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Ineffective esophageal motility phenotypes following fundoplication in gastroesophageal reflux disease

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Abstract

Background—Ineffective esophageal motility (IEM) is associated with reflux disease, but its natural history is unclear. We evaluated patients undergoing repeat esophageal high resolution manometry (HRM) for symptomatic presentations after antireflux surgery (ARS) to understand the progression of IEM.

Methods—Patients with repeat HRM after ARS were included. Ineffective esophageal motility was diagnosed if 5 sequences had distal contractile integral (DCI) <450 mmHg cm s. Augmentation of DCI following multiple rapid swallows (MRS) was assessed. The esophagogastric junction (EGJ) was interrogated using the EGJ contractile integral (EGJ-CI). Esophageal motor function was compared between patients with and without IEM.

Key Results—Sixty-eight patients (53.9 ± 1.8 years, 66.2% female) had pre- and post-ARS HRM studies 2.1 ± 0.19 years apart. Esophagogastric junction-CI augmented by a mean of 26.3% following ARS. Four IEM phenotypes were identified: 14.7% had persistent IEM, 8.8% resolved IEM after ARS, 19.1% developed new IEM, and 57.4% had no IEM at any point. Patients with IEM had a lower DCI pre- and post-ARS, lower pre-ARS EGJ CI, and lower pre-ARS-integrated relaxation pressure ($p = 0.02$ for all comparisons); presenting symptoms and other EGJ metrics were similar ($p = 0.08$ for all comparisons). The IEM phenotypes could be predicted by MRS DCI response patterns ($p = 0.008$ across groups); patients with persistent IEM had the least DCI augmentation ($p = 0.007$ compared to no IEM), while those who resolved IEM had DCI augmentation comparable to no IEM ($p = 0.08$).

Conclusions & Inferences—Distinct phenotypes of IEM exist among symptomatic reflux patients following ARS. Provocative testing with MRS may help identify these phenotypes pre-ARS.

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CONFLICTS OF INTEREST

No conflicts of interest exist.

AUTHOR CONTRIBUTION

MM study design, data collection and analysis, manuscript preparation, and review; AS, YK data collection and analysis, critical review of manuscript; AP data analysis, critical review of manuscript; CPG study concept and design, data analysis, manuscript preparation, critical review, and final approval of manuscript.

Keywords

gastroesophageal reflux disease; high resolution manometry; ineffective esophageal motility; multiple rapid swallows

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic condition where gastric content refluxes into the esophagus through mechanisms predominantly involving dysfunction of the lower esophageal sphincter (LES), typically resulting in heartburn and regurgitation.¹ In the majority of patients, proton pump inhibitors (PPIs) are highly effective in controlling GERD symptoms and healing reflux-induced damage.² Antireflux surgery (ARS) similarly provides for resolution of reflux, representing a viable treatment option for well-characterized reflux with structural disruption at the esophagogastric junction (EGJ), or as an alternative option for patients averse to taking long-term acid-suppressive medications.

Although upper endoscopy and barium esophagram evaluate esophageal mucosa and anatomic EGJ relationships, respectively, high resolution esophageal manometry (HRM) evaluates peristaltic function, and identifies conditions that would contraindicate or modify planned ARS.^{3,4} Esophageal motor dysfunction has been well characterized in GERD, particularly at the LES, but also in the esophageal body, where breaks or fragmentation in the peristaltic contour and weak peristaltic vigor have been reported.^{5,6} Persisting symptoms following ARS may on occasion be related to ineffective esophageal motility (IEM)⁷ and abnormal distal esophageal bolus transit, especially when esophageal smooth muscle does not have the peristaltic reserve needed to overcome the obstructive effect of the fundoplication.⁸

While GERD can be associated with IEM, the effect of ARS in modulating IEM is unknown. Further, little is known about the value of repeat HRM in evaluating symptomatic patients following ARS. This study examines motor findings on repeat HRM in symptomatic post-ARS patients, and attempts to characterize IEM in the setting of ARS. Further, the study examines the value of conventional and novel HRM software tools in evaluating symptomatic presentations following ARS.

METHODS

All adult patients >18 years of age undergoing repeat esophageal HRM (Given Imaging, Duluth, GA, USA) following ARS at the motility laboratory at Washington University in St. Louis over a 7-year study period from January 1, 2007 to December 31, 2014 were eligible for inclusion. All HRM studies conducted over this time period were screened to identify patients undergoing 2 studies. The electronic medical records of these patients were reviewed to determine which patients with multiple HRM studies underwent ARS (Nissen, Toupet or Dor fundoplication) for GERD in between the tests. Patients with major motor disorders including achalasia, esophageal outflow obstruction, or scleroderma esophagus on preoperative HRM were excluded. Demographic data was abstracted from the institution's electronic medical records by a study investigator (MM) not involved in the clinical care of

these patients. Data collected included age, gender, presenting symptoms, descriptive hiatus hernia subtype at ARS, and type of ARS performed. This study protocol was approved by the Human Research Protection Office (institutional review board) at Washington University in St. Louis.

All HRM studies were performed by experienced nurses trained in clinical HRM, using a 36-channel solid state catheter system with circumferential sensors spaced 1 cm apart (Given Imaging). Patients arrived for HRM after an overnight fast, and withheld medications that could affect esophageal motor function, including anticholinergics, smooth muscle relaxants, and metoclopramide, for at least 5–7 days before HRM when 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 period, followed by 10 test swallows of 5 mL ambient temperature water spaced at least 20 s apart. One set of multiple rapid swallows (MRS) consisting of five 2 mL swallows in rapid succession <4 s apart were administered in most of the HRM studies using techniques described elsewhere⁸; when two sets were available, the better of the two MRS sequences was analyzed. Data acquisition was performed using dedicated software programs (ManoView; Given Imaging), and included a thermal compensation period immediately following catheter extubation.

Pre- and postoperative HRM studies were reviewed by one of the study investigators (MM) not involved in clinical management of the patients. Studies were evaluated for peristaltic function and esophageal body contraction using distal contractile integral (DCI) and distal latency.⁷ Ineffective esophageal motility was defined according to the Chicago Classification as ≤ 5 sequences in a 10 swallow sequence with DCI <450 mmHg s cm.⁷ Basal LES tone was assessed using conventional metrics (end expiratory LES pressure), and a novel EGJ metric, the EGJ-CI, calculated during the landmark phase to assess EGJ barrier function using methodology described elsewhere.⁹ The DCI metric was forced into a measurement box straddling the EGJ, and covering three consecutive respirations; when hiatus hernia size was ≥ 3 cm, only the EGJ was included in the EGJ-CI calculation. The measured value was then divided by duration of the three respirations in seconds to determine the EGJCI in mmHg cm.⁹ Lower esophageal sphincter relaxation was assessed using the integrated relaxation pressure (IRP).⁷ Distal contractile integral of post-MRS contraction sequences was measured, and compared to averaged DCI from wet swallows; the difference was calculated as a measure of post-MRS augmentation of smooth muscle contraction vigor.⁸

Grouped values are reported as mean $\pm$ SEM or median (interquartile range) as appropriate. Categorical and continuous data were compared using Fisher's exact test, chi-squared test, or by two-tailed Student's *t*-test; non-parametric data were compared using the Mann–Whitney *U*-test. Across-group differences were evaluated with ANOVA. Esophageal body metrics were compared between those with adequate esophageal peristalsis pre- and postoperatively to those with IEM that developed, persisted or resolved following ARS. Patients were also compared based on symptom of dysphagia or heartburn as a reason for postoperative HRM, as assessed by questionnaire prior to HRM. In all instances, $p < 0.05$ was required for statistical significance.

RESULTS

Within the 7-year study period, 68 patients (53.9 ± 1.8 years, 66.2% female) met inclusion criteria. Initial preoperative HRM was performed 0.3 ± 0.05 years before ARS, and follow-up HRM 1.8 ± 0.18 years following ARS. Most of the patients underwent a complete Nissen fundoplication (88.2%), while Toupet (10.3%) and Dor (1.5%) funduplications were performed in the remainder; there was adequate documentation of reflux or symptomatic hiatus hernia in all instances. Structural disruption at the EGJ was reported during ARS in 54 patients (38 axial hiatus hernia, 9 paraesophageal hernia, 5 combined axial and paraesophageal hernia, 2 with other intra-abdominal organs proximal to the diaphragmatic hiatus), 12 patients had no hiatus hernias, whereas the operative findings were inconclusive in 2 patients. Indications for HRM following ARS included suspicion of fundoplication failure with recurrent reflux symptoms (29 patients, 42.6%), transit symptoms following ARS (27 patients, 39.7%); an additional 12 patients (17.6%) had both reflux symptoms and transit symptoms.

High resolution manometry studies were repeated after a mean interval of 2.1 ± 0.19 years (range 0.1–6.4 years, median 1.2 years). Ineffective esophageal motility was noted on pre-ARS HRM in 16 patients (23.5%), and 23 patients (33.8%) had IEM on post-ARS HRM. For the entire cohort, proportions of effective sequences (7.1 ± 0.4 vs 6.1 ± 0.5), and mean DCI (1529.9 ± 163.8 mmHg cm s vs 1588.6 ± 190.1 mmHg cm s) did not significantly change between pre-ARS and post-ARS HRM studies, respectively. In contrast, EGJ-CI augmented by a mean of 26.3% overall, and post-ARS EGJ-CI was higher following Nissen fundoplication compared to partial fundoplication (48.0 ± 4 vs 23.9 ± 6 , $p = 0.03$). Integrated relaxation pressure augmented by a mean of 81.5% following ARS. Compared to recently reported normal ranges following ARS,¹⁰ 33 of 60 Nissen patients and 4 of 7 Toupet patients had lower IRP, but none had higher IRP. As many as 42.6% of the cohort had evidence of IEM at some point during either pre-ARS or post-ARS manometry. When compared to the 39 patients without IEM, those with IEM at any point were older, with a lower DCI both preoperatively and on follow-up, lower preoperative EGJ-CI and lower preoperative IRP (Table 1).

Four phenotypes of IEM were noted on further analysis of HRM data: 10 patients (14.7%) had persistent IEM (IEM on both pre- and post-ARS HRM), 6 (8.8%) had resolution of IEM (IEM on pre-ARS HRM but not post-ARS HRM), 13 (19.1%) developed new IEM (no IEM on pre-ARS HRM, IEM on post-ARS HRM), whereas the remainder 39 patients (57.4%) had no IEM on either pre- or post-ARS HRM. Patients who had persistent or new IEM were older compared to those who resolved IEM or never had IEM (Table 2). The change in mean DCI between pre-ARS and post-ARS HRM defined these four phenotypes (Fig. 1). The cohort that developed IEM had significantly lower change in mean DCI compared to the three remainder cohorts ($p = 0.002$ for each comparison, Fig. 1), while the cohort that recovered their IEM was different from those that developed IEM and had persistent IEM ($p = 0.011$) but not significantly different from the cohort with no IEM ($p = 0.8$). Despite the differences in DCI, mean change in EGJ-CI was similar across the four phenotypes ($p = 0.7$ for each comparison).

The IEM phenotypes could be predicted by MRS augmentation patterns of esophageal body contraction on pre-ARS HRM, available for analysis in 41 patients (Fig. 2). All IEM cohorts demonstrated significantly lower augmentation of pre-ARS DCI following MRS compared to the group with no IEM at any point ($p = 0.008$ across groups). Compared to DCI from routine wet swallows, median MRS DCI augmentation in the cohort without IEM was 1012.5 mmHg cm s, an increase of 59.2%; in contrast, median augmentation of 34.7 mmHg cm s (9.3% increase) was seen in the cohort with persistent IEM ($p = 0.007$ compared to no IEM cohort). Median augmentation was 253.8 mmHg cm s (31.7% increase) in those that developed IEM ($p = 0.03$ compared to no IEM). The cohort that resolved IEM following ARS had median augmentation of 347.3 mmHg cm s (93.3%), which was not significantly different from those with no IEM (Fig. 2, $p = 0.08$). Likelihood of a normal MRS response was highest in patients with no IEM or resolved IEM compared to those with persisting IEM or those that developed IEM ($p = 0.02$ across groups, Fig. 2). Change in DCI following MRS was no different between pre-ARS and post-ARS HRM studies when MRS was available in both instances ($p = 0.5$).

Symptom presentations were analyzed in the context of these phenotypes in the study cohorts. Presentations with transit symptoms (dysphagia) had higher postoperative EGJ-CI (51.3 ± 5 mmHg cm compared to 37 ± 5.3 mmHg cm with no dysphagia, $p = 0.06$) and higher IRP (10.3 ± 1.4 mmHg vs 7.0 ± 1.1 mmHg, respectively, $p = 0.09$), but the differences did not make statistical significance; presentations with reflux symptoms did not demonstrate differences in motor metrics or the likelihood of IEM. However, patients who developed IEM trended toward a higher likelihood of reflux symptoms (76.9%) compared to other groups ($p = 0.1$); dysphagia did not segregate the groups.

DISCUSSION

In this study evaluating HRM motor patterns before and after ARS in symptomatic individuals, we demonstrate that distinct cohorts exist that manifest differing motor characteristics following fundoplication. In patients with IEM in the setting of ongoing symptoms following ARS, three distinct IEM patterns were identified, persisting IEM, new IEM, and resolution of IEM on follow-up. These patterns could be predicted on provocative testing with MRS prior to fundoplication, in that the degree of augmentation of post-MRS smooth muscle contraction varied significantly within the groups with IEM, and in comparison to patients without IEM. While symptoms could not be predicted precisely, there was a trend toward higher reflux symptoms in the cohort that developed IEM on follow-up. Based on these results, we demonstrate further value to assessment of peristaltic reserve with provocative testing during HRM in patients with reflux symptoms.

Pressure topography and HRM have contributed greatly to our understanding of esophageal physiology and peristalsis. Prior to HRM, esophageal body hypomotility was defined by contraction amplitude, with IEM defined as the presence of $\geq 30\%$ of liquid swallows with a contraction amplitude of <30 mmHg in the distal esophagus.¹¹ While these values were chosen given their association with ineffective bolus transit on radiologic or scintigraphic imaging, the criteria shifted following the development of impedance catheters. Through impedance, it was shown that patients with $\geq 50\%$ ineffective liquid swallows were more

likely to have ineffective bolus transit, with a higher prevalence of heartburn (25.7% compared to 10.2% with normal bolus transit, $p = 0.03$) and a trend toward a higher prevalence of dysphagia (24.8% vs 12.3%, respectively, $p = 0.08$).¹² These IEM metrics have now been validated with criteria based on modern assessment of esophageal body contraction vigor using DCI, establishing that a DCI of <450 mmHg cm s correlates with conventional manometry metrics for ineffective peristalsis.¹³ Using this threshold, 50% ineffective sequences makes a diagnosis of IEM in a 10 test swallow protocol,⁷ and this definition was used throughout this study.

While not specific for GERD, hypomotility is the most commonly described esophageal body motor disorder in GERD, involving 21–49% patients, with peristaltic dysfunction correlating with greater evidence of end organ damage from acid reflux, mainly in the form of erosive esophagitis and Barrett's esophagus.^{14,15} The likelihood of IEM is higher as populations age, and indeed, our IEM subjects were significantly older than their non-IEM cohorts.¹⁶ While Savarino *et al.* found that the prevalence of IEM was higher in patients with erosive esophagitis or Barrett's esophagus in comparison to those with non-erosive reflux disease and functional heartburn ($p < 0.01$),¹⁷ studies by Simren *et al.*¹⁸ and Fornari *et al.*¹⁹ determined that only severe IEM characterized by 90% ineffective swallows was associated with prolonged acid clearance and acid exposure time, potentially linking severe IEM with erosive disease and Barrett's esophagus. While the higher association of IEM with end organ damage in GERD appears to be sound, impact of reflux management on IEM is less well understood. There is evidence suggesting that esophageal body contraction amplitudes improve following ARS,²⁰ but then again, distal esophageal obstruction (as can be created by ARS) also can improve esophageal body contraction, particularly in the S2 segment.²¹ Others have suggested that the frequency of ineffective contractions and esophageal body contraction amplitude do not improve with healing of erosive esophagitis using medical therapy with PPIs.²²

In this study, using a cohort of GERD patients who underwent repeat HRM after ARS, we demonstrate that distinct phenotypes of IEM exist among GERD patients. While some resolved their IEM following ARS, others developed IEM and yet others had persistent IEM. Prior work suggests that the S2 segment is most frequently weak or absent in GERD-associated dysmotility,⁶ and this can contribute to delayed onset of smooth muscle contraction, the so called 'proximal latency' of smooth muscle contraction in the esophagus.⁵ Smooth muscle contraction, including second segment contraction may augment following provocative testing with MRS or solid bolus challenge^{23,24} – the likelihood of late postoperative dysphagia is significantly higher in individuals that do not augment smooth muscle contraction and do not have 'peristaltic reserve' on provocative testing.^{8,23} It is known that patients with smooth muscle fibrosis in the setting of connective tissue diseases may have worsening of esophageal body peristalsis; these cohorts generally have higher proportions of IEM and esophageal hypomotility compared to GERD patients being evaluated for ARS.²⁵ Our findings suggest that IEM may persist, or indeed develop in some individuals despite management of GERD; however, the precise pathophysiology of persisting or new IEM is unknown and needs further study.

In addition to the use of DCI in designating IEM, we used a novel metric to evaluate the EGJ barrier, the EGJ-CI.^{9,26} This is a DCI-like measurement that takes length and pressure within the EGJ into consideration, measured independent of time by dividing the recorded metric with the duration of respiration. This metric has been demonstrated to correlate with conventional EGJ metrics such as the LES end expiratory pressure. In this study, the EGJ-CI augmented following ARS, to a higher degree following circumferential Nissen fundoplication in contrast to partial Toupet and Dor fundoplications. The EGJ-CI is a promising new metric for assessment of the EGJ barrier, and further evaluation is warranted in prospective studies.

Our study has important limitations. As repeat HRM is unusual in asymptomatic patients doing well following ARS, we are limited to patients with symptomatic presentations. As ours is a tertiary referral center, these presentations may not be completely representative of overall symptomatic presentations following ARS. Additionally, many patients in our study had postoperative IRP values lower than the recently reported normative ranges, perhaps suggesting that fundoplication failure could have influenced results. Further, depending on who the symptomatic patient presented to, the order of investigations may not have consistently included HRM, introducing the possibility of referral bias. Another limitation is the relatively small number of patients in each subcategory of IEM (persistent, developed, resolved) in comparison to the group of patients without IEM during the study period. Not all patients had MRS studies, as part of the study predated the use of MRS in our institution. There were some patients with a single MRS sequence which may not always be representative, but the reproducibility of a well performed MRS sequence is high, around 77% in our experience.²⁷ Nevertheless, this represents one of the larger cohorts of post-ARS subjects with follow-up HRM, and we have made efforts to use uniform HRM study protocols and interpretation metrics to optimize the dataset. We believe our findings have clinical relevance in understanding IEM in GERD patients, and introduce important concepts for further study in this field. However, we recognize our retrospective and non-consecutive evaluation as a significant limitation, and prospective study of preoperative HRM with provocative testing is needed to truly understand the impact of IEM on surgical management of GERD.

In conclusion, we report the existence of distinct IEM phenotypes within the GERD spectrum, with the possibility of new development, persistence or recovery of IEM over time in the post-ARS setting. Assessment of esophageal smooth muscle peristaltic reserve prior to ARS may help identify these phenotypes. Further prospective study is needed to determine if understanding IEM in general, and the IEM phenotypes in particular, can contribute to optimal management of GERD patients, particularly in planning ARS.

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Key Messages

- Distinct phenotypes of ineffective esophageal motility (IEM) can be recognized on follow-up high resolution manometry in symptomatic reflux patients followed up after antireflux surgery (ARS).
- These phenotypes include patients with no IEM, persisting IEM, new IEM on follow-up, and resolved IEM.
- IEM phenotypes can be predicted by responses to provocative testing at the initial preoperative HRM study.

Figure 1.

Ineffective esophageal motility (IEM) phenotypes as defined by change in DCI between pre- and postantireflux surgery (ARS) high resolution manometry studies. While 14.7% had persistent IEM, 8.8% resolved IEM and 19.1% developed new IEM following ARS. The cohort that developed IEM had significantly lower median DCI change compared the other three groups ($p = 0.002$ for each comparison). The cohort that resolved IEM had values similar to those with no IEM ($p = 0.8$), but significantly different from those that developed or had persistent IEM ($p = 0.011$ for each comparison). Median esophagogastric junction contractile integral (EGJ-CI) change following antireflux surgery was similar in all four cohorts.

Figure 2.

Multiple rapid swallow (MRS) responses in the four IEM phenotypes. The cohorts that had persistent IEM or developed IEM had significantly lower DCI augmentation following MRS compared to those with no IEM ($p = 0.03$ for each comparison), while the cohort that resolved IEM was not significantly different from those with no IEM ($p = 0.08$). Likelihood of a normal MRS response was highest in those who resolved IEM or had no IEM ($p = 0.02$ across groups).

Table 1

Baseline characteristics of patients

	Any IEM (<i>n</i> = 29)	No IEM (<i>n</i> = 39)
Age (year) at first HRM*	58.8 ± 2.6	50.2 ± 2.4
Sex (F)	19 (66%)	26 (67%)
Preoperative metrics		
DCI*	748 ± 140	2111 ± 226
% effective swallows*	4.1 ± 0.7	9.2 ± 0.2
EGJ-CI*	26.7 ± 3.9	42.6 ± 5.0
LES basal pressure	10.0 ± 1.5	13.8 ± 1.7
IRP	3.6 ± 0.6	5.8 ± 0.8
Postoperative metrics		
DCI*	486 ± 52	2408 ± 261
% ineffective swallows*	2.5 ± 0.5	8.8 ± 0.3
EGJ-CI	38.6 ± 5.5	50.1 ± 4.9
LES basal pressure*	10.5 ± 1.6	16.2 ± 1.8
IRP	8.0 ± 1.4	9.6 ± 1.3

* *p* = 0.04 between patients with and without IEM.

IEM, ineffective esophageal motility; HRM, high resolution manometry; DCI, distal contractile integral; EGJ-CI, esophagogastric junction contractile integral; LES, lower esophageal sphincter; IRP, integrated relaxation pressure.

Table 2

Characteristics of patients with IEM

	Persistent IEM (n = 10)	Developed IEM (n = 13)	Resolved IEM (n = 6)	ANOVA, <i>p</i>-values
Age (year) at first HRM	63.7 ± 4.0	58.4 ± 3.7	51.5 ± 6.6	0.243
Sex (F)	6 (60%)	13 (100%)	5 (83%)	0.586
Pre-operative metrics				
DCI	652 ± 279	1011 ± 209	339 ± 37	0.176
% effective swallows	1.4 ± 0.4	7.5 ± 0.6	1.3 ± 0.4	<0.001
EGJ CI	30.0 ± 5.3	26.1 ± 7.2	22.4 ± 6.4	0.784
LES basal pressure	15.3 ± 2.0	7.2 ± 2.4	7.4 ± 2.0	0.031
IRP	5.4 ± 1.0	2.6 ± 0.8	2.7 ± 1.3	0.085
Post-operative metrics				
DCI	370 ± 81	477 ± 84	700 ± 59	0.072
% effective swallows	1.3 ± 0.6	1.6 ± 0.4	6.2 ± 0.8	<0.001
EGJ CI	45.6 ± 9.2	35.6 ± 9.6	33.6 ± 8.3	0.669
LES basal pressure	14.0 ± 2.8	7.9 ± 2.2	10.4 ± 4.1	0.260
IRP	10.0 ± 3.1	6.5 ± 1.9	8.0 ± 1.1	0.554

IEM, ineffective esophageal motility; HRM, high resolution manometry; DCI, distal contractile integral; EGJ-CI, esophagogastric junction contractile integral; LES, lower esophageal sphincter; IRP, integrated relaxation pressure.