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Exaggerated smooth muscle contraction segments on esophageal high-resolution manometry: prevalence and clinical relevance

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Abstract

Background—Two smooth muscle contraction segments (S2, S3) on esophageal high-resolution manometry (HRM) demonstrate varying contraction vigor in symptomatic patients. Significance of isolated exaggerated smooth muscle contraction remains unclear.

Methods—High-resolution manometry studies were reviewed in 272 consecutive patients (56.4 ± 0.8 years, 62% F) and compared to 21 healthy controls (27.6 ± 0.6 years, 52% F), using HRM tools (distal contractile integral, DCI; distal latency, DL; integrated relaxation pressure, IRP), Chicago Classification (CC) and multiple rapid swallows (MRS). Segments were designated merged when the trough between S2 and S3 was ≥ 150 mmHg, and exaggerated S3 when peak S3 amplitude was ≥ 150 mmHg without merging with S2. Presenting symptoms and global symptom severity (on 100 mm visual analog scale) were recorded. Prevalence of merged and exaggerated segments was determined, and characteristics compared to symptomatic patients with normal HRM, and to healthy controls.

Key Results—Merged segments were identified in 5.6%, and exaggerated S3 in another 12.5%, but only 17–50% had a CC diagnosis; one healthy control had merged segments. DCI with wet swallows was similar in cohorts with merged and exaggerated segments ($p = 0.7$), significantly higher than symptomatic patients with normal HRM and healthy controls ($p = 0.003$ for each comparison). Incomplete inhibition and prominent DCI augmentation on MRS ($p = 0.01$), and presenting symptoms (chest pain and dysphagia, $p = 0.04$) characterized exaggerated segments, but not demographics or symptom burden.

Conclusions & Inferences—Merged esophageal smooth muscle segments and exaggerated S3 may represent hypermotility phenomena from abnormal inhibition and/or excitation, and are not uniformly identified by the CC algorithm.

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AUTHOR CONTRIBUTION

MM data collection and analysis, manuscript preparation and review; SD study design, data collection and analysis, manuscript review; LHP data collection, manuscript review; YL data collection, manuscript review; AP data collection and analysis, manuscript review; CPG study concept and design, study supervision, data analysis and interpretation, manuscript preparation and review.

DISCLOSURE

No conflicts of interest exist for any of the authors.

Keywords

distal contraction vigor; exaggerated S3; high-resolution manometry; merged contraction segments

INTRODUCTION

High-resolution manometry (HRM) was first utilized for assessing esophageal motor function in the 1990s.^{1,2} One of the first revelations derived from HRM was that esophageal peristalsis consisted of a chain of relaxing sphincters and contracting segments (Fig. 1A). Firstly, the skeletal muscle segment or S1 contracts, followed by the proximal smooth muscle segment or S2, and finally the distal smooth muscle segment or S3.^{3,4} As many as 90% of asymptomatic controls demonstrate a distinct trough between S2 and S3, which is thought to represent a shift in neurotransmitter influences between the cholinergic dominant S2 and the non-cholinergic inhibitory influences mediated by nitric oxide in S3.^{4,5}

Early HRM evaluations of patients with ‘nutcracker’ esophagus demonstrated a blunting of the trough between S2 and S3 (Figure 1B), leading to exaggerated esophageal body contraction amplitudes.⁴ Imbalance between esophageal excitation and inhibition has been postulated as a potential mechanism for this phenomenon. Further, a variant of this phenomenon, where S3 contraction amplitudes are disproportionately exaggerated compared to S2 (Figure 1C), has also been potentially linked to this phenotype, and can be associated with esophageal perceptible symptoms.⁶ When interpreted using the Chicago Classification (CC),⁷ some of these exaggerated contraction patterns may be averaged out during the analysis process and may not register as abnormal.⁸

In this study, we sought to determine the prevalence and contraction metrics of symptomatic patients with exaggerated esophageal body contraction segments, identified from a consecutive cohort of patients undergoing esophageal HRM. The diagnostic sensitivity of CC for these motor patterns was determined. Esophageal motor metrics were compared to asymptomatic healthy controls and symptomatic patients without merged sequences to determine the clinical significance of exaggerated segmental contraction.

METHODS

All adult patients >18 years of age undergoing esophageal HRM (Given Imaging, Los Angeles, CA, USA) over a 6-month study period in 2012 were eligible for inclusion. Consecutive HRM studies were analyzed, and motor function assessed using CC criteria.⁷ Smooth muscle contraction segments were specifically scrutinized, and studies with exaggerated contraction segments were identified. For this study, exaggerated contraction segments consisted of merged smooth muscle contraction segments, and disproportionately exaggerated S3, as defined below. Comparator groups consisted of symptomatic patients with normal esophageal body motor function, and asymptomatic healthy volunteers who underwent HRM studies as part of institutional normative data collection. The review of HRM and clinical data for this study was approved by the Human Research Protection Office (institutional review board) at Washington University in St. Louis.

Esophageal HRM: data acquisition

All HRM studies were conducted by experienced nurses trained in clinical HRM, using a 36-channel solid state catheter system with circumferential sensors 1 cm apart (Given Imaging). Studies were performed following an overnight fast, after discontinuing medications with potential effects on esophageal motor function (anticholinergic medications, smooth muscle relaxants, metoclopramide) at least 5–7 days prior to the study whenever possible. The HRM catheter was calibrated, and passed transnasally after topical anesthesia to the nasal passages. The study protocol consisted of a 20 s swallow free landmark period, 10 test swallows of 5 mL ambient temperature water spaced at least 20 s apart, and multiple rapid swallows (MRS). Each MRS sequence consisted of 4–5 swallows of 2 mL water boluses <4 s apart. Dedicated software programs (ManoView; Given Imaging) provided data acquisition, display and analysis parameters for standard analysis of motor function using the CC.⁷

Esophageal HRM: analysis

High-resolution manometry studies were evaluated for peristaltic function, esophageal body contraction parameters, lower esophageal sphincter (LES) function, and a clinical diagnosis according to the CC⁷ using the following metrics: integrated relaxation pressure (IRP) to evaluate nadir LES postswallow residual pressure, distal contractile integral (DCI) to determine esophageal body contraction vigor by incorporating collective length, contraction amplitude and duration of the smooth muscle contraction segments, and distal latency (DL) to evaluate the timing and sequencing of smooth muscle contraction.

Studies in both symptomatic patients and normal controls were re-analyzed for extraction of specific motor metrics (described below) by study investigators not involved in clinical interpretation (SD, MM). Smooth muscle contraction segments were deemed *merged* when the trough between S2 and S3 was ≥ 150 mmHg (Figure 1B), assessed using the isobaric contour tool. Peristaltic segments with an *exaggerated S3* were identified when the S3 peak contraction amplitude was ≥ 150 mmHg with a clear trough separating S2 from S3 of <150 mmHg (Figure 1C). Cohorts with any merged segments and exaggerated S3 segments were identified; for inclusion in the study, these cohorts were required to have normal IRP and DL as defined by CC.⁷ A symptomatic cohort with normal esophageal body motor parameters was identified for comparison. In all patient cohorts, patients with prior esophageal or gastric surgery were excluded. Finally, studies in asymptomatic controls were analyzed using the same metrics.

Multiple rapid swallows sequences were analyzed to assess postdeglutitive inhibition and the subsequent contraction response using the DCI metric, using methodology described elsewhere.⁹ Normal responses, characterized by profound inhibition during MRS followed by augmented contraction, were recorded. Aberrant responses, such as when contraction took place during the phase of profound inhibition or when the following contraction phase was either suboptimal or exaggerated, were also noted; esophageal body contraction metrics were quantified using DCI.^{9,10}

Symptom assessment

Esophageal symptoms were assessed using a symptom questionnaire that patients completed upon presentation for HRM studies; this has been validated for use in descriptive reporting of esophageal symptoms,¹¹ and has been utilized in several reports from our institution.^{12,13} Patients rated symptom frequency and severity on five-point Likert scales where 0 designated no symptoms and 4 designated extremely frequent or severe symptoms. The product of symptom frequency and symptom severity constituted the dominant symptom intensity (DSI) score. Global symptom severity (GSS) was assessed on a 100 mm visual analog scale as described elsewhere.⁹

Statistical analysis

Grouped values are reported as mean $\pm$ SEM unless indicated otherwise. Categorical and grouped data were compared using Fisher's exact test, chi-squared test, or two-tailed Student's *t*-test as appropriate. Across-group differences were evaluated with ANOVA. Cohorts with any merged segments and exaggerated S3 segments were identified, and their prevalence assessed. HRM metrics, MRS responses, and symptom burden were compared between the three study cohorts and normal controls. The yield of CC analysis in identifying subjects with merged segments and exaggerated S3 segments was assessed. In each case, $p < 0.05$ was required for statistical significance.

RESULTS

A total of 272 subjects (56.4 ± 0.8 years, 62% female) underwent esophageal HRM during the study period. Within this cohort, 18 subjects (5.6%) had a mean of four merged segments in the 10 swallow complement, and 34 (12.5%) had a mean of four sequences with exaggerated S3. Within the merged segments cohort, 11 subjects also had at least one sequence with exaggerated S3, bringing the overall total of exaggerated S3 to 45 subjects (16.5%). Of the 21 healthy controls (27.6 ± 0.6 years, 52% F), only one subject had merged segments, and none had exaggerated S3. While the healthy control cohort was significantly younger than the patient cohorts, other HRM metrics assessed were similar between the study cohorts (Table 1). Symptom burden was similar between the patient groups.

As required by study inclusion criteria, DL and IRP were normal in all the study groups (Table 1). Mean DCI with wet swallows was significantly higher in the cohorts with merged segments and exaggerated S3 compared to asymptomatic controls and symptomatic patients with normal manometry ($p = 0.003$ for each comparison, Fig. 2). Despite this, only three (17%) of subjects with merged segments (hypercontractile disorder: two, hypertensive peristalsis: one) and 17 (50%) with exaggerated S3 fulfilled CC designation of a hypermotility disorder (hypercontractile disorder: 10, hypertensive peristalsis: 2; rapid peristalsis with normal latency: 5); this accounted for all subjects with hypercontractile disorder and hypertensive peristalsis in the study cohort. Subjects meeting Chicago criteria for a hypermotility disorder had significantly higher mean DCI than subjects without a hypermotility disorder, both in the merged segment cohort and in the exaggerated S3 cohort ($p = 0.003$ for each comparison).

On MRS, the likelihood of incomplete inhibition was highest in the presence of merged segments. The single control subject with merged segments also demonstrated incomplete inhibition during MRS. Both the merged segments and the exaggerated S3 cohorts had significantly higher frequency of incomplete inhibition compared to normal controls ($p < 0.005$ for each comparison, Fig. 3); the merged segments cohort had higher incomplete inhibition proportions compared to symptomatic subjects with normal manometry ($p = 0.01$, Fig. 3). While subjects meeting CC criteria for hypermotility had numerically higher proportions of abnormal inhibition, this was not significantly different from the rest of each cohort, both for merged segments and for exaggerated S3 ($p = 0.3$ for each comparison, Fig. 3).

The contraction phase following MRS was significantly more exaggerated in the merged segment and exaggerated S3 cohorts compared to normal controls and symptomatic patients with normal manometry (Fig. 3). The pattern of post-MRS exaggerated contraction followed the contraction pattern noted with wet swallows, i.e., the merged segment cohort had 50.0% post-MRS sequences with merged segments, and the exaggerated S3 cohort had 70.6% post-MRS sequences with exaggerated S3 (Fig. 4). The single control subject with merged segments also demonstrated augmented post-MRS contraction with persistence of merged segments. Means of the merged segments and exaggerated S3 cohorts were significantly higher than those of normal controls and symptomatic patients with normal manometry ($p < 0.05$ for each comparison, Fig. 5). Subjects meeting CC criteria for hypermotility again demonstrated higher contraction vigor following MRS, but differences were not significant from the remainder of each cohort ($p = 0.1$ for each comparison; Fig. 3).

On symptom assessment, reflux symptoms were more likely in symptomatic patients with normal manometry ($p = 0.04$ compared to other two groups combined, Table 2). In contrast, chest pain and dysphagia were proportionately higher in the cohorts with merged segments and exaggerated S3 compared to symptomatic patients with normal manometry, and differences were statistically significant ($p = 0.04$ across groups, $p = 0.002$ for dysphagia, Table 2). Dominant symptom score and GSS were not different between these cohorts, whether CC diagnoses were fulfilled or not. Dominant symptom intensity scores were not significantly different between cohorts with and without incomplete inhibition during MRS within the merged segments and exaggerated S3 groups (incomplete inhibition: 9.3 ± 0.9 , complete inhibition: 9.7 ± 1.2 , $p = 0.8$); numeric differences in GSS scores similarly did not reach statistical significance (incomplete inhibition: 56.8 ± 0.5 ; complete inhibition: 67.1 ± 0.5 , $p = 0.14$).

DISCUSSION

In this study, we demonstrate that merged smooth muscle contraction segments and disproportionate exaggeration of the third contraction segment are associated with an imbalance of excitatory and inhibitory influences in the esophageal body. These patterns can be encountered when HRM is performed on symptomatic patients, but can also rarely be seen in healthy individuals. While most of these patterns do not fulfill metrics for a CC diagnosis, those that do demonstrate higher contraction metrics, both with wet swallows and with MRS. We conclude that merging of the smooth muscle contraction segments and

disproportionate exaggeration of S3 represent phenomena within the spectrum of hypermotility, and that the CC algorithm identifies the extreme extents of this spectrum, but lesser abnormalities may be lost in the averaging process involved in calculating HRM metrics.

The presence of smooth muscle contraction segments was first identified by Clouse in the 1990s.^{3,4} He noted that similar to the opossum esophagus, the human smooth muscle esophagus is composed of two smooth segments separated by a pressure trough. It is theorized that this pressure trough represents the shift between the cholinergic predominant S2 and the noncholinergic predominant S3.² This theory is supported by evidence that the second esophageal segment demonstrates augmented esophageal contraction in response to the cholinergic effects of cisapride, while the third esophageal segment does not.⁵ Similarly, the second segment demonstrates higher contraction vigor with distal structural obstruction of the distal esophagus, while the third segment augments in spastic states and situations associated with increased esophageal perception.^{6,14}

Changes in the behavior of the smooth muscle contraction segments may help define motor patterns in the esophagus. While there is modest variation in individual smooth muscle contraction vigor between swallows in the same individual,¹⁵ the two smooth muscle contraction segments are generally equivalent in contraction vigor in normal volunteers.^{6,14} With exaggerated smooth muscle contraction, the distal segment (S3) may demonstrate higher contraction vigor compared to the second segment (S2),^{6,14} and the trough between the two segments may be blunted.⁴ This was first studied by Clouse, where he compared the contraction parameters of 10 patients with nut-cracker esophagus to those of normal controls. While over 90% of asymptomatic controls demonstrated a distinct trough between esophageal smooth muscle segments, all 10 patients with nutcracker esophagus demonstrated increased contraction volumes in both smooth muscle contraction segments with a greater relative increase in the contraction volume of the later smooth muscle segment. Our results expand on these early observations, and describe the prevalence of these segmental contraction abnormalities in symptomatic patients undergoing esophageal HRM. We demonstrate that these segmental contraction patterns demonstrate contraction metrics that are very different from healthy controls and symptomatic patients with normal manometry, and are similar, albeit to a lesser degree of contraction vigor, to hypermotility patterns (hypertensive peristalsis, hypercontractile esophagus) identified by CC.

Our findings demonstrate that both merged smooth muscle contraction segments and exaggerated S3 contraction patterns are related to a similar imbalance between contraction and inhibition, as suggested by our MRS findings. These abnormal contraction and inhibition responses were significantly different from that encountered in healthy controls, and in symptomatic patients with normal motility (Fig. 5). There was a significantly higher likelihood of abnormal inhibition, and a profoundly augmented contraction response in subjects with these exaggerated smooth muscle contraction patterns. However, one of our normal subjects demonstrated merged segments, indicating that these patterns can be encountered in asymptomatic individuals. Overall symptom burden was not different between groups, but those with merged segments and exaggerated S3 had higher proportions

of chest pain and dysphagia rather than reflux type symptoms reported by those with normal manometry.

Patients with merged segments and exaggerated S3 segments resemble each other in terms of HRM metrics and symptoms, and are significantly different from normal controls and symptomatic patients with normal manometry. Others have demonstrated using balloon distension studies that perceptive thresholds for sensory perception are lower when esophageal body contraction amplitudes are exaggerated, with a correlation between threshold of pain perception and contraction amplitudes.^{16,17} Therefore, there could be a relationship between the exaggerated segmental contraction abnormalities we studied and perceptive esophageal symptoms, and further study is needed. While the most profound merged segments and exaggerated S3 segments typically register as abnormal by the CC, the more subtle patterns may be lost when averaged using mean DCI, but remain visually evident.

Our study has a few limitations. Our normal cohort was significantly younger than each patient cohort. While the influence of age on esophageal motor function is not fully known, we acknowledge that age matched controls would have been more a more ideal comparison group; however, the strict requirement of asymptomatic healthy individuals on no medications and no comorbid disorders limited the age distribution of the normal controls, who were recruited as part of determining our institutional normative thresholds for esophageal HRM. Our study was not designed to compare symptoms across all motor disorders, to assess treatment response to interventions, or to follow motor function following therapy; we acknowledge that these elements could enhance our understanding of the relevance of these motor patterns. Esophageal motor function was assessed only with HRM and not with superimposed impedance, which could have elucidated concurrent bolus transit with the exaggerated motor patterns. Our study describes minor peristaltic disorders, with the true clinical significance of these findings questioned in the literature. Nevertheless, these motor patterns are encountered in clinical practice, and may provide an explanation for chest pain or dysphagia in the absence of other etiologies. Our study helps characterize these minor peristaltic disorders, which we believe deserve descriptive mention in reporting of motor function, with the understanding that the true clinical relevance of minor peristaltic disorders remains in question.

We conclude that merged smooth muscle contraction segments and exaggerated third contraction segments without merging represent hypermotility phenomena, likely related to abnormal esophageal inhibition, or an imbalance between excitatory and inhibitory influences in the esophageal body. These abnormalities may be seen in asymptomatic individuals, may not uniformly trigger a CC designation, but may be clinically important to characterize. Further prospective study of these segmental contraction abnormalities may help uncover pathophysiologic mechanisms and clinical relationship with symptoms.

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Key Messages

- Isolated exaggerated smooth muscle contractions segments may be part of the spectrum of esophageal hypermotility, and are not often identified by the Chicago Classification algorithm.
- The aim of this study was to characterize prevalence and significance of isolated exaggeration of smooth muscle contraction segments that are intermittently encountered on esophageal high-resolution manometry (HRM).
- Consecutive HRM studies were reviewed; individual swallow sequences were characterized as *merged* or *exaggerated* based on predefined criteria; clinical presentation and prevalence were compared to symptomatic patients without merged symptoms and to normal controls.
- We report low prevalence of both *merged* smooth muscle contraction segments and disproportionately *exaggerated S3* (third segment) on HRM, and that these abnormalities can rarely be seen in healthy individuals.
- When encountered, these abnormalities are associated with abnormal esophageal inhibition and exaggerated contraction metrics on esophageal provocative testing, similar to hypermotility disorders identified by the Chicago Classification.

Figure 1.

Esophageal body contraction segments on high-resolution manometry. (A) A normal esophageal body contraction sequence demonstrating three sequential contraction segments (S1, S2, and S3) separated by distinct troughs. (B) Disproportionate distal shift in contraction vigor in segment 3 (S3). (C) Merged smooth muscle contraction segments (S2 and S3) with no discernible trough between the two segments.

Figure 2.

Comparison of distal contractile integral (DCI) between study cohorts and healthy controls. Mean DCI was significantly higher in the merged segments and exaggerated S3 cohorts compared to healthy controls and symptomatic subjects with normal manometry (* $p < 0.003$ for each comparison). Within the merged segments and exaggerated S3 cohorts, proportions fulfilling Chicago Classification (CC) criteria for a hypermotility disorder (hypertensive peristalsis, hypercontractile disorder) had significantly higher DCI compared to proportions that had a normal CC designation (** $p < 0.003$ for each comparison).

Figure 3.

Multiple rapid swallow (MRS) responses in the study cohorts and healthy controls. Cohorts with merged segments and exaggerated S3 had significantly higher proportions of abnormal esophageal body inhibition during the swallow phase of MRS compared to healthy controls (* $p < 0.005$ for each comparison); symptomatic subjects with normal manometry resembled healthy controls ($p = 0.07$). Contraction following MRS was exaggerated more often in the same two cohorts compared to healthy controls and symptomatic patients with normal manometry ($p < 0.005$). Patterns of MRS contraction resembled smooth muscle contraction patterns following wet swallows, i.e., the merged segment cohort had predominantly merged segments following MRS, and the exaggerated S3 cohort had predominantly exaggerated S3 following MRS.

Figure 4.

Responses to multiple rapid swallows. (A) Normal response with complete inhibition during swallows and augmented contraction following MRS. (B) Abnormal inhibition and exaggerated, merged contraction with MRS in a patient with merged segments on test swallows. (C) Normal inhibition and exaggerated S3 contraction with MRS in a patient with exaggerated S3 on test swallows.

Figure 5.

Distal contractile integral (DCI) response to multiple rapid swallows (MRS). Cohorts with merged segments and exaggerated S3 demonstrate similar patterns of exaggerated contractile response compared to healthy controls and symptomatic subjects with normal manometry (* $p < 0.05$ for each comparison). Within the merged segments and exaggerated S3 cohorts, there was no difference in DCI response to MRS between proportions fulfilling Chicago Classification (CC) criteria for a hypermotility disorder (**hypertensive peristalsis, hypercontractile disorder) and those with a normal CC designation ($p = 0.1$).

Table 1

Baseline demographic and clinical characteristics

	Healthy controls (<i>n</i> = 21)	Merged segments (<i>n</i> = 18)	Exaggerated S3 (<i>n</i> = 34)	Normal manometry (<i>n</i> = 37)
Age	27.6 ± 0.6 [*]	51.7 ± 2.8	57.6 ± 2.2	54.4 ± 2.7
Gender	52%	61%	62%	70%
Symptom burden				
DSI		8.2 ± 1.2	10.1 ± 0.9	10.1 ± 0.8
GSS		50.2 ± 6.9	66.7 ± 3.5	64.6 ± 3.9
HRM metrics				
DCI (mmHg.cm.s)	1618.6 ± 265	4017.2 ± 784 [†]	4541.4 ± 656 [†]	1123.1 ± 97
DL (s)	8.5 ± 0.4	6.6 ± 0.2	6.9 ± 0.3	7.0 ± 0.2
IRP (mmHg)	7.1 ± 0.9	5.2 ± 0.8	7.3 ± 0.9	3.7 ± 0.4

DSI, dominant symptom intensity; GSS, global symptom severity; HRM, high-resolution manometry; DCI, distal contractile integral; DL, distal latency; IRP, integrated relaxation pressure.

^{*} *p* < 0.001 for each comparison with the other study groups.

[†] *p* = 0.003 for each comparison with healthy controls and symptomatic patients with normal manometry.

Table 2

Comparison of dominant symptoms across study groups

	Merged segments (<i>n</i> = 18)	Exaggerated S3 (<i>n</i> = 34)	Normal manometry (<i>n</i> = 37)
Heartburn	6 (33%)	10 (29%) [†]	19 (51%)
Regurgitation	4 (22%)	5 (15%)	6 (16%)
Chest pain	4 (22%) [*]	3 (9%)	1 (3%)
Dysphagia	4 (22%)	15 (44%) [*]	8 (22%)
Other	0	1 (3%)	3 (8%)

Proportions were significantly different between normal manometry and the other two groups combined within heartburn ($p = 0.04$) and dysphagia ($p = 0.002$). $p = 0.04$ across groups.

^{*} $p = 0.04$ compared to normal manometry.

[†] $p = 0.05$ compared to normal manometry.