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Original Article

The Upper Esophageal Sphincter Distensibility Index Measured Using Functional Lumen Imaging Probe Identifies Defective Barrier Function of the Upper Esophageal Sphincter

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Background/Aims
The mechanism via which supra-esophageal symptoms are generated is unclear. We assessed upper esophageal sphincter (UES) function in novel fashion using functional lumen imaging probe (FLIP) topography. We hypothesize that symptoms related to aspiration of esophageal contents may be associated with a more distensible UES.

Methods
FLIP and reflux symptom index score data from patients undergoing diagnostic evaluation for an esophageal complaint over a 10-month period were analyzed retrospectively. UES distensibility on FLIP was studied at 40-70 mL volumes with in-depth analysis at 50 and 60 mL. Symptoms were compared between patients with low, middle, and high UES-distensibility index (UES-DI). Receiver-operating characteristic analysis was performed to determine associations between the UES-DI and individual reflux symptom index symptom item scores.

Results
One hundred and eleven subjects were included. Overall, the associations between UES-DI and symptoms that could be related to supra-esophageal aspiration were strongest at the 50 mL FLIP volume. Choking item score was highest in the high UES-DI group (2.8) vs 1.4 ($P < 0.001$) in the middle UES-DI and 1.1 ($P = 0.004$) in the low UES-DI groups. Similarly, the cough item score was highest in the high UES-DI group (2.7) vs 1.5 ($P = 0.009$) and 0.9 ($P = 0.002$) groups.

Conclusion
A higher UES-DI measures defective barrier function which could may be the main pathophysiology that generates supra-esophageal symptoms.
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Key Words
Cough; Esophageal sphincter, upper; Retrospective studies

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Introduction

The upper esophageal sphincter (UES) is the anatomical barrier between the pharynx and the esophagus. A key function of the UES is to serve as a protective barrier against retrograde flow of esophageal contents into the pharynx and airway structures. Anatomically, the UES high pressure zone is comprised of 3 elements - the most proximal portion of the cervical esophagus, the cricopharyngeus, and the inferior pharyngeal constrictor muscle.[1-5] During swallowing, there is a significant effect of traction forces and likely of bolus dynamics towards UES properties.[6-8] At rest, active neural signaling to the cricopharyngeus and its passive properties UES pressure.[1,9,10]

The best technique for assessing UES function as relevant to symptom presence remains unknown. Manometric studies of the UES, including with high-resolution manometry (HRM), have provided important insights into UES function during deglutition.[5,11] However, manometric UES pressures are highly variable even in asymptomatic individuals, which is likely due to reactivity and the hyperdynamic behavior of the UES.[12]

At the present moment, a key gap in our knowledge of esophageal pathophysiology is with respect to the mechanism of generation of supra-esophageal symptoms. As many as 1 in 5 patients reports symptoms such as cough, hoarseness, and globus. These symptoms are often generically grouped and attributed to laryngopharyngeal reflux, but they are often unresponsive to acid suppressive therapy.[13,14] HRM studies have demonstrated that a hypotonic UES and impaired UES reflexes are associated with supra-esophageal symptoms.[15,16] Thus, a reasonable hypothesis is that defective UES barrier function could be a cause of supra-esophageal symptoms.

The functional lumen imaging probe (FLIP) is a novel technology which accurately measures distensibility of the esophagus over 1-cm longitudinal increments during step-wise volumetric distension. Although the application of FLIP in the esophagus to date has focused on the distal esophageal smooth muscle and lower esophageal sphincter, characterization of UES diameter and compliance has been shown to be feasible.[17-19] Inflation of the FLIP balloon slowly distends the proximal esophagus while continuously measuring the response in UES diameter, thus precisely mimicking physiologic UES behavior in the presence of contents in the proximal esophagus. As FLIP is performed during sedated upper endoscopy, it has the added benefit of reducing reactivity of the UES. We thus hypothesize that FLIP is the ideal technique to measure the UES barrier function. Our specific hypothesis is that a higher measurement for the UES distensibility may indicate defective barrier against retrograde movement of esophageal contents. The aim of this study is to assess whether distensibility index (DI) of the UES using FLIP is associated with cough and other symptoms indicative of aspiration or micro-aspiration.

Materials and Methods

Subjects

This study was a single center retrospective study reviewed by the university Institutional Review Board (STU 00109825). This study included consecutive adult patients at our institution from August 2019 to June 2020 who underwent our standard institutional protocol of esophagogastroduodenoscopy (EGD) with FLIP (both distal and proximal esophageal ramps) for an esophageal complaint (non-obstructive dysphagia, non-cardiac chest pain, or proton pump inhibitor-unresponsive gastroesophageal reflux disease [GERD] or laryngeal symptoms) under monitored-anesthesia care. Exclusions for undergoing FLIP were if there was an established diagnosis of esophageal stricture or eosinophilic esophagitis, or if these were diagnosed during EGD prior to FLIP. Patients with erosive esophagitis without peptic stricture, presence of hiatal hernia of any size, achalasia, and whom had prior history of foregut surgery underwent FLIP and were included. Our institutional protocol is to perform a proximal esophageal sequence for all FLIP studies which includes measurements of the UES. Patients who underwent EGD with FLIP under general anesthesia (per anesthesiologist discretion) were excluded as the endotracheal tube alters FLIP distensibility measurements of the UES. Patients who experienced significant discomfort during UES-FLIP sequence despite propofol sedation, such that the protocol could not be completed, were excluded.

Diagnostic Testing: Upper Endoscopy and Functional Lumen Imaging Probe

All diagnostic testing was performed by a single esophageal specialist. Upper endoscopy procedure was done in the left lateral position under administration of propofol-based sedation by an anesthesiologist. Deep sedation was achieved in accordance with parameters recommended by the American Society of Gastrointestinal Endoscopy (ASGE).[20] After endoscopic visualization was completed, gastroscope was removed and FLIP studies were performed. FLIP catheter was zeroed to atmospheric

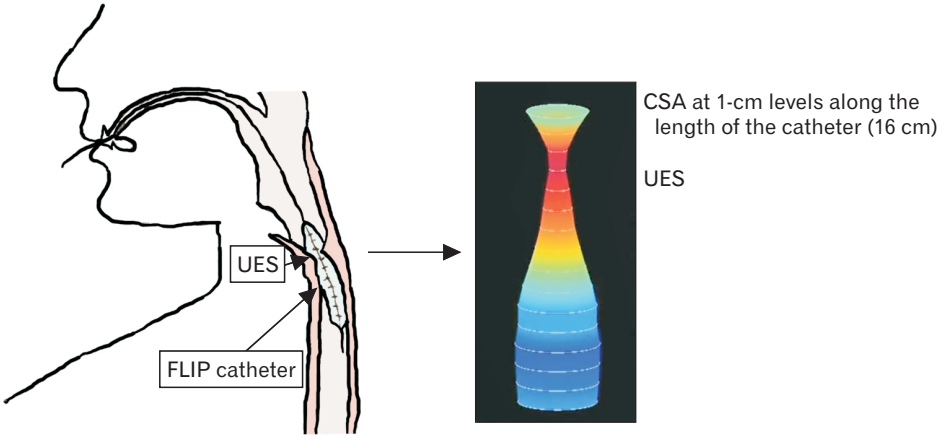

Figure 1. Placement of functional lumen imaging probe (FLIP) catheter across upper esophageal sphincter (UES) and real-time data output is shown. CSA, cross-sectional area.

pressure prior to insertion. All studies were performed with 16-cm FLIP (EndoFLIP EF-322N; Medtronic, Inc, Shoreview, MN, USA). Distal esophageal and EGJ assessment of FLIP was performed per established protocol, as previously described in literature.[21] After completion of the distal esophageal ramp, the FLIP balloon was deflated to 30 mL.

Protocol for Functional Lumen Imaging Probe Assessment of the Upper Esophageal Sphincter

The UES-FLIP protocol performed at our institution was derived by a single esophageal specialist with expertise in FLIP (A.S.J.) and an otolaryngologist with expertise in oropharyngeal dysphagia and UES-spectrum disorders (A.T.T.). Key points discussed were (1) length of FLIP probe to be used (8-cm vs 16-cm), (2) maximum pressure allowed, (3) maximum volume, and (4) inflation increments (5 mL vs 10 mL). As the expected UES responses on FLIP are largely unknown in a patient population, we decided on a protocol which would test UES behavior under the full range of FLIP volumes, while maintaining the manufacturer-specified maximum pressure threshold of 100 mmHg for safety. After completion of the EGJ ramp and deflation to 30 mL, the probe was pulled back until a waist marking the UES was visualized at the top of the FLIP 2.0 topography screen (Fig. 1). Then, the FLIP was inflated in increments of 10 mL in a stepwise fashion to a maximum of 70 mL. Each distension volume was maintained for 15 seconds prior to increasing to the next increment. If, at a given volume, intrabag pressure exceeded 100 mmHg, further measurement at that volume was ceased. At that time, FLIP was deflated down to the previous 10 mL incremental volume. Provided the pressure dropped to < 100 mmHg, a second attempt at measurement at the desired volume was made. If the pressure remained > 100 mmHg, the FLIP study was ceased and balloon deflated. In all patients, direct visualization of the entire esophagus was performed to note any trauma related to FLIP inflation.

Table 1. Patient Characteristics (N = 111)

Characteristics	
Age (yr)	55.0 ± 15.8
Female	77 (69.4)
Ethnicity	
White, non-Hispanic	65 (58.6)
Black	35 (31.5)
Asian	4 (3.6)
Hispanic	1 (0.9)
Not available	5 (4.5)
BMI (kg/m^2)	28.15 ± 6.37
GerdQ	8.71 ± 3.44
RSI	19.75 ± 10.61
Indication for referral	
Dysphagia	36 (32.4)
Heartburn and/or regurgitation	24 (21.6)
Laryngeal symptoms	36 (32.4)
Non-cardiac chest pain	15 (13.5)
Endoscopic findings	
LA-A or LA-B esophagitis	16 (14.4)
LA-C or LA-D esophagitis	1 (0.9)
Hiatal hernia ≤ 3 cm	32 (28.8)
Hiatal hernia > 3 cm	3 (2.7)

BMI, body mass index; GerdQ, gastroesophageal reflux disease questionnaire; RSI, reflux symptom index; LA, Los Angeles classification.
Data are presented as mean ± SD or n (%).

FLIP studies were exported after each procedure and analyzed retrospectively using a customized MATLAB software code (Mathworks, Natick, MA, USA) which outputs median volume, cross-sectional area, pressure, and distensibility at each 10-mL incremental fill volume. The DI (mm^2/mmHg) of the UES was calculated by the software by dividing by the cross-sectional area by

the intraballoon pressure. At volumes where the maximum pressure threshold was reached, distensibility measurements were still recorded and analyzed.

Symptom Questionnaires

Patients completed a series of standardized esophageal questionnaires at the initial clinic visit to assess symptom burden, including the Gastroesophageal Reflux Disease Questionnaire and Reflux Symptom Index (RSI), available in Supplementary Tables 1 and 2 respectively.

Statistical Methods

Descriptive statistics are given for the entire sample as counts (percentage), mean, and standard deviation (SD) as relevant.

Table 2. Correlation of Upper Esophageal Sphincter–Distensibility Index With Symptoms

Symptom	40 mL		50 mL		60 mL		70 mL	
	R	*P*-value	R	*P*-value	R	*P*-value	R	*P*-value
1- Hoarseness	0.136	0.153	0.128	0.182	0.027	0.778	−0.071	0.458
2- Throat clearing	0.118	0.216	0.081	0.400	0.037	0.702	0.001	0.994
3- Postnasal drip or throat mucus	0.133	0.163	0.148	0.122	0.152	0.111	0.103	0.281
4- Dysphagia	0.077	0.422	−0.026	0.786	−0.192	0.043	−0.104	0.276
5- Coughing after eating or lying down	0.166	0.081	0.205	0.031	0.182	0.056	0.127	0.185
6- Breathing difficulty or choking	0.244	0.010	0.300	0.001	0.260	0.006	0.163	0.088
7- Troublesome or annoying cough	0.276	0.003	0.339	< 0.001	0.253	0.007	0.114	0.232
8- Globus	0.112	0.242	0.095	0.322	0.010	0.921	−0.043	0.655
9- Heartburn, regurgitation, chest pain, or dyspepsia	0.056	0.562	0.016	0.865	−0.026	0.783	−0.047	0.625
Total RSI	0.234	0.013	0.227	0.017	0.121	0.207	0.040	0.966

Pearson R-values and *P*-values correlating upper esophageal sphincter–distensibility index with symptom categories from the reflux symptom index (RSI) questionnaire are demonstrated above.
$P < 0.05$ is considered statistically significant.

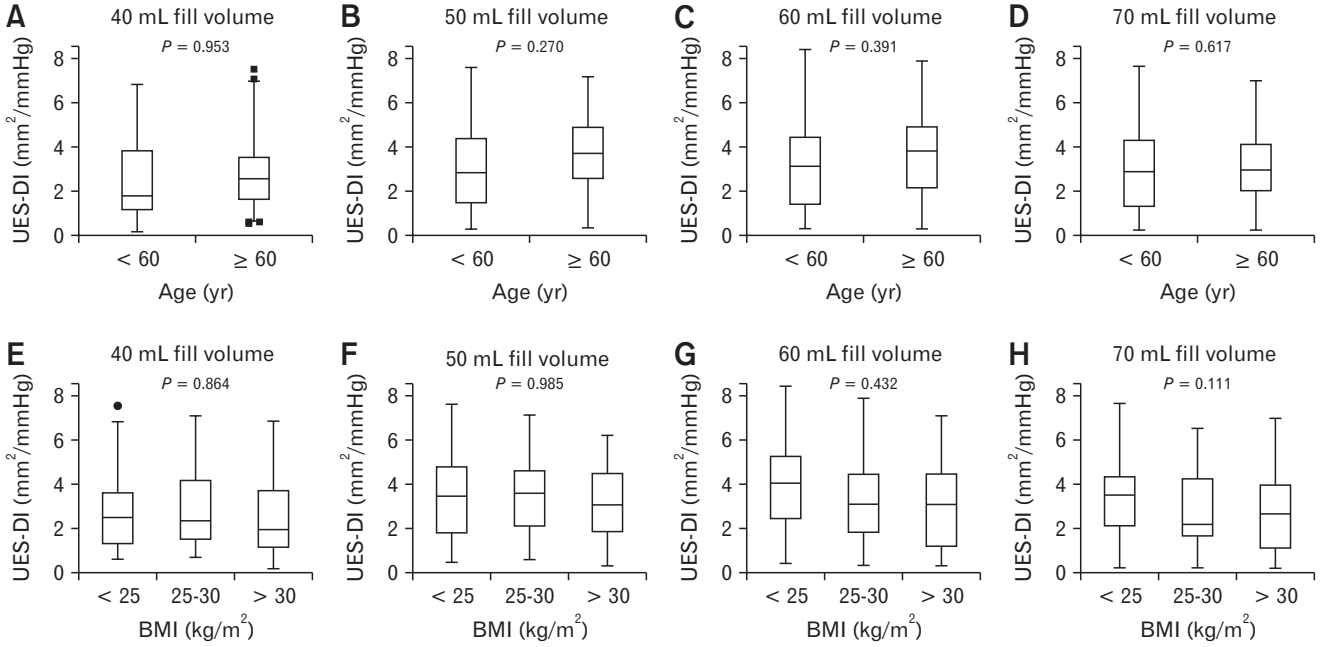

Figure 2. Distribution of upper esophageal sphincter–distensibility index (UES-DI) at 40, 50, 60, and 70 mL fill volumes based on age less than or greater than 60 years (A-D), and body mass index (BMI, kg/m^2) characterization as healthy (< 25), overweight (25-30), or obese (> 30) (E-H) are shown. *P*-values (two-sided *t* test for age groups, one-way ANOVA for BMI groups) for comparisons groups are shown.

We derived Pearson's R for the UES-DI (mm^2/mmHg) at each FLIP volume—40, 50, 60, and 70 mL in association with each individual item score (1-9) from the RSI as well as the total RSI score. Based on results from that correlation analysis, we further studied the 50 mL and 60 mL volumes. As there was no control group, we divided the sample into 3 groups (at each FLIP volume of 50 mL and 60 mL) based on the UES-DI: (1) low (UES-DI in the lowest 25% of the sample), (2) middle (UES-DI in the middle 50% of the sample), and (3) high (UES-DI in the top 25% of the sample). Then we studied the primary outcome of the association of the UES-DI with the presence of elevated (score 4 or 5) individual symptom item score taken from the RSI using logistic regression and receiver-operative characteristic curve analysis. Age, biological sex, and body mass index (BMI) were used as additional independent variables for logistic regression. Associations with an area under the curve (AUC) of 0.70 or greater were selected for analysis of specific UES-DI thresholds, which were chosen using Youden's index. Descriptive measures were compared between groups using two-tailed *t* test or one-way ANOVA. Categorical analyses were performed using Fisher's exact test. A $P < 0.05$ was considered statistically significant. Graphpad Prism version 9.0.2 (GraphPad Software, San Diego, CA, USA) was used for statistical analysis.

Results

Patient Characteristics

Table 1 summarizes the demographic and clinical data for the 111 included subjects (ages 21-86, 69.4% female).

Safety and Tolerability of Upper Esophageal Sphincter-Functional Lumen Imaging Probe Studies

Twelve patients experienced agitation during distension of the FLIP probe across the UES despite being under deep sedation. The procedure was aborted in these patients, and they are not

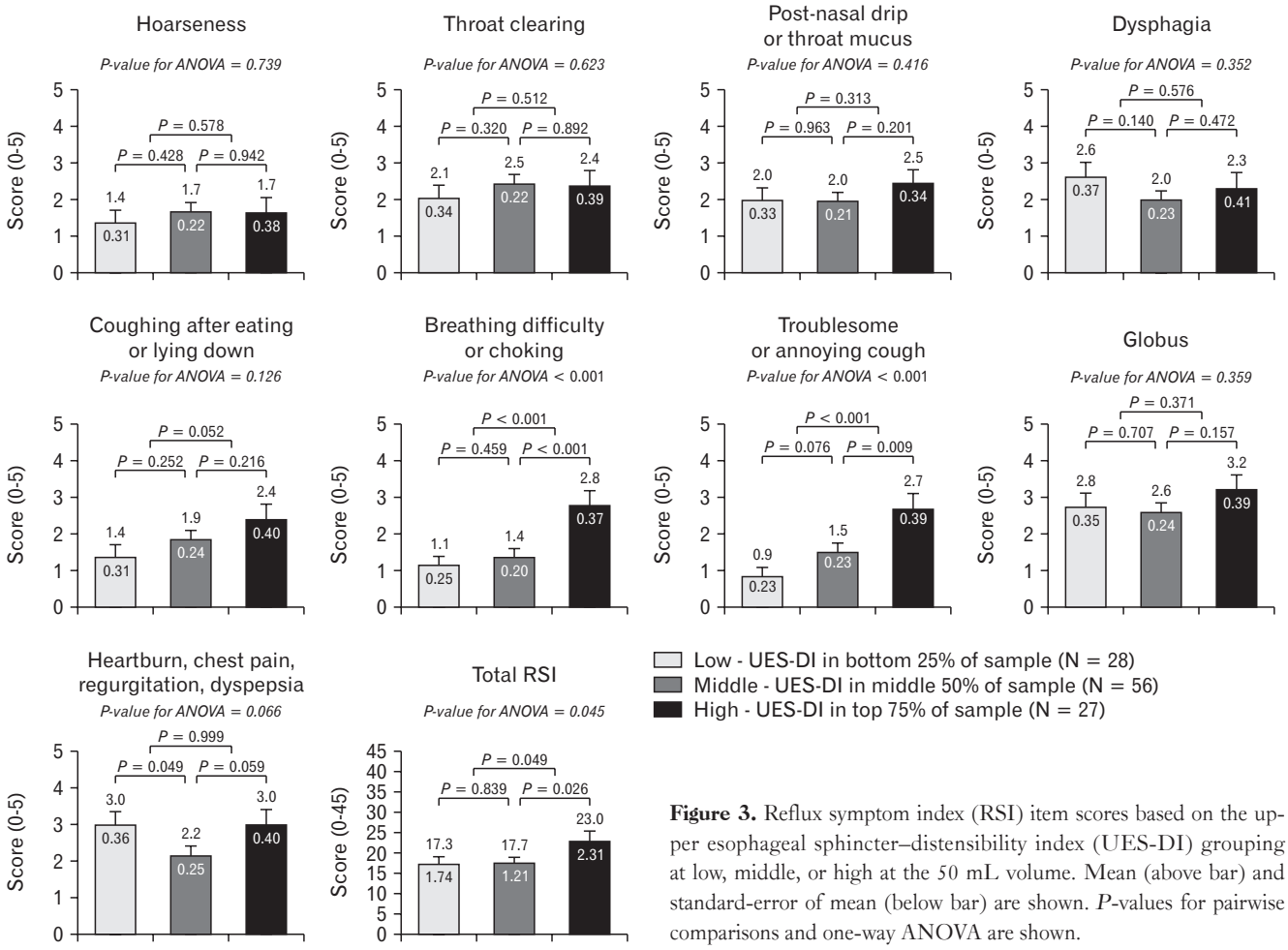

Figure 3. Reflux symptom index (RSI) item scores based on the upper esophageal sphincter–distensibility index (UES-DI) grouping at low, middle, or high at the 50 mL volume. Mean (above bar) and standard-error of mean (below bar) are shown. *P*-values for pairwise comparisons and one-way ANOVA are shown.

included in the final analysis. Otherwise, inflation of the FLIP balloon across the UES was well tolerated in the included sample of 111 patients. No studies were aborted due to deterioration of respiratory parameters. Upon direct endoscopic visualization after FLIP, no patients had mucosal disruption or bleeding in the hypopharynx or proximal esophagus. Mean ± SD pressures at each volume in the sample were as follows: 40 mL: 20.5 ± 12.5 mmHg, 50 mL: 27.6 ± 14.6 mmHg, 60 mL: 39.9 ± 17.2 mmHg, and 70 mL: 56.6 ± 20.0 mmHg. No patients reached the maximum pressure threshold of 100 mmHg at 40 mL or 50 mL volumes. FLIP intrabag pressure exceeded 100 mmHg at the 60 mL volume in 1 patient during first attempt but not second attempt; the pressure maximum was exceeded on both attempts at the 70 mL volume in this patient. In 2 additional patients, intrabag pressure exceeded 100 mmHg at the 70 mL volume during both first and second attempt.

Association of Upper Esophageal Sphincter-Distensibility Index With Age and Body Mass Index

The UES-DI (mm^2/mmHg) at 40, 50, 60, and 70 mL FLIP volumes based on age less than or greater than 60 years, and based on BMI in 3 groups: < 25, 25-30, ≥ 30 kg/m^2 is shown in Figure 2. There were no differences in the UES-DI based on these groupings.

The Upper Esophageal Sphincter–Distensibility Index at 50-mL and 60-mL Volumes Correlates With Symptom Indices for Cough and Choking Sensation

Table 2 shows Pearson's R for the UES-DI (mm^2/mmHg) at all volumes 40-70 mL with individual item scores and total RSI score. Significant correlations were noted between UES-DI and items 6 (breathing difficulty or choking) and item 7 (troublesome or annoying cough), with a range of R values from 0.24-0.34 (*P*-values of 0.01 or lower) at the 40, 50, and 60 mL volumes. Item

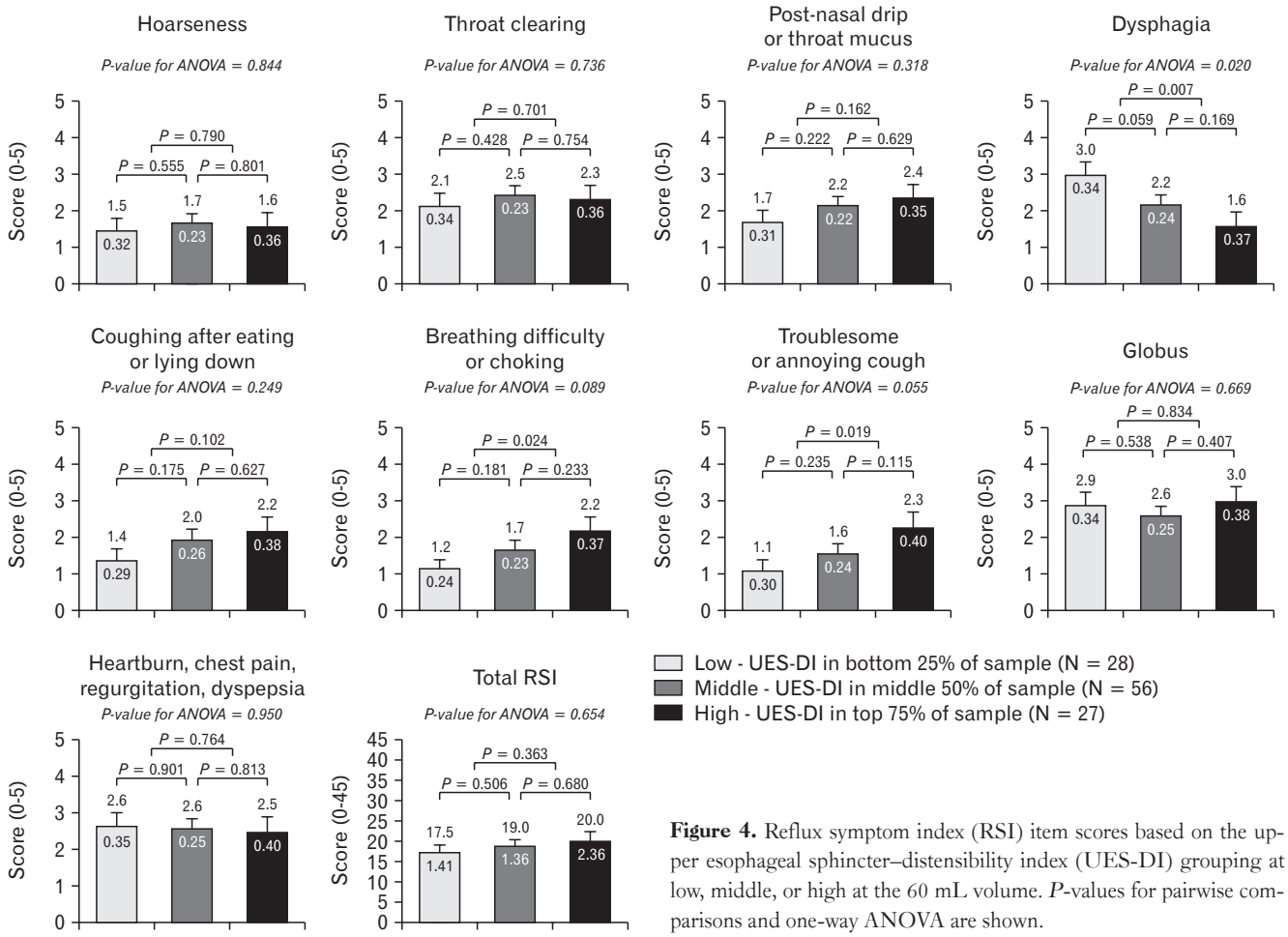

Figure 4. Reflux symptom index (RSI) item scores based on the upper esophageal sphincter–distensibility index (UES-DI) grouping at low, middle, or high at the 60 mL volume. *P*-values for pairwise comparisons and one-way ANOVA are shown.

5 (coughing after eating or lying down) correlated with the UES-DI at the 50 mL volume (R-value = 0.21 [$P = 0.031$]). Notably, item 4 (dysphagia), correlated with the UES-DI at the 60 mL volume (R-value = −0.19 [$P = 0.043$]). Total RSI correlated at 40 mL and 50 mL volumes (R-value = 0.23 for both [$P = 0.013$ and 0.017, respectively]).

Based on these correlations, we chose to further study the UES-DI at the 50 mL and 60 mL volumes.

High Upper Esophageal Sphincter–Distensibility Index Is Associated With Symptom Profiles Suggestive of Aspiration

To account for the lack of a control group, the sample was divided into 3 groups at each studied volume (50 mL and 60 mL) based on the distribution of the UES-DI. These were (1) low (UES-DI in the lowest 25% of the sample), (2) middle (UES-DI in the middle 50% of the sample), and (3) high distensibility (UES-DI in the highest 25% of the sample). Mean (SEM) symptom scores for RSI items 1-9 and total RSI based score on this grouping is shown in Figures 3 and 4.

A high UES distensibility was associated with higher scores for item 5, item 6, and total RSI. High UES-DI was associated with higher scores for breathing difficulty or choking (50 mL volume score 2.8 vs 1.4 for middle [$P < 0.001$] and 1.1 for low [$P = 0.004$]; 60 mL volume score 2.2 vs 1.7 for middle [$P = 0.233$] and 1.2 for low [$P = 0.024$]). High UES-DI was also associated with higher scores for troublesome or annoying cough (50 mL volume score 2.7 vs 1.5 for middle [$P = 0.009$] and 0.9 for low [$P < 0.001$] UES-DI; 60 mL volume score 2.3 vs 1.6 for middle [$P = 0.115$] and 1.1 for low [$P = 0.019$]). Total RSI score was also higher in patients with high UES-DI (50 mL volume score 23 vs 17.7 for middle [$P = 0.026$] and 17.3 for low [$P = 0.049$]).

A low UES distensibility was associated with higher scores for item 4 (dysphagia) at the 60 mL volume. Dysphagia score was 3.0 in the low UES-DI group compared to 2.2 in the middle ($P = 0.059$) and 1.6 in the high ($P = 0.007$) groups.

Figure 5 shows an example of the software output from a patient with low and high UES distensibility.

Multivariate Analysis Shows That a Upper Esophageal Sphincter–Distensibility Index Higher Than 3-4 mm^2/mmHg Is Associated With Symptoms of Aspiration

We tested the accuracy of the UES-DI in predicting severe symptoms defined as an individual RSI symptom item score of 4 or 5, or total RSI score ≥ 30. Of individual symptom items, we tested item 5 (coughing after eating or lying down), item 6 (breathing difficulty or choking), and item 7 (troublesome or annoying cough).

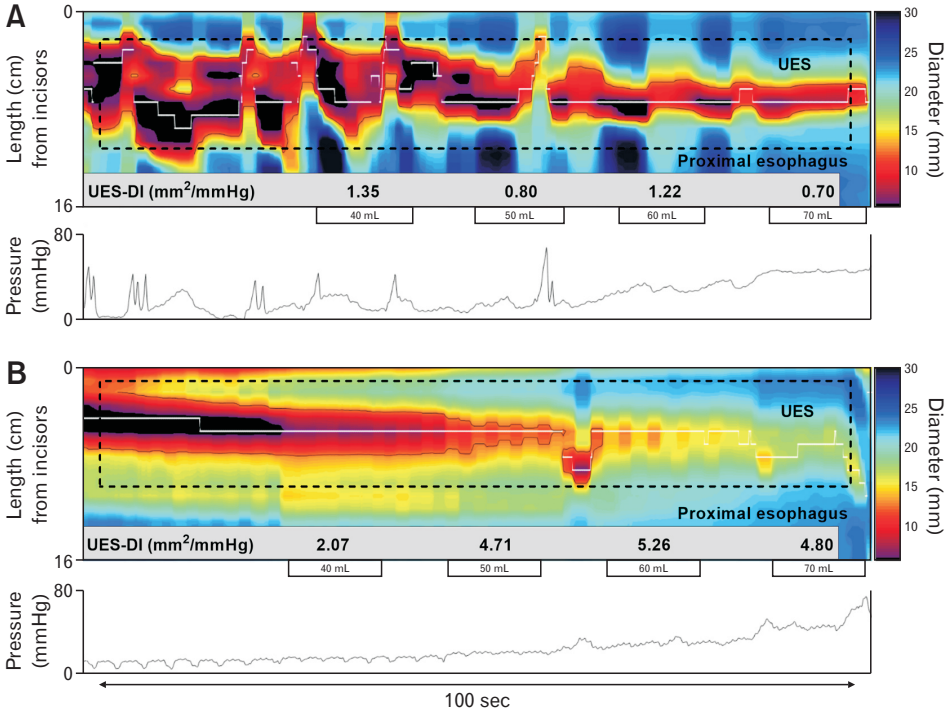

Figure 5. Example of upper esophageal sphincter–distensibility index (UES-DI) calculated using customized software. (A) Shows an example of a patient with predominant symptom of dysphagia and low UES distensibility. (B) Shows an example of a patient with cough and a high UES distensibility.

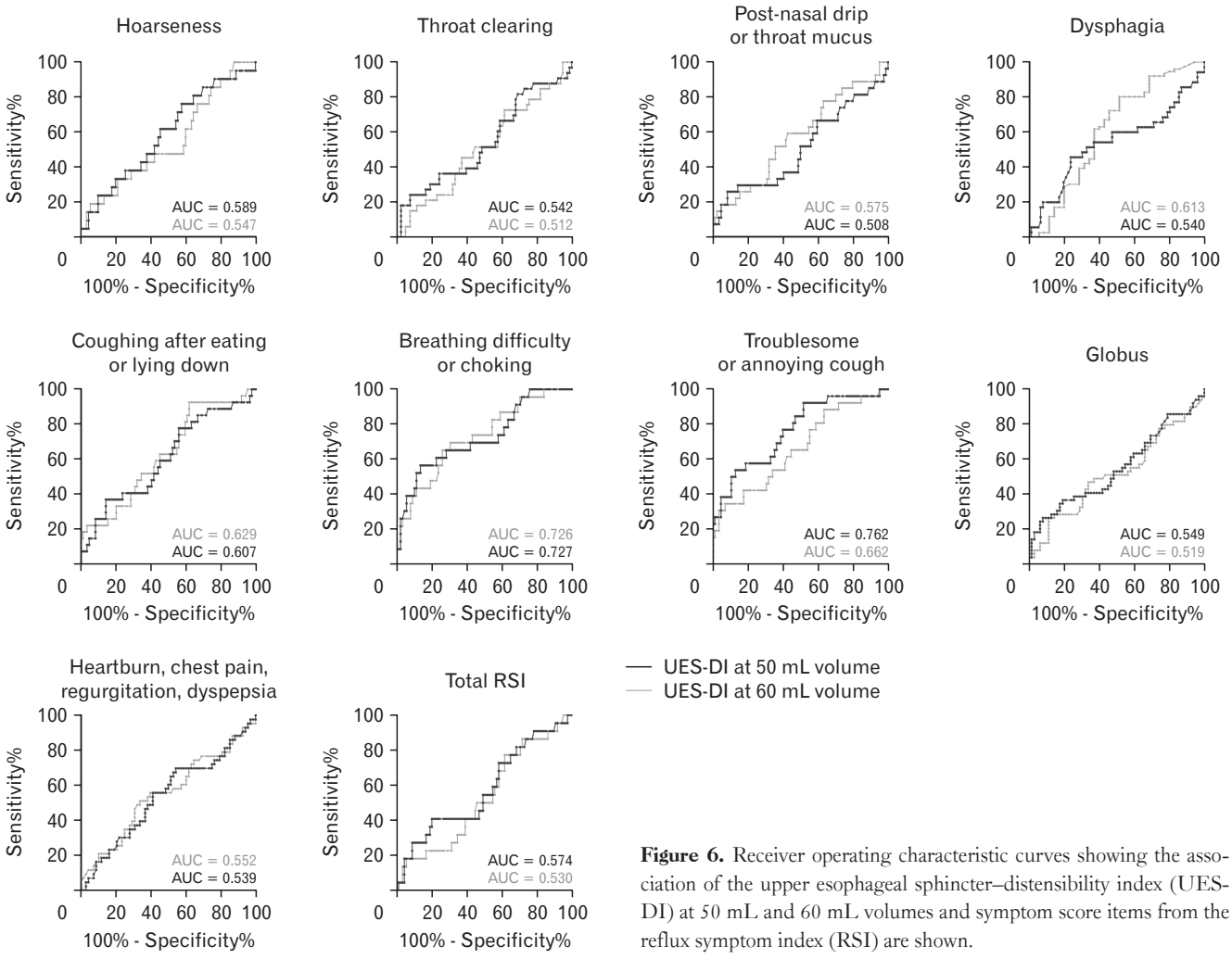

Figure 6. Receiver operating characteristic curves showing the association of the upper esophageal sphincter–distensibility index (UES-DI) at 50 mL and 60 mL volumes and symptom score items from the reflux symptom index (RSI) are shown.

Logistic regression analysis using age, sex, BMI, presence of hiatal hernia, and the UES-DI measurements at 50 mL and 60 mL showed the following: (1) UES-DI at 60 mL was associated with severe cough after eating or lying down ($P = 0.047$) and (2) UES-DI at 50 mL was associated with severe breathing difficulty or choking ($P = 0.015$). Age, sex, BMI, or presence of hiatal hernia were not associated with higher scores for cough-predominant symptoms or total RSI score.

We constructed receiver-operative characteristic curves of the UES-DI at 50 mL and 60 mL volumes in association with the same symptom score outcomes (Fig. 6). AUC was > 0.70 for item 6 (breathing difficulty or choking) at both 50 mL and 60 mL volumes and for item 7 (troublesome or annoying cough) at the 50 mL volume. These curves were selected for further analysis with cutoff thresholds chosen based on Youden's index. At the 50 mL volume, a UES-DI of > 3.45 mm^2/mmHg had a sensitivity of 70% and specificity of 58% in association with a score of 4 or 5 for breathing difficulty or choking ($P = 0.021$); and a UES-DI of > 3.83 mm^2/mmHg had a sensitivity of 92% and specificity of 48% in association with troublesome or annoying cough ($P = 0.023$). At the 60 mL volume, a UES-DI of > 3.03 mm^2/mmHg had a sensitivity of 83% and specificity of 45% in association with breathing difficulty or choking ($P = 0.017$).

Although the AUC for item 4 (dysphagia) curves was < 0.70 at both 50 mL and 60 mL volumes, we did perform a threshold analysis for the UES-DI at the 60 mL volume given the differences in scores we noted based on the distensibility groupings in Figure 3. At the 60 mL volume, a UES-DI of < 1.96 mm^2/mmHg had a sensitivity of 80% and specificity of 49% in association with a dysphagia score of 4 or 5 ($P = 0.007$).

In summary, a higher UES-DI (in the 3-4 mm^2/mmHg or higher) was associated with symptoms of cough and choking

sensation. Conversely, a lower UES-DI (less than ~2 mm^2/mmHg as measured at the 60 mL volume) was associated with dysphagia.

The Upper Esophageal Sphincter–Distensibility Index Does Not Correlate With Manometric Resting and Residual Upper Esophageal Sphincter Pressure

HRM was available in 32 patients. Mean resting UES pressure on HRM and residual pressure were correlated with UES-DI at all volumes 40-70 mL. Pearson R values for UES resting pressure with the UES-DI were (1) 40 mL: −0.062 ($P = 0.735$), (2) 50 mL: −0.120 ($P = 0.513$), (3) 60 mL: −0.012 ($P = 0.948$), and (4) 70 mL: 0.108 ($P = 0.557$). Pearson R-values for UES residual pressure with the UES-DI were (1) 40 mL: 0.156 ($P = 0.393$), (2) 50 mL: 0.136 ($P = 0.457$), (3) 60 mL: 0.269 ($P = 0.136$), and (4) 70 mL: 0.093 ($P = 0.615$). Thus, there was no correlation of UES-DI with manometric UES pressure.

Discussion

This was a retrospective descriptive pilot study in over 100 patients in which we studied a novel application of FLIP in assessing properties of the UES. We examined the association of the UES–DI on FLIP topography with supra-esophageal symptoms suggesting aspiration of esophageal contents measured by the RSI score. We found that patients with higher UES-DI at 50 mL and 60 mL volumes have higher scores for the cough and choking sensation. On multivariate analysis, we found that a UES-DI in the 3-4 mm^2/mmHg range or higher was associated with cough and choking symptoms, whereas a UES-DI of < 2 mm^2/mmHg was weakly associated with dysphagia.

Patients with supra-esophageal symptoms are a complex and heterogenous group who unfortunately often struggle with a high symptom burden. Defective barrier function of the UES has been theorized as an important mechanism for the genesis of chronic cough and supra-esophageal symptoms.[16] Unfortunately, no technique has proven to be reliable towards measuring UES barrier function in the clinical setting. Our results show that a higher UES-DI measured on FLIP is associated with higher scores for the cough and choking sensation items from the RSI, suggesting that these patients have more aspiration and micro-aspiration related to a defective UES barrier. We favor the mechanism of increased distensibility of the UES in this setting to be an impaired esophago-UES sensory reflex; however, variations in the elastic properties of the cricopharyngeus and/or other changes in neural signaling are also possibilities. Identifying a UES which is defective in its barrier function has therapeutic relevance as it can be augmented with existing therapies such as the upper-esophageal sphincter assist device.[22] Our data also shows a weak correlation of dysphagia with a low UES-DI. This could be explained by cricopharyngeal bar type physiology, which may be primary or adaptive in response to an esophageal motor disorder or GERD.[23] Importantly, our study shows that UES assessment using a FLIP protocol very similar to the established protocol for the distal esophagus is very safe and well tolerated during propofol-based endoscopy. However, the ideal protocol for FLIP assessment of the UES remains to be determined.

Results from our study are consistent with the physiological profile of the UES linked to supra-esophageal symptoms in prior studies. Nadaleto et al[15] found a shorter UES length and greater percentage of UES hypotonicity on HRM in patients with extra-esophageal symptoms versus typical GERD symptoms. In another elegant study, Babaei et al[16] studied UES responses measured on HRM to rapid saline injection and slow acid infusion in healthy controls, typical GERD patients, and those with supra-esophageal symptoms. The authors found that patients with supra-esophageal symptoms had diminished UES contraction in response to slow acid infusion and abnormal UES relaxation in response to saline injection.[16] Manomeric assessment of the UES is limited due to variability in normative data and confounding effect of UES reactivity.[12,24-26] In our study, HRM UES pressures did not correlate with FLIP UES-DI in our sample. FLIP is performed during sedated upper endoscopy when UES reactivity is diminished. FLIP is also ideal for assessing UES behavior in response to proximal esophageal contents, as the inflation port on the FLIP bag is in the distal portion.

The feasibility of the FLIP technique in assessing the UES during deglutition has already been demonstrated previously. Regan et al[27] measured changes from rest in the UES with dry and liquid swallows using the 8-cm endoFLIP catheter. They found a resting UES diameter of 4.9 mm which increased to 8-10 mm with 5 mL and 10 mL swallows.[27] Since then, 2 studies have used sedated FLIP assessment of the UES – the first to diagnose pharyngeoesophageal junction stricture in head and neck cancer patients, and the second to guide cricopharyngeal myotomy for Zenker's physiology,[18,19] Our study is the first to assess UES distensibility in patients with presumed laryngopharyngeal reflux. Future studies will need to generate high quality normative data of the UES using FLIP and ideally control for depth of sedation.

Our study has several key limitations. A critical limitation is that we do not have data in asymptomatic controls. Despite our systematic protocol using EGD and FLIP for all patients who war-

ranted evaluation for non-obstructive dysphagia, non-cardiac chest pain, or proton pump inhibitor-unresponsive symptoms, there is a risk of selection bias in this retrospective study. As patients who receive general anesthesia did not undergo UES-FLIP (due to effect of the endotracheal tube on measurements), patients with organic upper GI tract disease are likely underrepresented. Although all sedation was propofol-based, depth of sedation was not standardized beyond use of ASGE guidelines. We did not test the association of symptoms or UES-DI measurements with pH data or esophageal motility diagnoses. Strengths of our study are the large sample size, uniform FLIP protocol performed by a single endoscopist, and software-based calculation of the UES-DI at multiple volumes.

In conclusion, FLIP is a novel application in assessing barrier function of the UES. A high UES-DI correlates with symptoms suggestive of a defective UES barrier against aspiration of esophageal contents. Normative data and future prospective studies will be needed to support these findings.

Supplementary Materials

Note: To access the supplementary tables 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/jnm21197.

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