) has replaced conventional manometry because of better diagnostic accuracy and reproducibility. A few HRM studies have evaluated esophageal involvement in Western SSc patients.[5] The classic sclerosis esophagus was found in as many as 55.0% of Western SSc patients. Crowell et al[6] reported that this classic esophageal manometric abnormality was found in only one-third of patients, and normal motility was found in 26.0%, implying a heterogeneous spectrum of esophageal dysmotility among Western SSc patients. Esophageal dysmotility in East Asian SSc patients has not been determined based on HRM examination.

Ethnic and geographical differences are closely related to the prevalence of erosive esophagitis among the general population.[7,8] The prevalence of erosive esophagitis is reportedly higher in Western populations than in East Asian populations. The estimated prevalence of erosive esophagitis in Western patients with SSc is 30.0-40.0%, although rates up to 60.0% have been reported.[9-12] Its prevalence among East Asian patients with SSc is unknown.

Most Western SSc studies have indicated that the presence of esophageal symptoms is not a reliable predictor of esophageal dysmotility.[12-15] Symptoms of gastroesophageal reflux have been reported to be a poor indicator of erosive esophagitis in Western SSc patients.[10] Little is known about the associations of esophageal symptoms with esophageal dysmotility and erosive esophagitis in East Asian patients with SSc. The perception of esophageal symptoms in some SSc patients is explained by reflux or mucosal or esophageal dysmotility. However, to our knowledge, the determinants of esophageal symptom perception in SSc patients who have neither gastroesophageal reflux disease nor dysmotility have never been reported.

To develop a better understanding of esophageal involvement in South Koreans with SSc, the specific aims of this study are to characterize esophageal motor function; evaluate the relationships among HRM, esophagogastroduodenoscopy (EGD), and 24-hour esophageal multichannel intraluminal impedance monitoring combined with pH-metry (MII-pH) data; and elucidate the determinants of esophageal symptom perception.

## Materials and Methods

### Patient Characteristics and Ethics Statement

Consecutive SSc patients referred from the SSc clinic for esophageal manometry between June 2013 and September 2018 were included. SSc was diagnosed using the 2013 American College of Rheumatology SSc criteria.[16] SSc was categorized as limited cutaneous systemic disease (lcSSc) or diffuse cutaneous systemic disease (dcSSc) according to the distribution of skin involvement, as proposed by LeRoy et al.[17] Patients with incomplete clinical assessments were excluded. Complete data were available for 46 patients (lcSSc, 26; dcSSc, 20) with consecutive HRM studies conducted between June 2013 and September 2018. Relevant data were collected on each patient, including age, sex, and body mass index (BMI), as well as clinical information. The study was approved by the institutional review boards of participating hospital (2019-04-033-001) and informed consent was obtained from all participants.

### High-resolution Manometry Procedure

A solid-state HRM assembly (Sierra Scientific Instruments, Given Imaging, Los Angeles, CA, USA) with 36 solid-state sensors spaced at 1-cm intervals was used. We measured data on basal LES pressure, integrated relaxation pressure (IRP), distal contractile integral (DCI), and distal latency (DL) to classify esophageal motility disorders according to the Chicago classification of esophageal motility disorders, version 3.0. The esophagogastric junction (EGJ) contractile integral (EGJ-CI) was measured as reported previously by Gor et al[18] from the landmark period. Hypotensive mean EGJ pressure at rest was defined as less than 13 mmHg. The combination of absent contractility and hypotensive EGJ pressure is defined as classic sclerosis esophagus.[6] The multiple rapid swallow (MRS) test was assessed for complete deglutitive inhibition and optimal post-MRS contraction. Deglutitive inhibition was defined

as incomplete if a contraction segment with an isobaric contour greater than 20 mmHg, length greater than 3 cm, and DCI greater than 100 mmHg·sec·cm, was present during the MRS test. The post-MRS contraction after MRS was designated as suboptimal if the augmentation ratio (ie, the DCI after MRS divided by the median of the non-failed patients [ie, DCI > 100]) was less than 1. An abnormal MRS response was defined as the presence of either incomplete deglutitive inhibition or suboptimal post-MRS contraction (Supplementary Figure).

## Esophagogastroduodenoscopy Examination

EGD examinations were performed in 41 SSc patients using the GIF-HQ290 or GIF-Q260 endoscope (Olympus Medical Systems Corp, Tokyo, Japan) with/without narrow band imaging by 2 gastroenterologists (T.H.L. and J.S.L.) at our center. Five patients in whom EGD was performed at an outside hospital were excluded from our analysis. A cervical inlet patch was identified as a well-circumscribed, pinkish-yellow area with a distinct border during white light endoscopy. Reflux esophagitis was defined as grade A or more severe, in accordance with the Los Angeles classification.[19] The gastroesophageal flap valve, which is created by intraluminal extension of the angle of His, was graded I to IV according to the grading system recently described by Hill et al.[20]

## Multichannel Intraluminal Impedance Monitoring Combined With pH-metry Procedure

MII-pH examination (Sandhill Scientific, Inc, Highland Ranch, CO, USA) was performed at least 7 days after proton pump inhibitor withdrawal. The pH electrode was placed 5 cm above the upper margin of the manometrically defined LES, and esophageal impedance electrodes' values (z1, z2, z3, z4, z5, and z6) were determined at 6 sites (3, 5, 7, 9, 15, and 17 cm above the LES, respectively). The DeMeester score, acid exposure upright (%), acid exposure recumbent (%), acid exposure total (%), bolus exposure upright (%), bolus exposure recumbent (%), bolus exposure total (%), proximal acid events, proximal nonacid events, proximal total events, distal acid reflux events, distal non-acid reflux events, and distal total reflux events were measured.[21] Pathologic acid exposure (PAE) was defined when the distal esophageal acid exposure time was greater than 4.2% at a pH < 4 over 24 hours. Symptoms were considered associated with reflux if they occurred within a 2-minute window after onset of the reflux episode.[21] Symptom association (SA) was considered positive if the symptom index was 50.0% or greater; SA probability was considered positive if it was 95.0% or greater.[22] All parameters were measured using Bio View Analysis software (Sandhill Scientific, Inc).

## Esophageal Symptoms

Esophageal symptoms included heartburn, regurgitation, chest pain, dysphagia, globus sensation, and others (belching, cough, asthma, etc). Each symptom was classified as present or absent. If symptoms such as heartburn, regurgitation, chest pain, dysphagia, and globus sense were present, they were rated according to frequency and severity using a 5-point Likert scale (0-4). We asked patients to rate the frequency of their symptoms as follows: 0, no symptoms; 1, less than once per month; 2, two to four times per month; 3, one to six times per week; and 4, daily. The patients also rated the severity of their symptoms as follows: 0, no symptoms; 1, can be ignored with effort; 2, cannot be ignored but does not influence daily activities; 3, cannot be ignored and limits concentration on daily activities; and 4, cannot be ignored and markedly limits daily activities, often requiring rest. The individual symptom score for each symptom was calculated as the product of the frequency and severity scores.

## Clinical Evaluation

Generally, the disease duration in SSc studies is defined as the time elapsed since the onset of the first Raynaud's phenomenon.[23] The modified Rodnan skin score (mRSS) is a measure of skin thickness and is used as a primary or secondary outcome measure in clinical trials of systemic sclerosis.[24] Measurement of skin thickness is used as a surrogate for disease activity, severity, and mortality in dcSSc patients.[24] In our study, mRSS was assessed by a rheumatology expert (H.S.K.). With respect to disease status in SSc patients, there is no gold standard instrument. However, the identification of organ damage has been used as a measure. Therefore, we evaluated the relationship between HRM metrics and the presence of interstitial lung disease.

## Statistical Methods

Quantitative and qualitative data are presented as medians (interquartile range [IQR]) and numbers (percentage), respectively. Comparisons of data from the HRM, EGD, and MII-pH tests were performed using the Mann–Whitney test and chi-squared test or Fisher's exact test when appropriate. The Spearman's correlation coefficient was used to analyze the relationship among the disease duration, mRSS, and HRM metrics. For multiple comparisons, *P*-values were adjusted by the Bonferroni procedure. A *P*-value < 0.05 was considered statistically significant.

## Results

The SSc patients (n = 46) were mostly women (91.3%), with a median (IQR) age of 53.0 (42.8-58.3) years and BMI of 22.0 (20.3-24.1) kg/m$^2$. The lcSSc and dcSSc subtypes were diagnosed in 26 (56.5%) and 20 (43.5%) patients, respectively. There were 36 SSc patients (78.3%) with any esophageal symptoms, with regurgitation (16, 34.8%) and globus sensation being the most commonly reported symptoms. Table 1 shows the baseline clinical characteristics of the patients with lcSSc and dcSSc.

**Table 1.** Baseline Characteristics of Patients With Limited or Diffuse Systemic Sclerosis

| Variables | lcSSc (n = 26) | dcSSc (n = 20) | *P*-value[a] | Total (N = 46) |
|---|---|---|---|---|
| Female | 24 (92.3) | 18 (90.0) | 0.783 | 42 (91.3) |
| Age (yr) | 54.0 (44.8-58.3) | 49.0 (37.3-60.5) | 0.690 | 53.0 (42.8-58.3) |
| BMI (kg/m$^2$) | 21.9 (20.1-24.2) | 22.1 (20.5-23.9) | 0.973 | 22.0 (20.3-24.1) |
| Esophageal symptoms | | | | |
| Heartburn | 11 (42.3) | 2 (10.0) | 0.016 | 13 (28.3) |
| Regurgitation | 10 (38.5) | 6 (30.0) | 0.550 | 16 (34.8) |
| Chest pain | 10 (38.5) | 4 (20.0) | 0.177 | 14 (30.4) |
| Dysphagia | 7 (26.9) | 4 (20.0) | 0.585 | 11(23.9) |
| Globus | 8 (30.8) | 8 (40.0) | 0.515 | 16 (34.8) |
| Belching | 8 (30.8) | 4 (20.0) | 0.410 | 12 (26.1) |
| Cough | 6 (30.8) | 5 (25.0) | 0.667 | 11 (23.9) |
| Asthma | 0 (0.0) | 2 (10.0) | 0.184 | 2 (4.3) |
| EGD assessment | 24 (92.3) | 17 (85.0) | 0.640 | 41 (89.1) |
| CIPs | 1 (4.2) | 0 (0.0) | > 0.999 | 1 (2.4) |
| Erosive esophagitis | 1 (4.2) | 4 (23.5) | 0.141 | 5 (12.2) |
| GEFV (III-IV) | 3 (12.5) | 5 (29.4) | 0.241 | 8 (19.5) |
| MII-pH assessment | 24 (92.3) | 13 (65.0) | 0.029 | 37 (80.4) |

[a]Comparison between limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc).
BMI, body mass index; EGD, esophagogastroduodenoscopy; CIP, cervical inlet patch; GEFV, gastroesophageal flap valve; MII-pH, multichannel intraluminal impedance monitoring combined with pH-metry.
Values are represented as numbers (%) or medians (interquartile range).

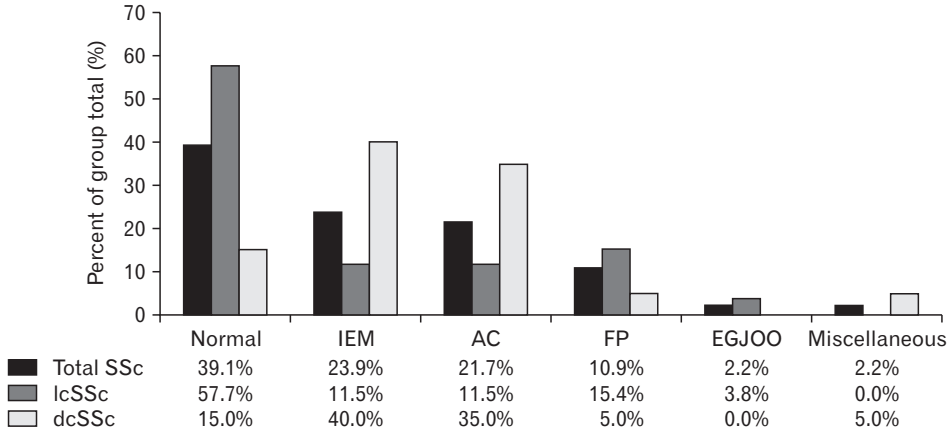


**Figure.** High-resolution manometry (HRM) diagnosis based on the Chicago classification of esophageal motility disorders, version 3.0. IEM, ineffective esophageal motility; AC, absent contractility; FP, fragmented peristalsis; EGJOO, esophagogastric junction outflow obstruction. Miscellaneous motility indicates compartmentalized pressurization; SSc, systemic sclerosis; lcSSC, limited cutaneous systemic sclerosis; dcSSc, diffuse cutaneous systemic sclerosis.

## High-resolution Manometry Diagnosis Using the Chicago Classification of Esophageal Motility Disorders, Version 3.0

The most common diagnosis by HRM among the total SSc patients was normal (39.1%), followed by ineffective esophageal motility (IEM, 23.9%), absent contractility (AC, 21.7%), fragmented peristalsis (FP, 10.9%), and EGJ outflow obstruction (EGJOO, 2.2%) (Figure). One patient had an abnormal HRM finding that was not addressed by the Chicago classification of esophageal motility disorders, version 3.0, but was classified as compartmentalized pressurization. Hypotensive EGJ pressure was found in 16 patients (34.8%). Importantly, classic sclerosis esophagus was observed in only 7 patients (15.2%). The distributions of normal, minor esophageal motility disorders (IEM, FP, and compartmentalized pressurization) and major motility disorders differed significantly between the lcSSc and dcSSc subtypes ($P = 0.013$; Table 2).

## High-resolution Manometry Metrics and Multiple Rapid Swallow

The lcSSc subtype had a significantly higher median DCI (872.1 mmHg·sec·cm) than that of the dcSSc subtype (90 mmHg·sec·cm, $P = 0.024$). Other metrics such as EGJ pressure, 4-second IRP (4s-IRP), DL, and EGJ-CI were similar in the 2 subtypes.

All SSc patients who performed the MRS test had abnormal MRS findings (97.8%) except for 1 dcSSc patient who did not perform the test. Incomplete inhibition during the MRS test was observed in 28.9% and suboptimal post-MRS contraction in 88.9%. The median (IQR) DCI ratio of the total SSc patients was 0.0 (0.0-0.1), with a median (IQR) 4s-IRP during the MRS test of 4.9 (2.0-6.9) mmHg. The median DCI ratio was significantly lower in

**Table 2.** High-resolution Manometry Diagnosis Based on the Chicago Classification of Esophageal Motility Diagnosis, Version 3.0, and High-resolution Manometry Metrics in Patients With Limited or Diffuse Systemic Sclerosis

| HRM | lcSSc (n = 26) | dcSSc (n = 20) | *P*-value[a] | Total (N = 46) |
|---|---|---|---|---|
| Diagnosis | | | 0.013 | |
| Normal | 15 (57.7) | 3 (15.0) | | 18 (39.1) |
| Minor motility | 7 (26.9) | 10 (50.0) | | 17 (37.0) |
| IEM | 3 | 8 | | 11 |
| Fragmented peristalsis | 4 | 1 | | 5 |
| Compartmentalized pressurization | 0 | 1 | | 1 |
| Major motility | 4 (15.4) | 7 (35.0) | | 11 (23.9) |
| Absent contractility | 3 | 7 | | 10 |
| EGJOO | 1 | 0 | | 1 |
| Metrics | | | | |
| Median EGJ pressure (mmHg) | 19.5 (10.1-27.4) | 16.6 (10.2-26.2) | 0.634 | 18.9 (10.4-26.8) |
| Median IRP (mmHg) | 6.1 (3.8-10.8) | 6.6 (4.7-8.2) | 0.868 | 6.5 (3.9-9.3) |
| Median DCI (mmHg·sec·cm) | 872.1 (118.2-1415.1) | 90 (0-729.7) | 0.024 | 520 (0.0-1340.0) |
| Median DL[b] (sec) | 6.3 (5.6-7.2) | 7.6 (6.3-8.4) | 0.051 | 6.7 (5.7-7.6) |
| Median EGJ-CI (mmHg/cm) | 18.8 (8.6-33.8) | 20 (10.7-32.6) | 0.842 | 19.3 (9.7-32.9) |
| MRS test[c] | | | | |
| Abnormal MRS | 26 (100.0%) | 18 (94.7) | 0.422 | 44 (97.8) |
| Incomplete inhibition during MRS | 10 (38.5) | 3 (15.8) | 0.097 | 13 (28.9) |
| Suboptimal post-MRS contraction | 22 (84.6) | 18 (94.7) | 0.378 | 40 (88.9) |
| Median post-MRS/SS DCI ratio | 0.5 (0.0-1.1) | 0.0 (0.0-0.1) | 0.006 | 0.0 (0.0-0.95) |
| Median 4s-IRP during MRS (mmHg) | 5.1 (2.1-8.0) | 4.7 (1.9-6.3) | 0.505 | 4.9 (2.0-6.9) |

[a]Comparison between limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc).

[b]Patients with absent contractility were excluded from this analysis.

[c]One dcSSc patient did not perform the multiple rapid swallow (MRS) test due to dysphagia.

HRM, high-resolution manometry; IEM, ineffective esophageal motility; EGJOO, esophagogastric junction outflow obstruction; EGJ, esophagogastric junction; EGJ-CI, EGJ-contractile integral; SS, single swallow; DCI, distal contractile integral; 4s-IRP, 4-second integrated relaxation pressure.

Values are represented as numbers (percentage) or medians (interquartile range).

**Table 3.** Motility Patterns and Erosive Esophagitis Based on Both Pathologic Acid Exposure and Symptom Association in Symptomatic Systemic Sclerosis Patients

| Variables | PAE+ (n = 6) | PAE− SA+ (n = 13) | PAE− SA− (n = 11) |
|---|---|---|---|
| Proportion | 20.0% | 43.0% | 37.0% |
| HRM diagnosis (Chicago classification of motility diagnosis, version3.0) | | | |
| Major motility disorders | 3 (50.0) | 3 (23.1) | 1 (9.1) |
| Minor motility disorders and normal | 1 (50.0) | 10 (76.9) | 10 (90.9) |
| Erosive esophagitis[a] | 4 (66.7)[b] | 0 (0.0) | 0 (0.0) |

[a]Endoscopy was not performed in two symptomatic systemic sclerosis patients who were pathologic acid exposure (PAE)− and symptom association (SA)+.
[b]Adjusted *P*-value < 0.001, after Bonferroni correction, comparison among patients with PAE+, PAE− SA+, or PAE− SA−.
PAE was defined when the distal esophageal acid exposure time was more than 4.2% at a pH < 4 over 24 hours.
SA was considered positive if the symptom index was 50.0% or greater; SA probability was considered positive if it was 95.0% or greater.
Values are represented as numbers (percentage).

the dcSSc patients than in the lcSSc patients (0.0 vs 0.5, $P = 0.006$) (Table 2).

EGJ pressure positively correlated with the DCI (rho = 0.445, $P = 0.002$). Disease duration negatively correlated with mean EGJ pressure (rho = −0.392, $P = 0.007$) and mean DCI (rho = −0.427, $P = 0.003$). However, neither mean DL nor mean IRP correlated with disease duration. Of the HRM metrics, only the DCI and EGJ pressure reflected disease duration. We found that none of our HRM metrics reflected disease activity as measured by mRSS. None of the HRM parameters were related to the presence of interstitial lung disease.

## Endoscopic Diagnosis

Erosive esophagitis was observed in 12.2% of total SSc patients, and the rate of erosive esophagitis was similar in the lcSSc and dcSSc patients (Table 1).

The associations among demographics (ie, sex, age, and BMI), SSc subtype, and HRM data were further evaluated in SSc patients with respect to the presence of erosive esophagitis. Demographics and SSc subtypes were comparable between the 2 groups (Supplementary Table 1). However, more patients with erosive esophagitis had AC compared with patients without erosive esophagitis (80.0% vs 13.9%, $P = 0.006$). A lower median 4s-IRP (1.8 mmHg vs 6.6 mmHg, $P = 0.024$) and lower DCI (0.0 mmHg·sec·cm vs 737.4 mmHg·sec·cm, $P = 0.004$) were found in patients with erosive esophagitis compared with patients without erosive esophagitis. The proportion of abnormal MRS tests was similar between patients with and those without erosive esophagitis.

## Normal Motility Versus Absent Contractility in Systemic Sclerosis Patients

The association among demographics, SSc type, esophageal symptoms, and endoscopic findings was further assessed in SSc patients with AC compared with those with normal motility (Supplementary Table 2). The rate of lcSSc was higher in patients with normal motility than in those with AC (85.3% vs 30.0%, $P = 0.005$). The presence of each esophageal symptom did not differ significantly between patients with AC and those with normal motility.

## Multichannel Intraluminal Impedance Monitoring Combined With pH-metry Test in Symptomatic Systemic Sclerosis Patients

The MII-pH test was performed in 30 of 36 (83.0%) symptomatic patients with SSc. PAE was observed in 6 patients (20.0%), and positive SA in 18 patients (60.0%) (Table 3). The proportion of SSc patients with esophageal symptoms not explained by reflux or mucosal or motor esophageal abnormalities was 33.0%. The symptomatic patients (37.0%) had negative PAE and SA, which was suggestive of functional heartburn/chest pain. Only one of these patients had a major motility disorder (ie, EGJOO) and erosive esophagitis was not found. Other symptomatic patients (43.0%) had negative PAE and positive SA, which was suggestive of reflux hypersensitivity. Major motility disorders were observed in 3 patients (23.1%; negative PAE and positive SA), and erosive esophagitis was not observed. Esophageal symptoms in these patients were partly explained by reflux hypersensitivity.

There were no significant differences in the median acid expo-

sure upright, recumbent, or total time between the lcSSc and dcSSc patients (Supplementary Table 3).

## Discussion

This is the first study to examine esophageal involvement based on HRM and EGD findings and to elucidate the associations of the esophageal symptoms between esophageal dysmotility and erosive esophagitis in South Koreans with SSc. Our findings provide unique insight into the perception of esophageal symptoms, which can lead to optimal clinical management of SSc patients who have neither dysmotility nor erosive esophagitis.

There are heterogeneous esophageal motility disorders with a higher prevalence of normal contraction detected by HRM. Specifically, the most common HRM diagnosis among the total SSc patients was normal (39.1%) followed by IEM (23.9%), AC (21.7%), FP (10.9%), and EGJOO (2.2%). Classic sclerosis esophagus was found in only approximately 15.0% of our SSc patients. Recent HRM studies of Western patients with SSc demonstrated diverse esophageal motility patterns, where AC was the most prevalent.[6,25] On one hand, our findings of diverse esophageal motility patterns urge clinicians to keep an open mind about esophageal dysmotility in SSc patients. On the other hand, our study was designed as a cross-sectional study. It may be described as a snapshot of HRM findings in our population at a single point in time. Therefore, some HRM findings, such as the presence of normal or minor esophageal motility disorders, might change over time. In our study, heterogeneity in the spectrum of esophageal motility disorders may reflect progression of esophageal smooth muscle involvement (ie, a movement along the disease continuum).

MRS during the HRM test is a provocation test to assess peristaltic reserve. In our study, almost all SSc patients had abnormal MRS findings suggestive of impaired peristaltic reserve. This was the most common esophageal motility finding among our SSc patients, which is in line with a previous Western HRM study.[26] In addition, impaired peristaltic reserve was observed in all of the SSc patients with normal motility in a standard HRM study.

Our observations imply that South Koreans with SSc had a low frequency of erosive esophagitis compared with Western studies, in which the estimated prevalence was 30.0-40.0%.[9-12] The factors underlying the significant racial difference in the prevalence of erosive esophagitis may include differences in the frequencies of *Helicobacter pylori* infection,[27] gastric acid secretion,[28] dietary habits, obesity prevalence, and unspecified genetic factors that predispose to erosive esophagitis.[29] In the present study, erosive esophagitis was related to AC but not to esophageal symptoms.

Lahcene et al[30] reported that there was significant difference in the frequency of erosive esophagitis between SSc patients with esophageal motility disorders and patients without esophageal motility disorders (44.6% vs 8.0%, $P < 0.001$). Aggarwal et al[31] reported that diverse esophageal motility disorders were found in systemic sclerosis. Their study also indicated that the prevalence of erosive esophagitis was higher in SSc patients with AC than in those with normal motility (47.9% vs 11.8%, $P = 0.030$).[31] In our study, erosive esophagitis was more prevalent in patients with AC than in those with normal motility (44.4% vs 0.0%, $P = 0.010$). Our data also indicated that lower median 4s-IRPs (1.8 mmHg vs 6.6 mmHg, $P = 0.024$) and a lower DCI (0.0 mmHg·sec·cm vs 737.4 mmHg·sec·cm, $P = 0.004$) were found in patients with erosive esophagitis compared with patients without erosive esophagitis. The prevalence of erosive esophagitis in our SSc patients with AC was 44.0% and lies within the range of previous studies. Given our results and those of previous studies, we conclude that esophageal dysmotility contributes to GERD in SSc patients.

Our study indicate that severe esophageal dysmotility such as AC is related to the presence of erosive esophagitis but not to the presence or severity of esophageal symptoms. Surprisingly, we detected normal acid exposure and positive SA on the MII-pH test, suggesting reflux hypersensitivity, in 43.0% of all 30 symptomatic patients. In addition, 37.0% of all symptomatic SSc patients had normal acid exposure and negative SA, suggestive of functional heartburn/chest pain or other extra-esophageal causes. Our observations imply that reflux hypersensitivity and functional heartburn/chest pain may play major roles in esophageal symptom development in a subset of SSc patients. These conditions are recognized as separate entities in the GERD spectrum and are primarily treated with neuromodulators and or psychologic interventions. Our observations provide unique and much-needed insight into the pathophysiology of esophageal symptoms, which can lead to the optimal clinical management of SSc patients.

In our study, there were no significant differences between the 2 groups in any of the baseline characteristics except for heartburn. However, significant differences in the distribution of normal, minor esophageal motility disorders, and major motility disorders were observed. In addition, patients with dcSSc had a significantly lower median DCI than those with lcSSc. There is controversy over the relationship between SSc subtype and esophageal dysmotility (Supplementary Table 4).[6,30,32-38] Some studies show no relationship.[6,32] Others find that esophageal motility disorders are more frequent and more severe in patients with dcSSc.[33-35]

Limitations of our study include a relatively small sample size, its retrospective nature, and a lack of controls (ie, Western SSc patients). Future prospective multi-national studies including MII-pH data will help further reveal the differences in esophageal involvement between South Koreans and Western SSc patients and provide clear knowledge regarding the determinants of esophageal symptom perception.

In conclusion, esophageal involvement in South Koreans with SSc was characterized by heterogeneous motility patterns with a higher prevalence of normal motility and a lower prevalence of erosive esophagitis. The perception of esophageal symptoms may be partly explained by reflux hypersensitivity and functional heartburn/chest pain in SSc patients who have neither gastroesophageal reflux disease nor esophageal dysmotility.

## Supplementary Materials

Note: To access the supplementary tables and figure mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm19148.

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