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Upper Esophageal Sphincter (UES) Metrics on High-resolution Manometry (HRM) Differentiate Achalasia Subtypes

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Abstract

Background—The upper esophageal sphincter (UES) reflexively responds to bolus presence within the esophageal lumen, therefore UES metrics can vary in achalasia.

Methods—Within consecutive patients undergoing esophageal high resolution manometry (HRM), 302 patients (58.2 ± 1.0 yr, 57% F) with esophageal outflow obstruction were identified, and compared to 16 asymptomatic controls (27.7 ± 0.7 yr, 56% F). Esophageal outflow obstruction was segregated into achalasia subtypes 1, 2, and 3, and esophagogastric junction outflow obstruction (EGJO with intact peristalsis) using Chicago Classification v3.0. UES and lower esophageal sphincter (LES) metrics were compared between esophageal outflow obstruction and normal controls using univariate and multivariate analysis. Linear regression excluded multicollinearity of pressure metrics that demonstrated significant differences across individual subtype comparisons.

Key results—LES integrated relaxation pressure (IRP) had utility in differentiating achalasia from controls ($p < 0.0001$), but no utility in segregating between subtypes ($p = 0.27$). In comparison to controls, patients collectively demonstrated univariate differences in UES mean basal pressure, relaxation time to nadir, recovery time, and residual pressure (UES-RP) ($p = 0.049$). UES-RP was highest in type 2 achalasia ($p < 0.0001$ compared to other subtypes and controls). In multivariate analysis, only UES-RP retained significance in comparison between each of the subgroups ($p = 0.02$ for each comparison). Intrabolus pressure was highest in type 3 achalasia; this demonstrated significant differences across some but not all subtype comparisons.

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Conclusions and inferences—Nadir UES-RP can differentiate achalasia subtypes within the esophageal outflow obstruction spectrum, with highest values in type 2 achalasia. This metric likely represents a surrogate marker for esophageal pressurization.

Graphical Abstract

Abbreviated abstract: Elevated integrated residual pressure (IRP) at the lower esophageal sphincter (LES) on esophageal high resolution manometry (HRM) defines esophageal outflow obstruction, but UES metrics can also be abnormal in these disorders. We characterized UES metrics in esophageal outflow obstruction, and report that nadir UES residual pressure (UES-RP) is consistently higher compared to normal controls. Values are highest in type 2 achalasia, potentially a consequence of esophageal pressurization. Characterizing UES abnormalities, particularly nadir UES-RP, can complement esophageal body and LES metrics in segregating achalasia subtypes.

Keywords

Achalasia; esophagogastric junction outflow obstruction (EGJOO); High-resolution manometry (HRM); Upper esophageal sphincter; Esophageal pressurization

BACKGROUND

Achalasia is classically defined by the hallmark finding of esophageal outflow obstruction from impaired relaxation of the lower esophageal sphincter (LES)^{1, 2}. The prevailing theory of disease pathophysiology proposes that the myenteric plexus responsible for coordinating peristalsis and sphincter relaxation succumbs to inflammation or irreversible degeneration¹. Thus, motor dysfunction is restricted to smooth muscle segments of the esophagus. Nonetheless, abnormalities of the upper esophageal sphincter (UES), the skeletal muscle barrier between the esophagus and the pharynx, have been consistently reported in achalasia^{3–10}. Elevations in both UES basal pressures and post swallow residual pressures have been reported, with improvement of the latter following pneumatic dilation^{6, 7}. Some suggest that UES motor abnormalities correlate with worse treatment response^{8, 9}. These UES abnormalities are thought to represent a reflexive UES response to esophageal pressurization, a consequence of esophageal outflow obstruction.

Despite description of UES abnormalities, no study to date has assessed these findings within achalasia subtypes to determine if further conclusions can be drawn regarding associations with specific achalasia subtypes or severity. Therefore, in this study, we

analyzed a consecutive cohort of patients with an HRM diagnosis of achalasia or esophageal outflow obstruction based on the Chicago Classification, v3.0¹¹. All relevant UES parameters were extracted and analyzed for metrics that might segregate achalasia subtypes or further elucidate the relationship between achalasia and the UES. We hypothesized that UES abnormalities, particularly UES residual pressure (UES-RP) would correlate with achalasia subtypes demonstrating the highest degree of esophageal pressurization.

MATERIALS AND METHODS

Study Sample

All adult patients undergoing clinical esophageal HRM studies at our institutional motility laboratory between 2012 and 2016 were eligible for inclusion in this study. Inclusion criteria consisted of evidence of esophageal outflow obstruction based on interrogation of the esophagogastric junction (EGJ) using software metrics embedded in HRM analysis software (integrated relaxation pressure, IRP). Patients with prior disruption of the EGJ or LES for achalasia management (pneumatic dilation, myotomy) and those with prior foregut surgery were excluded. Further exclusion criteria consisted of unintelligible and critically imperfect studies where esophageal outflow obstruction could not be clearly established.

Asymptomatic healthy controls evaluated with esophageal HRM as part of the institution's normative data collection were used as a comparison group. The evaluation and review of HRM and associated clinical records for this study was approved by the Human Resources Protection Office (institutional review board) at Washington University School of Medicine, St. Louis.

High Resolution Manometry

The study employed a solid-state, 4.2 mm, 36-channel HRM assembly with high-fidelity circumferential sensors at 1-cm intervals (Medtronic, Duluth, GA). The response characteristics of this device, calibration procedure, and post-study thermal correction measures have been described in detail previously^{12, 13}. Experienced nurses performed transnasal placement of the solid-state manometry catheter through an anesthetized nasal canal. Patients were studied with a slight leftward tilt and the head of bed elevated to 15° for ease of swallowing. Sensors were positioned to record from the hypopharynx, the entire esophagus including both UES and LES, and the stomach, with 3–5 sensors positioned in the stomach. The manometric protocol consisted of a landmark phase recording during quiet rest to assess basal sphincter pressure (recorded either at the beginning or the end of the study based on patient tolerance), and ten 5-mL ambient temperature water swallows 20–30 seconds apart¹². No dry swallows were performed or used for analysis. All pressure measurements were referenced to atmospheric pressure, except for the integrated relaxation pressure (IRP), referenced to the gastric baseline pressure. Analysis of Clouse plots was performed via computerized HRM analysis software (Manoview, Medtronic, Duluth, GA).

HRM Data Analysis

Patients were assessed for esophageal outflow obstruction, defined as a LES integrated relaxation pressure (IRP, or post-deglutitive maximal 4-second relaxation interval in the 10-second window following UES relaxation) >15 mmHg. Diagnoses were further refined

according to the Chicago classification¹¹: a) 100% failed swallows without esophageal pressurization in type 1 achalasia; b) 20% swallows with pan-esophageal pressurization >30mmHg in type 2 achalasia; c) 20% swallows with premature contractions defined as distal latency <4.5s in type 3 achalasia; and d) esophagogastric junction outflow obstruction (EGJOO) none of the above criteria were fulfilled. HRM metrics from a cohort of healthy volunteers previously described¹² were used for comparison purposes.

The anatomic parameters of the UES were derived using a 30mm Hg isobaric contour tool; this pressure was chosen because panesophageal compartmentalization of pressure requires this isobaric contour tool in the diagnosis of type 2 achalasia. UES sphincter segment length, mean basal pressure, residual pressure (the nadir UES pressure during relaxation), the time to nadir pressure, and recovery time were extracted from the analysis software; these are independent of the isobaric contour utilized. Other recorded parameters included the LES length, LES end-expiratory pressure, and maximum intrabolus pressure (IBP) in the distal esophagus averaged over all swallows. In type 2 achalasia patients, the peak pan-esophageal pressurization among all swallows was recorded. In type 3 achalasia and EGJOO patients, esophageal body contraction parameters including the distal contractile integral (DCI), mean wave amplitude and duration, and distal latency (DL) were measured. Esophageal HRM studies were evaluated by an investigator (PB) not involved in clinical care of the patients.

Statistical Analysis

HRM parameters are reported as mean $\pm$ standard error of the mean (SEM) unless otherwise stated. One-way ANOVA analysis was used to isolate parameters with significance among the subtypes: this comparison was made with and without inclusion of the normal controls. All parameters that could be measured across all achalasia subtypes were then assessed by univariate analysis for significance. Because one of the aims of the study was to identify variables with the utility to segregate between the achalasia subtypes, normal controls were excluded from this step and each subsequent step.

Univariate regression tables were generated for comparison between every combination of subtype in dichotomous fashion, and variables that proved significant at any point were forward selected into the multivariate analysis, again conducted for each pairing of subtypes. For pressure metrics that continued to show independent correlations with differing subtypes, linear regression was employed to generate a Variance Inflation Factor (VIF) that would serve as a metric for multicollinearity.

RESULTS

Patient Characteristics

Over the study period, 302 patients (age 58.2 ± 0.97 y, 60.0% female) were identified fulfilling study definitions of esophageal outflow obstruction out of a total of 2674 patients undergoing esophageal HRM (11.3%). Of these, 179 were diagnosed as one of the three achalasia subtypes, and 123 as EGJOO. Within the achalasia subset, type 2 was the most frequent subtype identified (122 patients, 68.1%). Patients with achalasia subtypes 1 and 2 were younger on average than their counterparts with other forms of outflow obstruction, but

this did not reach statistical significance. A cohort of 16 asymptomatic healthy patients (age 27.7 ± 0.7 y, 56.3% female) who underwent esophageal HRM as part of our institutional normative data collection served as controls. UES and LES metrics were recorded for each of the subtypes and controls, while esophageal body metrics were measured only in subtypes with appropriate esophageal body contraction waveforms (Table 1).

Comparison to Healthy Controls

UES manometric parameters that differed between study cohorts included the length, basal pressure, residual pressure, relaxation time to nadir, and recovery time. In aggregate, patients with outflow obstruction had decreased UES basal pressures (65.3 ± 2.2 mmHg vs. 90.3 ± 6.4 mmHg, $p=0.049$), increased nadir UES-RP (5.1 ± 0.4 mmHg vs. -5.1 ± 1.4 mmHg, $p<0.001$), and increased relaxation times to nadir (210 ± 10.5 ms vs. 123 ± 13.8 ms, $p=0.015$) relative to healthy controls. The UES recovery time showed significant variation between cohorts ($p<0.001$), but this represented a mixed effect as type 2 achalasia patients demonstrated longer times while the remaining subtypes were shorter.

Esophageal body and LES parameters revealed elevated IBP, LES end-expiratory pressure, and LES IRP ($p<0.001$ for all) for the study cohorts with esophageal outflow obstruction. Patients with type 3 achalasia and EGJOO further demonstrated increased smooth muscle mean wave amplitude, mean wave duration, and DCI ($p<0.001$ for all) compared to controls. Patients with type 3 achalasia demonstrated a short mean distal latency (mean 4.3 ± 0.1 s) consistent with the Chicago Classification definition.

Comparison Within Esophageal Outflow Obstruction Subtypes

Prominent pressure metrics at the UES, esophageal body, and LES were characterized across all subtypes (Table 1). Of note, while the LES IRP of patients with achalasia demonstrated significant differences compared to healthy controls, this effect was not consistently seen between subtypes, and therefore did not stratify achalasia subtypes or EGJOO (Figure 1). In contrast, IBP (Table 1) and UES residual pressures (Figure 2) were successful in stratifying esophageal outflow obstruction into recognized subtypes. With both these metrics, values increased with progression from the normal phenotype to EGJOO and then achalasia. UES-RP was highest in type 2 achalasia (Figure 3), while IBP was most elevated in type 3 achalasia. Type 1 achalasia demonstrated the lowest values among the esophageal outflow subgroups for both of these metrics, where IBP approximated that noted in healthy controls.

Manometric differences were further evaluated using univariate analysis of each dichotomous comparison between esophageal outflow obstruction subtypes (Supplemental Table 1). Variables with significant differences between subtypes ($p<0.05$) were carried over into an equal number of multivariate analyses (Supplemental Table 2). Basal pressure values, both at the UES and the LES, did not show any difference across subtypes and thus were not included in multivariate analysis. Further comparisons between subtypes (Table 2) yielded additional loss of significance for the following UES metrics: relaxation time to nadir, recovery time, and length (with the exception of a shorter UES length in type 3 achalasia). The UES residual pressure remained significantly elevated in type 2 achalasia patients compared to each of the other subtypes, and in type 3 achalasia compared to EGJOO. IBP

was significantly lower in type 1 achalasia compared to all other groups. IBP was also lower in type 2 vs type 3 achalasia (adjusted OR = 0.95, 95% CI = 0.91–0.99). These differences did not retain statistical significance in all of the other dichotomous groupings.

Linear regression analysis of the UES residual pressure, intrabolus pressure, and LES IRP produced a VIF of 1.17 indicating a low concern for multicollinearity. Finally, maximum peak panesophageal pressurization in type 3 achalasia patients was found to correlate poorly with the UES-RP ($R^2=0.041$).

DISCUSSION

In this study evaluating a large cohort of consecutive patients with esophageal outflow obstruction identified using current diagnostic criteria according to the Chicago Classification v3.0, we demonstrate that UES metrics effectively segregate esophageal outflow obstruction into achalasia subtypes and EGJOO, especially type 2 achalasia. In particular, the UES-RP is most distinctive within the esophageal outflow obstruction phenotypes, where it is consistently higher than in normal controls. Within achalasia subtypes, UES-RP is highest in type 2 achalasia, and lowest in type 1 achalasia. While the relationship to esophageal pressurization in terms of IBP could not be demonstrated, type 2 achalasia by definition is associated with panesophageal pressurization, and we speculate that this may have a role in elevating UES-RP. Our findings suggest that evaluation of UES metrics can provide clues to the identification and further subtyping of esophageal outflow obstruction, particularly type 2 achalasia.

In their recent review of achalasia, Kahrilas and Boeckxstaens¹ posit a model that implicates the severity of plexitis as the precursor for disease progression into each of the various clinical subtypes. On one arm are cases of cytotoxic neuronal loss leading initially to type 2 achalasia, which can potentially progress to type 1 achalasia if left untreated¹⁴. On the other are patients without apoptosis but with chronic inflammation and its attendant circulating cytokine milieu that disrupts the excitatory and inhibitory balance of the esophageal body and LES; this is thought to manifest as type 3 achalasia without the potential to progress to another more severe phenotype¹⁵. Suggested as a precursor for both disease processes is EGJOO, although it is known that a multitude of other causes can result in manometric findings that would result in similar manometric patterns². Within this framework, additional manometric findings that add to segregation of the subtypes of esophageal outflow obstruction can only enhance the clinical identification of each subtype. Within our findings, UES-RP had highest yield in defining type 2 achalasia. The mechanism of conversion of type 2 achalasia to type 1 achalasia involves esophageal dilation and potentially loss of tone in the esophageal smooth muscle^{2, 14, 16}. This reduces esophageal pressurization, and we speculate that this in turn lowers UES-RP. Values were intermediate in type 3 achalasia, where pressurization within the esophagus is segmental rather than panesophageal. Heterogeneity within EGJOO is the likely reason for variable results in this patient population.

This study is the first to date to segregate UES abnormalities by achalasia subtypes and EGJOO in patients with esophageal outflow obstruction on HRM. We propose that elevated

UES residual pressures carry utility as an independent marker for esophageal pressurization consistent with each achalasia subtype class physiology. While elevated LES IRP remains the defining feature of achalasia as a blanket diagnosis, our findings suggest UES residual pressure fluctuation to be a close correlate with the lower esophageal spasticity of type 3 achalasia, the panesophageal pressurization of type 2 achalasia, and the aperistalsis of type 1 achalasia. Our intrabolus pressure results also fit this model, as patients with spastic or type 3 achalasia had the highest IBP elevations, albeit segmental. On multivariate analysis, however, the IBP failed to segregate type 2 or type 3 achalasia patients from those with EGJOO, while the UES-RP remained successful.

The elevation of UES residual pressures in achalasia compared to healthy controls has been demonstrated previously³⁻⁷. The fact that UES-RP but not UES basal pressure is elevated suggests that this is a reflexive response to esophageal pressurization rather than an involuntary pressure artifact¹⁷ – this is well demonstrated with esophageal pressurization from infused water to simulate refluxed volume within the esophageal body. As a cross-sectional analysis of patients who underwent HRM for any indication, this study was not designed to investigate disease pathophysiology or clinical outcomes. The lack of other non-obstructive cohorts, and the non-availability of impedance data limit our study design. A further limitation is our inability to correlate manometric diagnoses with symptoms of achalasia or with treatment outcomes because of the retrospective design. We also did not utilize objective testing (e.g. videofluoroscopy) to rule out oropharyngeal dysphagia. Finally, our normal cohorts were significantly younger than achalasia patients, which could have influenced some of our manometric analyses. Nevertheless, we believe our results provide characterization of manometric abnormalities encountered at the UES within esophageal outflow obstruction cohorts, and lay ground work for further prospective evaluation of these findings.

In summary, we have shown that UES residual pressures can segregate achalasia subtypes and EGJOO from a population with esophageal outflow obstruction on manometry. Observed trends were independent of and more significant than other metrics for esophageal pressurization, but not to the point of establishing a new standard for diagnosis. We anticipate that most likely utility of improved understanding of UES metrics in achalasia will be to further qualify borderline situations, particularly with EGJOO, currently a diagnosis of exclusion on HRM with unclear relationship to recognized achalasia subtypes. Further HRM studies assessing relationships to symptoms and outcome will be necessary to determine if UES metrics are to have any application in this domain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

- Elevated integrated residual pressure (IRP) at the lower esophageal sphincter (LES) on esophageal high resolution manometry (HRM) defines esophageal outflow obstruction, but UES metrics can also be abnormal in these disorders
- Nadir UES residual pressure (UES-RP) is consistently higher in esophageal outflow obstruction disorders compared to normal controls. It is highest in type 2 achalasia, potentially a consequence of esophageal pressurization.
- Characterizing UES abnormalities, particularly nadir UES-RP, can complement esophageal body and LES metrics in segregating achalasia subtypes

Figure 1.

High resolution manometry (HRM) pressure metrics in esophageal outflow obstruction compared to normal controls. While LES end expiratory pressure and IRP were significantly higher in esophageal outflow obstruction compared to normal controls, these two metrics were not discriminative of achalasia subtypes and esophagogastric junction outflow obstruction (EGJOO). Intrabolus pressure was higher in achalasia subtypes 2 and 3, and in EGJOO compared to achalasia subtype 1 and normal controls.

Figure 2.

Spectrum of nadir upper esophageal sphincter residual pressure (UES-RP) across esophageal outflow obstruction subtypes compared to normal controls. UES-RP was consistently high in achalasia subtype 2 compared to achalasia subtypes 1 and 3, and EGJOO; nadir values are negative in normal controls.

Figure 3.

Comparison of mean UES and LES residual pressures (UES-RP vs. IRP) in esophageal outflow obstruction subtypes and normal controls. LES IRP defined esophageal outflow obstruction, but did not segregate subtypes (lack of separation along the y axis). While UES-RP was significantly higher in all achalasia subtypes compared to controls, this metric was most elevated in achalasia type 2 (separation along $\times$ axis).

High-resolution manometry parameters within esophageal outflow obstruction subtypes compared to controls

Table 1

Subtype	Achalasia type 1 (n=15)	Achalasia type 2 (n=122)	Achalasia type 3 (n=42)	EGJOO (n=123)	Controls (n=16)	p-value* across all groups	p-value* across esophageal outflow obstruction spectrum
Age	54.2 ± 4.97	57.2 ± 1.75	59.7 ± 2.35	59.1 ± 1.28	27.7 ± 0.71	<0.0001	0.578
Gender (% female)	60.0%	50.0%	52.4%	65.9%	56.3%	0.147	0.079
UES							
Length (cm)	2.89 ± 0.16	3.03 ± 0.06	2.66 ± 0.09	2.98 ± 0.06	3.10 ± 0.11	0.027	0.019
Mean basal pressure (mmHg)	64.2 ± 12.0	66.7 ± 3.88	55.8 ± 5.44	67.2 ± 3.05	90.3 ± 6.38	0.049	0.39
Residual pressure (mmHg)	2.77 ± 0.88	9.17 ± 0.55	3.68 ± 0.77	1.83 ± 0.46	-5.07 ± 1.39	<0.0001	<0.0001
Relaxation time to nadir (ms)	227 ± 37.8	243 ± 20.5	210 ± 25.0	176 ± 11.9	123 ± 13.8	0.015	0.04
Recovery time (ms)	524 ± 44.6	659 ± 17.8	544 ± 30.3	536 ± 16.8	609 ± 32	<0.0001	<0.0001
Esophageal Body							
Intraboli pressure (mmHg)	15.0 ± 1.76	29.8 ± 0.09	32.0 ± 2.02	24.4 ± 0.80	12.1 ± 0.90	<0.0001	<0.0001
Peak panesophageal pressurization (mmHg)		46.0 ± 1.26					
DCI (mmHg cm s)			4350 ± 619	3090 ± 237	1620 ± 232	<0.001	
Mean wave amplitude (mmHg)			126 ± 11.2	102 ± 4.67	95.6 ± 8.97	<0.0001	
Mean wave duration (s)			4.71 ± 0.19	4.67 ± 0.13	3.69 ± 0.18	<0.001	
Distal latency (s)			4.30 ± 0.14	7.26 ± 0.21	7.93 ± 0.36	<0.0001	
LES							
Length (cm)	3.13 ± 0.18	3.26 ± 0.06	3.26 ± 0.10	3.41 ± 0.06	3.21 ± 0.13	0.343	0.256
Intraabdominal length (cm)	1.47 ± 0.15	1.69 ± 0.05	1.67 ± 0.09	1.70 ± 0.05	1.64 ± 0.14	0.612	0.461
End-expiratory pressure (mmHg)	25.8 ± 3.01	32.8 ± 1.25	33.0 ± 2.35	30.7 ± 1.40	13.2 ± 2.00	<0.0001	0.276
Integrated relaxation pressure (mmHg)	25.9 ± 4.52	27.0 ± 0.70	26.7 ± 1.41	19.7 ± 0.40	6.56 ± 0.99	<0.0001	<0.0001

UES indicates Upper esophageal sphincter; LES Lower esophageal sphincter; EGJOO esophagoesophageal junction outflow obstruction; DCI distal contractile integral.

* Analysis of variance (ANOVA) test employed to derive p-values. In rows without listed p-values, insufficient population numbers were present from which to perform ANOVA tests. On the final column, negative control group excluded to derive p-values. All data listed as mean ± standard error of mean (SEM).

Table 2

Multivariate Analysis of HRM Parameters Between Achalasia Subtypes

	Adjusted Odds Ratio	P-value	95% Confidence Interval
Achalasia 1 vs Achalasia 2			
UES Length	1.07	<i>NS</i>	
UES Residual Pressure	0.67	0.01	0.5–0.91
UES Relaxation Time to Nadir	1.00	<i>NS</i>	
UES Recovery Time	0.99	0.02	0.98–0.999
Intrabolus Pressure	0.69	<0.001	0.56–0.85
LES IRP	1.02	<i>NS</i>	
Achalasia 2 vs Achalasia 3			
UES Length	1.71	<i>NS</i>	
UES Residual Pressure	1.22	<0.0001	1.11–1.34
UES Relaxation Time to Nadir	1.00	<i>NS</i>	
UES Recovery Time	1.00	0.01	1.001–1.01
Intrabolus Pressure	0.95	0.03	0.91–0.99
LES IRP	1.03	<i>NS</i>	
Achalasia 3 vs EGJOO			
UES Length	0.38	0.01	0.19–0.77
UES Residual Pressure	1.11	0.02	1.02–1.22
UES Relaxation Time to Nadir	1.00	<i>NS</i>	
UES Recovery Time	1.00	<i>NS</i>	
Intrabolus Pressure	1.01	<i>NS</i>	
LES IRP	1.16	<0.001	1.07–1.26
Achalasia 2 vs EGJOO			
UES Length	0.69	<i>NS</i>	
UES Residual Pressure	1.31	<0.0001	1.20–1.42
UES Relaxation Time to Nadir	1.00	<i>NS</i>	
UES Recovery Time	1.00	<0.01	1.001–1.01
Intrabolus Pressure	0.99	<i>NS</i>	
LES IRP	1.2	<0.0001	1.12–1.30