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Assessment of Upper Esophageal Sphincter Function on High-resolution Manometry:

Identification of Predictors of Globus Symptoms

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Abstract

Background—Globus is commonly encountered in clinical practice, but high-resolution manometry (HRM) characteristics are incompletely characterized. We evaluated HRM metrics in globus subjects, compared with age-matched and sex-matched dysphagia subjects and healthy controls.

Study—Twenty-four subjects with globus (53.3±2.3 y, 58% female) were compared with 24 age-matched and sex-matched subjects with nonobstructive dysphagia (52.5±2.5 y, 58% female), and 21 healthy controls (27.6±0.6 y, 52% female). Sphincter and segment anatomy, and pressure volume metrics assessed skeletal (proximal contractile integral) and smooth muscle contraction (distal contractile integral). Parameters significantly different across groups on univariate analysis were subjected to multivariate logistic regression and receiver-operating characteristic analysis to identify HRM predictors of globus.

Results—Upper esophageal sphincter (UES) postswallow residual pressures were highest in globus (2.6±0.5 vs. 2.3±0.5mm Hg in dysphagia and 0.6±0.6mm Hg in controls, $P=0.03$); 66.7% had recordable UES residual pressure, in contrast to 9.5% of controls, and 37.5% of dysphagia patients ($P=0.0002$). Although different from controls, UES length and basal pressure, and segment 1 parameters did not differ from dysphagia controls. In a multivariate model, measurable UES residual pressure (odds ratio, 6.33; 95% confidence interval, 1.79–25.96) independently predicted globus. Receiver-operating characteristic analysis identified a threshold of 0.4mm Hg UES residual pressure in segregating globus (sensitivity 66.7%, specificity 71.5%, positive predictive value 55.2%, and negative predictive value 80.0%).

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The authors declare that they have nothing to disclose.

Conclusion—HRM with measurement of UES residual pressure allows objective assessment of patients with globus sensation, and has potential to complement current diagnostic strategies.

Keywords

globus; high-resolution manometry; upper esophageal sphincter

Globus sensation has been defined as a nonpainful, persistent or intermittent sensation of discomfort or of “something stuck,” localized to the neck, constant, and occurring between meals.¹ Isolated globus has been characterized to occur without accompanying esophageal-type dysphagia, without evidence of gastroesophageal reflux disease (GERD), and without evidence of histopathologic-based esophageal motility disorders (such as achalasia or scleroderma esophagus).¹ In clinical practice, <10% patients have isolated globus sensation; the remainder have associated dysphagia, reflux symptoms, or noncardiac chest pain.^{2,3} The most frequently associated symptom is dysphagia, but as both physicians and patients may mistake globus itself for dysphagia, this characterization is not well defined. Visceral hypersensitivity and GERD have been reported as potential etiologic factors, but understanding of pathophysiology remains incomplete. Elevated upper esophageal sphincter (UES) pressures have been associated with globus on conventional manometry,^{2,4} but other studies report conflicting results.^{5,6} Furthermore, these studies compared UES pressures in globus to those with GERD. In contrast, the relationship of globus with dysphagia, the most common accompanying or confounding symptom, has not been well characterized.

In recent years, high-resolution manometry (HRM) has revolutionized the understanding of esophageal motor function. HRM provides detailed information on esophageal motor function, including UES and skeletal muscle of the proximal esophagus. Although HRM has tremendous potential in UES evaluation, only limited studies have addressed globus using HRM in the literature. One study found that respiration-related change in resting UES pressure was significantly amplified in globus patients compared with normal controls and GERD patients.⁷ This hyperdynamic UES response was not associated with other abnormalities of distal esophageal function.⁷ Another study reports transition zone defects in globus patients with clinical GERD diagnoses, which could predict a response to antisecretory therapy.⁸

In this study, we aimed to determine UES parameters that could be of value in assessing patients with globus symptoms. We hypothesized that UES and skeletal muscle in the proximal esophagus could demonstrate motor findings in patients with globus, given the anatomic localization of this symptom. We compared multiple motor parameters between patients with globus sensation, normal volunteers, and patients with esophageal-type dysphagia without globus to determine independent motor predictors of globus on HRM.

MATERIALS AND METHODS

Patients

Patients with globus were identified from a pool of 2674 patients undergoing HRM at the motility laboratory at Barnes-Jewish Hospital between December 2006 and March 2012,

from retrospective interrogation of prospectively acquired clinical and HRM data. Consecutive patients referred for HRM specifically for evaluation of globus as a symptom were included. Globus was diagnosed by the treating gastroenterologist after a careful history and investigation that included endoscopy in all instances to exclude an organic etiology for globus. Assessment of esophageal motor function was solicited for further investigation. When they presented for HRM, patients filled out self-report questionnaires from which associated symptoms were extracted, and global symptom severity assessed from a 10 cm visual analog scale. A cohort of age-matched and sex-matched patients with dysphagia without globus were also identified from the same patient pool; these patients were selected during the same calendar month as the globus patients to ensure uniformity of HRM technique and catheter. For all cohorts, exclusion criteria included prior foregut surgery, histopathology-based motor disorders (eg, achalasia, scleroderma esophagus), incomplete symptom data, and unintelligible studies. Normal controls consisted of healthy volunteers recruited by advertisement, without history of gastrointestinal symptoms or upper gastrointestinal surgery, and on no medications. Evaluation and review of HRM and associated clinical records for this study was approved by the Washington University Institutional Review Board.

HRM

A solid-state HRM assembly with 36 solid-state sensors spaced at 1-cm intervals (OD, 4.2 mm) was used (Sierra Scientific Instruments, Given Imaging, Los Angeles, CA). The response characteristics of this device, calibration procedure, and poststudy thermal correction measures have been described in detail elsewhere.⁹ Subjects underwent transnasal placement of the solid-state manometry catheter, after topical anesthesia applied to the nostril. Studies were performed after an overnight fast, in the supine position slightly tilted to the left, with the head of bed elevated 15 degrees for ease of swallowing. The manometry catheter was positioned to record from the hypopharynx to the stomach with about 5 intragastric sensors. The manometric protocol included a 5-minute period to assess basal sphincter pressure and ten 5-mL ambient temperature water swallows. No dry swallows were used for analysis. All pressure measurements were referenced to atmospheric pressure.

HRM Data Analysis

The boundaries and length of the UES and adjacent skeletal muscle contraction segment in the proximal esophagus were established using a 30mm Hg isobaric contour tool, available as an onscreen software option in the analysis software (Manoview; Given Imaging). Basal UES sphincter pressure, nadir (residual) pressure during relaxation, time to nadir pressure, and recovery time were extracted from the analysis software. Peak skeletal muscle contraction amplitude and mean wave duration were also assessed. The integrity and contraction vigor of the skeletal muscle contraction segment was assessed with the proximal contractile integral (PCI), defined as the product of length, time, and amplitude of the skeletal muscle segment above a threshold of 20mm Hg, similar to the distal contractile integral (DCI) which assesses exactly the same parameters in the smooth muscle contraction segments.¹⁰ The pressure trough between UES and skeletal muscle contraction segment for this calculation was identified by altering the isobaric contour threshold using the onscreen tool (Fig. 2).

Esophageal body contraction parameters were recorded from the analysis software. Analysis parameters included mean contraction amplitudes in the smooth muscle contraction segments, wave duration, contraction front velocity, DCI, and segment length. Chicago Classification designation was determined in all instances and reported. Esophageal body motor pattern was further characterized as hypomotility, hypermotility, or normal as described below: (a) esophageal body hypomotility: 50% failed peristalsis, or transmitted swallows with averaged amplitudes of 30mm Hg; (b) esophageal body hypermotility: named motor disorders including diffuse esophageal spasm, defined as 20% simultaneous sequences, increased mean wave amplitude (>180mm Hg in the smooth muscle esophagus for a designation of “nutcracker esophagus”), prolonged mean wave duration (>5.7 s), increased frequency of double-peaked wave (>15%), and the presence of any triple-peaked waves; (c) normal esophageal body motility when neither hypomotility nor hypermotility features were identified.¹¹

Statistical Analysis

All HRM quantitative parameters are reported as mean±SE of the mean (SEM) unless otherwise described. Qualitative data are described as percentage of the sample. Student *t* test was used for comparison between groups, and 1-way analysis of variance for comparison across all 3 groups. Parameters with significant difference between groups in univariate analysis were further assessed by multivariate logistic regression to determine independent predictors of globus. A *P* value <0.05 was required for statistical significance in all instances.

RESULTS

Over the 5.25-year study period, 24 patients (age 53.3±2.3 y, 58.3% female) were identified who underwent HRM primarily for the evaluation of globus symptoms, and constituted approximately 1% of the total HRM pool of 2674 subjects. From the same pool, 24 matched patients with a dominant symptom of dysphagia without globus (age 52.5±2.5 y, 58.3%) were also identified, who underwent HRM in the same calendar year as the globus patients. The 2 patient groups were compared with 21 normal controls (age 27.6±0.6 y; range, 18 to 32 y; 52.4% female) (Table 1). All patients underwent upper endoscopy to exclude a structural or mucosal etiology for symptoms. Despite the clinical diagnosis of globus as the primary disorder and designation as the dominant symptom, subjects checked other secondary symptoms in the self-report questionnaire; dysphagia was checked by 19 patients, heartburn by 7 patients, and reflux and noncardiac chest pain by 2 patients each. Among the 24 dysphagia patients, additional symptoms included heartburn in 9 patients, reflux in 5 patients, and noncardiac chest in 6 patients. On visual analog scale, the global symptom severity was scored at 4.87±0.64 by globus patients, and 6.07±0.59 by dysphagia patients, reflecting their symptomatic state over the preceding 2 weeks.

UES Parameters

The proportions of patients with normal, decreased (<34mm Hg), or increased (>104mm Hg) mean basal UES pressure was significantly different in the 3 groups (*P*=0.03). Normal UES basal pressure was seen more often in normal controls (90.5%) and dysphagia patients

(83.3%) compared with globus patients (75.0%). Elevated UES basal pressure was seen most often in globus patients (16.7%); 9.5% of normal and none of dysphagia patients had elevated pressure. In contrast, decreased UES basal pressure was seen most often in dysphagia patients (16.7%); only 8.3% of globus patients and none of the normal controls had decreased pressure. Significant quantitative differences were detected in UES length ($P=0.0028$), UES mean basal pressure ($P=0.03$), and residual pressure ($P=0.03$) among the 3 groups (Table 1). UES residual pressure were further characterized into 2 qualitative scales, depending on whether the residual pressure was 0mm Hg (no residual pressure) or >0mm Hg (measurable residual pressure, Fig. 1). Using this characterization, 16 (66.7%) of globus patients had measurable UES residual pressure after wet swallows, significantly higher than normal controls and dysphagia patients (9.5% and 37.5%, respectively; $P=0.0002$ compared with globus). In contrast, only 2 normal controls had measurable UES residual pressure, and the vast majority (90.5%) had a UES residual pressure of 0mm Hg. A trend toward a prolonged UES relaxation time to nadir was detected in globus patients, longer than in dysphagia patients and normal controls ($P=0.07$). No significant differences were detected in relaxation duration ($P=0.22$) and recovery time ($P=0.36$).

Skeletal Muscle Parameters

A trend towards shorter skeletal muscle length was detected in both globus and dysphagia patients ($P=0.08$) compared with controls. Significant differences were noted in skeletal peak amplitude ($P=0.049$) and PCI ($P=0.01$). An identifiable pressure trough between UES and skeletal muscle was found exclusively in 26 swallows of 5 (20.8%) patients with globus sensation (Fig. 2), and absent in all swallows in normal controls and dysphagia patients. Two unique pressure trough patterns were identified (Fig. 2). One pattern, seen in 3 globus patients, had a trough with a lower nadir pressure than the transition zone nadir pressure, identified by moving the pressure parameters of the isobaric contour. With this pattern, the peristaltic contour was intact at 30mm Hg isobaric contour setting, and the trough could only be seen at higher isobaric contour pressure settings (Fig. 2A). The second pattern, seen in 2 globus patients, consisted of a pressure trough seen at the 30mm Hg isobaric contour pressure setting (Fig. 2B). None of the remaining 19 globus patients, or patients in the other 2 groups, had similar pressure troughs despite careful scrutiny with isobaric contour set at various pressure thresholds.

Lower Esophageal Sphincter and Esophageal Body Parameters

No significant differences in lower esophageal sphincter resting or residual pressure, mean wave amplitude, duration, contractile front velocity, and DCI were detected in the esophageal body in the 3 groups ($P>0.05$, Table 1). When the esophageal motor pattern was characterized, Chicago Classification criteria for minor motor disorders was met by 4 globus subjects (16.7%), all with hypomotility features (large breaks, frequent failed peristalsis). Of the dysphagia subjects, 7 (29.2%) had minor motor disorders (hypomotility in 5, hypermotility in 2, $P=NS$ compared with globus subjects). Contraction wave abnormalities were seen in 29.2% of globus patients, and 25.0% of dysphagia patients ($P=NS$). Overall, the esophageal body motor pattern did not predict globus symptoms.

Further Analysis

UES, skeletal muscle contraction segment, and smooth muscle motor parameters that were significantly different on univariate analysis were further assessed in a multivariate logistic regression model, with globus as the outcome variable. In multivariate regression analysis, UES residual pressure remained highly predictive of globus (odds ratio, 6.33; 95% confidence interval, 1.79–25.96); UES mean basal pressure (odds ratio=1.02, 95% confidence interval, 1.00–1.05) was a weak predictor. Receiver-operating characteristic analysis identified 0.4mm Hg as the optimal UES residual pressure threshold segregating globus subjects (Fig. 3), with a sensitivity of 66.7%, specificity of 71.1%, positive predictive value of 55.2%, and negative predictive value of 80.0%.

DISCUSSION

In this study, we demonstrate the value of HRM in the evaluation of the UES and the adjacent skeletal muscle segment. We show that UES relaxation is deep and profound in the healthy adult; patients with globus have measurable and higher residual pressures during the period of UES relaxation. Both measurable UES residual pressures and high UES basal pressures were independently predictive of globus sensation. Finally, we report that the currently accepted HRM thresholds for postswallow UES residual pressure may be too high to detect subtle abnormalities, as profound UES relaxation in controls approximates to residual pressures close to 0mm Hg. Our work adds to the growing body of literature evaluating the UES and proximal esophagus using HRM.

HRM with one pressure sensor per centimeter from the pharynx to the stomach is a relatively new advance in esophageal motor evaluation, and has revolutionized the understanding of esophageal motor function.⁹ HRM is superior in assessing UES dynamics, a significant advance from the pull-through technique of conventional manometry. UES opening is easily identified by change in UES color contours to that similar to intraesophageal resting pressure; this allows accurate assessment of UES relaxation. In addition to qualitative visual assessment of UES function, quantitative assessments of UES, skeletal muscle segment, smooth muscle segments, and LES were compared between the 3 study groups. There is ample evidence of superiority of HRM over conventional manometry in characterizing esophageal peristaltic patterns, with potential to augment the assessment of the UES and the proximal esophagus.⁹ Therefore, HRM is an ideal tool to interrogate proximal esophageal and UES function.

Despite the explosion of HRM literature and a new classification system dedicated to disorders of the smooth muscle esophagus, reports of HRM characterization of proximal esophageal function are infrequent in the literature. The transition zone between skeletal and smooth muscle contraction segments has received some attention, and transition zone defects have been linked to dysphagia, GERD, and even globus.^{8–10,12} PCI has been reported as a metric to assess the integrity of the proximal contractile segment by Ghosh et al¹⁰ where the distribution of PCI values encountered in 309 patients was reported, but the length of skeletal muscle and normal PCI values were not. Our study attempts to fill this void in the understanding of UES and skeletal muscle function. We have used rigorous measurements to first define morphology and normal function of the proximal esophagus in

healthy volunteers, and used these metrics to better understand proximal esophageal function in patients with globus.

Globus is of interest to clinicians and gastroenterologists, as patients may be referred to gastroenterologists with this symptom. Prior evaluations for underlying causes of globus have largely focused on psychosomatic origins or the relationship with GERD.^{2,13,14} It is only after the advent of HRM and the ability to better define the UES that attention is slowing shifting to motor evaluation. In the first study of its kind, normal respiratory variation of UES pressure was noted to be amplified in globus patients studied with HRM techniques.⁷ Neither esophagogastric junction respiratory variation, distal esophageal motility, nor postdeglutitive UES relaxation correlated with the presence of globus sensation. Nadir UES relaxation pressure qualitatively measured in that study suggested normal thresholds of 11.9mm Hg.⁷ Our observation, however, is that normal UES relaxation pressures are extremely low in normal subjects, most without measurable relaxation pressures. This might indicate the need to revisit normative contraction and relaxation metrics in the UES. Our data also suggest that globus may be associated with higher postdeglutitive UES relaxation pressures than normal patients or those with other esophageal symptoms. Taking our results and those of Kwiatek and colleagues into consideration, it is possible that the hyperdynamic nature of UES function leads to higher residual pressures in globus patients, findings that are not evident in other dysphagia states or in normal subjects. Although less likely, it is also possible that UES residual pressures have high variability, but larger studies will be needed to address this issue further. In addition, we describe 2 unique proximal esophageal motor patterns associated with troughs between the UES high-pressure zone and skeletal muscle contraction segment that was only seen in the globus patients. These 2 patterns may indicate disordered continuity of peristalsis, but further research is needed to determine how often this pattern is seen in nonglobus patients.

Prior manometric studies using conventional manometry in the last 2 decades have provided evidence for the relationship between esophageal function and globus. These older studies link globus to elevated UES pressure resulting from gastroesophageal reflux, without need for and possibly to prevent direct exposure of the hypopharynx to gastric acid.^{2,4} Other studies have reported conflicting findings, with normal UES resting pressures in many globus patients.⁵ Psychological and psychiatric characteristics could be relevant to the discomfort experienced etiological significance remains unclear.¹³ The association between distal esophageal motor function and globus is more intriguing. Although the Kwiatek et al's⁷ study did not identify distal esophageal motor abnormalities, another study found spastic processes in the distal esophagus in 27 of 30 patients with globus.¹⁵ Although minor motor disorders were seen in globus patients, proportions were not different from dysphagia patients, and the true significance of esophageal body motor patterns needs further study in a larger cohort of patients.

Our study has a few limitations. First, this is a retrospective analysis, and globus patients were identified from referrals for manometry which could have introduced a selection and referral bias—it is unknown how often globus remains uninvestigated with manometry in clinical practice, and our sample may not be representative. Secondly, there is an obvious

age discrepancy between the normal control group (27.6 ± 0.6 y), compared with globus patients (53.3 ± 2.3 y) and dysphagia controls (52.5 ± 2.5 y). Age may affect the response of the proximal esophagus to wet swallows¹⁶; basal UES pressure could also vary with age¹⁷; however, we were unable to recruit healthy controls without comorbidities or medication use in older populations. In view of the potential age-associated effect, we used a multivariate regression analysis to assess independent predictors of globus, potentially more robust than univariate analysis to remedy this shortcoming. Comparison with healthy age-matched control subjects would be of better value in assessing the discrimination of UES residual pressure between globus and normal controls. Thirdly, only 24 globus patients were included in our study during 5.5 years. This is partly because we did not want to include subjects with globus as a secondary symptom; however, future studies may need to address patients with globus in conjunction with other esophageal symptoms to further evaluate the validity of our findings. A larger sample could potentially have demonstrated more persuasive data. Finally, our data only represent studies performed in a single position, that is, supine. It is well known that UES pressures are affected by location of the catheter within the sphincter, and altering the patient's position (eg, to the sitting position) may provide further information regarding the influence of position on UES metrics.

In conclusion, we demonstrate elevated UES basal pressure with globus, consistent with prior reports. More importantly, we show the high association of elevated postswallow UES residual pressures with globus, a metric that was independently predictive of this symptom on multivariate analysis. Two unique proximal esophageal motor patterns are reported in a proportion of globus patients, which require further assessment to determine morphologic abnormalities associated with globus. These findings add to the growing body of literature evaluating the UES and proximal esophagus using HRM, and help physicians evaluate relationships between esophageal motor patterns and difficult symptom like globus.

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FIGURE 1.

A High-resolution manometry (HRM) study in a normal subject, showing normal upper esophageal sphincter (UES) after swallow residual pressures. The isobaric contour tool is set to 30mm Hg. Note the deep blue topographic contour during the relaxation phase of the UES, which matches the blue color in the esophageal body. The residual pressure was not measurable in this instance. B, HRM in a patient with globus. With the isobaric contour tool at 30mm Hg, the topographic color at expected UES relaxation is less blue, indicating measurable residual pressure.

FIGURE 2.

Two HRM manifestations of low-pressure troughs (arrows) between upper esophageal sphincter (UES) and skeletal muscle of the proximal esophagus in globus. A, The trough is visible at a nadir pressure lower than that at the transition zone. B, The trough is associated with a transition zone defect between skeletal and smooth muscle contraction segments. In both the instances, UES residual pressure is measurable.

FIGURE 3.

Receiver-operating characteristic (ROC) analysis demonstrating optimal upper esophageal sphincter (UES) residual pressure threshold of 0.4mm Hg in predicting globus subjects, with a sensitivity of 66.7% and specificity of 71.1%. Negative predictive value was 80.0%. The area under the curve was 0.65 indicating modest predictive value (95% confidence interval, 0.53–0.76).

TABLE 1

Univariate Comparisons of Clinical and Motor Characteristics Between Globus, Dysphagia, and Normal Subjects

Parameters	Globus n=24	Normal n=21	Dysphagia n=24	P
Age (y)	53.25±2.60	27.57±0.63	52.46±2.52	<0.0001*
Sex (% female)	58.3	52.4	58.3	NS
UES				
Length (cm)	2.28±0.11	2.70±0.12	2.13±0.11	0.0028*
Mean basal pressure (mm Hg)	80.27±6.90	84.72±7.37	59.74±6.90	0.0328*
Residual pressure (mm Hg)	2.64±0.53	0.60±0.57	2.25±0.53	0.0267*
Relaxation time to nadir (ms)	211.38±22.12	135.38±23.65	177.75±22.12	0.0709
Relaxation duration (ms)	889.58±66.66	742.62±71.26	896.83±66.66	0.2186
Recovery time (ms)	678.21±53.35	607.24±57.04	719.08±53.35	0.3591
Skeletal muscle (S1)				
Length (cm)	4.39±0.29	5.18±0.30	4.30±0.29	0.0801
Peak amplitude (mm Hg)	103.79±9.01	133.00±9.63	104.26±9.01	0.0494*
Mean wave duration (s)	3.04±0.14	3.08±0.14	2.91±0.14	0.6679
PCI mean (mmHg cm s)	243±40	412±43	234±40	0.0054*
Esophageal body (S2, S3)				
Mean wave amplitude (mm Hg)	76.97±10.19	94.35±10.89	80.43±10.19	0.4778
Mean wave duration (s)	3.52±0.29	3.51±0.31	3.93±0.29	0.5156
Mean DCI (mmHg cm s)	1660±512	1619±548	2260±512	0.6226
Mean contractile front velocity (cm/s)	2.95±0.48	3.56±0.52	3.97±0.48	0.3332
LES				
Length (cm)	3.20±0.16	2.91±0.18	2.66±0.16	0.0747
Intra-abdominal LES length (cm)	2.01±0.18	2.07±0.19	1.51±0.18	0.0601
End-expiratory pressure (mm Hg)	12.43±1.77	10.91±1.90	11.90±1.77	0.8416
Residual pressure mean (mm Hg)	7.32±0.98	7.07±1.05	7.45±0.98	0.9638

One-way analysis of variance was used in comparison of the 3 groups.

* $P < 0.05$ versus normal and dysphagia subjects.

CFV indicates contractile front velocity; LES, lower esophageal sphincter; PCI, proximal contractile integral; UES, upper esophageal sphincter.