Impaired motility in Barrett's esophagus: a study using high-resolution manometry with physiologic challenge

Short Title: Impaired motility in Barrett's esophagus

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Key Points

- Esophageal dysmotility is implicated in the pathogenesis of Barrett's esophagus, but has not been studied following solids and rapid drink challenge, which more accurately replicate normal swallowing behaviour.
- Significant motility impairments were demonstrated in Barrett's; whereas in endoscopy-negative reflux, motility was similar to the normal patterns seen in functional heartburn. This was only demonstrable through use of the adjunctive HRM tests.
- These findings advance our understanding of Barrett's pathogenesis and reiterate the value of performing such adjunctive tests during HRM.

Abstract

Background

Esophageal dysmotility may predispose to Barrett's esophagus (BE). We hypothesized that high-resolution manometry (HRM) performed with additional physiologic challenge would better delineate dysmotility in BE.

Methods

Included patients had typical reflux symptoms and underwent endoscopy, HRM with single water swallows and adjunctive testing with solids and rapid drink challenge (RDC) before ambulatory pH-impedance monitoring. BE and endoscopy-negative reflux disease (ENRD) subjects were compared against functional heartburn patient-controls (FHC). Primary outcome was incidence of HRM contractile abnormalities with standard and adjunctive swallows. Secondary outcomes included clearance measures and symptom association on pH-impedance.

Results

78 patients (BE 25, ENRD 27, FHC 26) were included. Water swallow contractility was reduced in both BE (median DCI 87mmHg.cm.s) and ENRD (442mmHg.cm.s) compared to FHC (602mmHg.cm.s; $P<0.001$ and 0.04 respectively). With the challenge of solid swallows and RDC, these parameters improved in ENRD (solids=1732mmHg.cm.s), becoming similar to FHC (1242mmHg.cm.s; $P=0.93$); whereas abnormalities persisted in BE

(818mmHg.cm.s; *P*<0.01 c.f. FHC). In BE and ENRD reflux events (67 vs. 57 events/24h) and symptom frequency were similar; yet symptom correlation was significantly better in ENRD compared to BE, which was comparable to FHC (symptom index 30% vs. 4% vs. 0% respectively). Furthermore, bolus clearance and exposure times were more pronounced in BE (*P*<0.01).

Conclusions

Reduced contractile effectiveness persisted in BE with the more representative esophageal challenge of swallowing solids and free drinking; whilst in ENRD and FHC peristalsis usually improved, demonstrating peristaltic reserve. Furthermore, symptom-association and refluxate clearance were reduced in BE. These factors may underlie BE pathogenesis.

Keywords

High-resolution manometry; Barrett's esophagus; dysmotility; peristaltic reserve; gastro-esophageal reflux disease

Introduction

Gastro-esophageal reflux disease (GERD) is characterized by a number of potential phenotypes; endoscopy-negative reflux disease (ENRD; also known as non-erosive reflux disease), erosive esophagitis and Barrett's esophagus (BE). BE is considered the most concerning of these GERD manifestations due to its status as a precursor to esophageal adenocarcinoma. Therefore it is useful to understand how the same insult, gastro-esophageal reflux, leads to such divergent manifestations; yet, a number of paradoxes remain. Firstly, esophageal acid exposure is not necessarily greater in BE compared to erosive esophagitis and ENRD;[1] therefore, at the least, other contributory factors must be present. Second, there is a poor correlation between reflux symptoms and endoscopic findings.[2] The majority of patients with persistent reflux symptoms who present to endoscopy have no endoscopic abnormalities whilst those with BE often have a relatively reduced symptom burden.[3] Furthermore, symptomatic response to acid suppression is also reduced in ENRD compared to erosive esophagitis and BE.[4]

Regarding the former, it has become apparent that clearance of refluxate probably plays a role.[5] Esophageal dysmotility has long been associated with reflux disease, but it has also been demonstrated that the incidence of esophageal motility abnormalities and impaired bolus transport increases in parallel with worsening severity of GERD manifestations (from ENRD to erosive esophagitis and BE).[5, 6] What remains uncertain is why across the different GERD phenotypes some patients develop problems with peristalsis while others do not. Nor is it clear if the disease profile leads to poor motility and clearance or if the dysmotility and reduced bolus clearance itself results in increased mucosal exposure to refluxate toxins and damage.

Most of the data demonstrating an association between reflux and esophageal dysmotility has been collected using conventional manometry systems. This technology has been shown to have reduced reproducibility and specificity for defining disease, often with ambiguous diagnostic criteria and wide intra- and inter-observer variability.[7] Yet despite the advent of esophageal high-resolution manometry (HRM) with its improved spatiotemporal representation of esophageal function, the majority of publications report function based on single water swallows while in the supine position. Using this methodology, studies have proposed that routine esophageal HRM cannot be used to differentiate GERD patients from healthy subjects;[8] however there is doubt as to whether this form of testing can act as a surrogate for normal eating and drinking behavior. The inclusion of solid swallows and free drinking while in the more physiological upright seated position using advanced HRM systems has been shown to be reproducible and accurate at detecting pathology.[9-13] Although the inclusion of solid swallows has provided insight into how erosive esophagitis can be differentiated from ENRD and health in terms of function,[14] to date no studies have assessed how this methodology can be used to define how BE compares to other reflux phenotypes in conjunction with ambulatory pH-impedance monitoring clearance parameters.

To help answer some of these paradoxes, we aimed to use HRM with adjunctive testing (solids and free drinking) followed by ambulatory pH-impedance monitoring to define esophageal motility within patients with BE and ENRD. Subjects with functional heartburn were used as patient-controls to allow for an informative analysis of symptom patterns in the study groups. We hypothesized that the use of the adjunctive physiologic testing during HRM would better delineate esophageal motility between the GERD phenotypes.

Methods

Patients

Patients presenting with at least one typical GERD symptom (heartburn or acid regurgitation) for at least 3 months who underwent reflux assessment by gastroscopy, HRM with solids and free drinking and completed 24h ambulatory combined esophageal pH and impedance testing were included; with BE subjects recruited between April 2014 and May 2016 and ENRD and FH subjects recruited between December 2015 and May 2016. Presence of dysphagia as the primary symptom was an exclusion criterion. Other exclusion criteria included: patients with a major esophageal motor disorder based on the Chicago classification (e.g. achalasia, Jackhammer esophagus, spasm), presence of any systemic disorder affecting esophageal motility (e.g. scleroderma, other connective tissue diseases, myopathy), presence of non-reflux related esophagitis (e.g. infectious, pill-induced, eosinophilic esophagitis), esophago-gastric surgery or chronic opiate use.

Study Design

This was a prospective observational study whereby patients with typical symptoms of reflux were divided into subgroups according to results of both gastroscopy and ambulatory pH-impedance monitoring. Gastroscopy findings were divided into (i) erosive esophagitis, classified according to the Los Angeles grading system; (ii) BE, defined by salmon-colored columnar mucosa visible in the distal esophagus extending at least 1cm above the top of the gastric folds, and confirmed histopathologically via mucosal biopsy with or without the presence of intestinal metaplasia;[15] or (iii) normal, without any mucosal or structural pathology.

HRM and ambulatory pH-impedance monitoring were performed for routine clinical indications of persistent or incomplete resolution of reflux symptoms despite anti-secretory therapy, prior to being considered for anti-reflux surgery. Erosive esophagitis did not form a subgroup as these patients rarely require confirmatory physiology testing. Of those tested, reflux disease was classified as normal or excessive based on an upper limit of normal for total percentage acid exposure time (AET) of 5% and/or an excessive number of impedance-recorded reflux events (>73).[16, 17] Consequently, patients had at least one typical symptom of reflux as a primary presenting complaint and were divided into 3 common sub-groups based on both endoscopy and physiology findings: (1) BE; (2) ENRD, with normal gastroscopy and excessive AET and/or impedance-detected reflux events; and (3) functional heartburn patient-controls (FHC), with normal gastroscopy, normal AET and normal impedance-recorded reflux events.

High Resolution Manometry

Equipment

HRM was conducted using a 20-channel water perfused system (Solar GI HRM, Medical Measurement Systems, Enschede, The Netherlands). A disposable silicone catheter of 4mm in diameter that was comprised of 20 thinner (0.4mm) polyvinyl tubes (MMS G-90500 Customized Single-Use HRM Esophageal 20ch Catheter, Mui Scientific, Mississauga, ON, Canada) was used. The catheter incorporates 20 side holes, one for each of these tubes, each of which acts as a manometric sensor. Aside from 5 side holes responsible for taking measurements of the LES that are spaced 1cm apart, the rest that span the esophagus are spaced 2cm apart. Distilled water was perfused through the catheter lumen at the constant rate of 0.6 mL/min. Pressure changes detected by each manometric sensor are transmitted to the external pressure transducer, which transforms them into data that can be visualized on the screen in the form of esophageal pressure topography plots. These data were automatically saved, stored and analyzed using proprietary software (MMS Investigation & Diagnostic Software version 9.3, Medical Measurement Systems, Enschede, The Netherlands).

Protocol

A standard HRM protocol was performed, whereby ten 5mL water swallows, each 30s apart, were administered using a syringe while in the left lateral position. Then, the patient was asked to sit upright and to drink 200mL of water through a straw without any breaks (Rapid Drink Challenge; RDC). Finally, five bread swallows (1cm^3 cubes of buttered white bread) were administered, again with 30s in between each bread swallow and taking into account that for the solid swallows more than one swallow was commonly required to completely clear the pharynx.

Analysis

Using the standard criteria detailed in the Chicago Classification for esophageal motility disorders, version 3.0, swallows were analyzed and calculation of manometry parameters of interest including integrated relaxation pressure (IRP), distal contractile integral (DCI) and distal latency (DL) was performed.[18] Then, peristaltic integrity was determined; an intact contractile front for a single water swallow was defined as requiring a maximum break of no greater than 5cm at 30mmg isobaric contour, a DCI >450mmHg.cm.s and a distal latency of >4.5s.[18] To account for the hydrostatic pressure impact of upright measurements, both the 30 and 40mmHg isobaric contours were used to measure for breaks and distal latency; 40mmHg was more likely to circumscribe the contractile wave while upright and was preferred. Also for upright swallows, both DCI of >450 and >500 mmHg.s.cm were separately measured to define peristaltic effectiveness. The presence or absence of a peristaltic contraction with intact contractile front within 30s of completion of RDC (defined by the same criteria) was also determined.

Esophageal combined pH-impedance monitoring

Equipment

Ambulatory combined pH-impedance monitoring was performed using a single use catheter with one antimony pH electrode and six impedance electrodes (pHTip, Unisensor AG, Attikon, Switzerland). The data collected was stored on a portable data logger (Ohmega, Medical Measurement Systems, Enschede, The Netherlands) carried by the patient.

Protocol

Introduced transnasally, the catheter was positioned in a fashion such that the pH electrode was 5cm proximal to the upper border of the LES, whose location was determined by the preceding HRM study. All patients were instructed to continue with their usual diet and activities during the study. They were asked to record the start and ending of meal times, body position (supine or upright) and the occurrence of symptoms attributable to reflux both.

Physiology study analysis

Data was analyzed using the proprietary software (MMS Investigation & Diagnostic Software version 9.3, Medical Measurement Systems, Enschede, The Netherlands). Meal times were excluded from the analysis. Standard criteria were used to measure both distal esophageal acid exposure and impedance-detected reflux events.[19] For pH, total percentage acid exposure was defined as time below pH of 4 divided by total duration of the study. Impedance analysis was performed firstly in an automated manner using the proprietary software, then followed by manual verification by an experienced physiologist. Care was taken to check for the presence of low baseline impedance that may confound interpretation of reflux events. For each reflux episode detected by impedance, the bolus clearance time was defined as the time period in seconds between liquid bolus entry to liquid bolus exit from a point 5cm above the LES. The total bolus exposure time was calculated by the summation of the bolus clearance times for every individual reflux event, divided by the total study duration and expressed as a percentage. The symptom index was calculated based on the relationship of symptoms to acid reflux events.[20]

Outcomes

The primary outcome measure was the DCI following administration of small volume water swallows, solid swallows and RDC. Secondary manometric outcomes included percentage of subjects with mean DCI > 450 (and 500) mmHg.cm.s and percentage of swallows with intact contractile front, as defined above. Other secondary outcomes related to findings from the ambulatory impedance-pH measurements and included: mean total percentage acid exposure time (AET), number of impedance-detected reflux events, bolus clearance time and total bolus exposure time (divided into upright and supine where appropriate) and symptom indices for acid reflux and impedance-detected reflux events. Finally assessments of outcome following Barrett's related endotherapy, as well as comparison between BE patients on and off acid suppression were described.

Statistics

Pairwise comparisons were performed for categorical characteristics between study groups using a chi-square or Fisher's exact test as appropriate, while continuous symptom and test result covariates were compared using a Wilcoxon rank sum test. For the percentage of swallows with intact contractile front, we reported the median (interquartile range; IQR) and made formal comparisons by a random effects logistic regression model to account for both within and between patient variability. Parametric continuous data was compared across three study groups using an ANOVA. A P-value of < 0.05 was considered statistically significant. Analysis was conducted using IBM SPSS Statistics for Mac, version 23.0 (IBM Corp, Armonk, NY, USA).

Results

Patient Characteristics

78 subjects (BE 25, ENRD 27, FHC 26 subjects) fulfilled the criteria for inclusion into the study. Overall, female subjects comprised the majority but sex distribution varied by subject group (Table 1). The mean age of ENRD (48 ± 14 years) and FHC subjects (44 ± 14 years) was similar but BE patients were older than both (mean age 57 ± 13 years; P<0.01 for both comparisons). 13 BE subjects (52%) were taking acid suppressing medication at the time of the studies (as per clinical request), while all ENRD and FHC subjects had stopped these drugs at least 7 days prior to the study. 8 (32%) BE subjects had previously undergone single or combinations of ablative therapy (radiofrequency ablation, photodynamic therapy), 6 of which were successful in clearing dysplasia but all had at least a 2cm remnant Barrett's segment at the time of testing. The median length of Barrett's was 6cm (range 2-14). Heartburn and regurgitation were more common than chest pain across all subject groups. Although regurgitation was reported significantly less frequently amongst FHC patients than both ENRD and BE (35% vs. 59% and 72% respectively; P=0.02), heartburn and chest pain were reported with similar

frequency across all groups. (Supplementary Figure 1). Dysphagia (as a secondary symptom) was reported in reduced, yet equal frequency in all groups.

Distal contractile integral with standard water swallows and adjunctive testing

With standard water swallows, the median DCI in BE was lower in magnitude than in ENRD, and both were significantly reduced when compared to the control subjects with functional heartburn (87 vs 442 vs 602 mmHg.cm.s respectively; $P<0.01$ and $P=0.04$ for pairwise comparisons of BE and ENRD to FHC, respectively; see Table 2).

In contrast, with solid swallows, BE subjects again demonstrated significantly lower median DCI than FHC (818 vs. 1242 mmHg.cm.s; $P<0.01$), but there was no significant difference between ENRD (1732mmHg.cm.s) and FHC ($P=0.93$). Similarly following RDC, the median DCI was significantly lower in BE compared to FHC, whereas again, there was no difference between ENRD and FHC (Table 2).

Comparison of other manometric parameters with standard water swallows and adjunctive testing

Percentage subjects with adequate mean DCI

The overall percentage of subjects with a mean DCI > 450 mmHg.cm.s for water swallows was reduced in magnitude in the BE and ENRD groups compared to the FHC group (24% vs. 48% vs. 73%); however, this only reached significance for the BE group (Table 2).

Following solid swallows, the percentage of subjects with mean DCI > 450 mmHg.cm.s remained significantly lower in BE compared to FHC (73% vs. 100%; *P*=0.006), whereas the percentage was almost identical in ENRD compared to FHC (96% vs. 100%; *P*=0.99). This finding persisted even when testing for the same percentage with a DCI > 500 mmHg.cm.s (Table 2).

When adequacy of contractile vigor was alternatively assessed by the incidence of ineffective esophageal motility, defined by Chicago Classification criteria,[18] comparative findings between the three groups were similar (Supplementary Table 3).

Percentage swallows with intact contractile front

With standard water swallows, the median proportion of swallows with intact peristalsis was significantly lower in both BE and ENRD groups compared to FHC (10% vs. 40% vs 65% respectively; *P*<0.001 for pairwise comparisons between both BE and ENRD and FHC; see Table 2). On the other hand, the percentage of solid swallows with intact contractile front was significantly reduced in BE compared to FHC (40% vs. 60%; *P*<0.001), but the difference was non-significant when ENRD was compared to FHC (75% vs. 60%; *P*=0.65; see Table 2).

In a similar fashion, the percentage of subjects with who demonstrated a peristaltic contraction with an intact contractile front within 30s of RDC was significantly reduced in BE compared to FHC, whereas no difference was observed between ENRD and the control group (Table 2).

Reproduction of dysphagia during HRM

Dysphagia was reported as a secondary symptom in 38% of the cohort at baseline; however, dysphagia was almost never reproduced during water swallows (4% of BE, 0% of ENRD and FHC). In contrast, dysphagia was reproduced with solid swallows in 32% of BE, 41% of ENRD and 19% of FHC subjects, and although to a lesser degree, following RDC.

Findings on combined 24h pH-impedance study

pH-Impedance monitoring

As per the definition, the median AET was within normal limits in FHC, and significantly lower compared to both BE and ENRD ($P<0.001$ for all pairwise comparisons; see Table 3). Furthermore the median total number of impedance-detected reflux events was within normal limits in FHC (22 episodes within 24 hours) which was significantly lower than that observed for both BE and ENRD ($P<0.001$ for both pairwise comparisons). There was no difference in the overall number of impedance-detected reflux episodes between BE and ENRD (67 and 57 episodes respectively; $P=0.45$ by Wilcoxon rank sum test).

The median bolus clearance time was significantly prolonged in BE compared to FHC (11.5s vs 10s respectively; $P=0.02$), but there was no difference between

ENRD and FHC (11s; *P*=0.15 c.f. FHC). The median total percentage bolus exposure time was significantly greater in both the BE and ENRD groups compared to FHC (1.8% vs. 1.2% vs. 0.5% respectively; *P*<0.001 for both pairwise comparisons with FHC; see Table 3).

Symptoms

During the pH-impedance study, the median number of symptoms reported by patients in the three patient groups was similar *(P* non-significant). The frequency that symptoms were associated with reflux events as measured by symptom index was, however, variable between the groups, with ENRD patients having a significantly greater symptom index-acid score than those with FHC (30% vs. 0%; P<0.001). On the other hand, BE subjects had a similarly low symptom index score to those with FHC (4%; *P*=0.13 c.f. FHC). These findings were replicated for symptom index for impedance-detected reflux events (Figure 1).

Effect of Barrett's therapy on physiological findings

8 (25%) of the BE patients had previously undergone, or were in the process of undergoing, endoscopic ablative therapies for Barrett's (6 radiofrequency ablation, 1 photodynamic therapy, 1 had both) and was successful in ablating dysplasia in all but 2 patients with persistent/recurrent low-grade dysplasia. No patient had a stricture or other structural pathology following therapy. At the time of testing, all had a minimum of at least 2cm segment of columnar lined mucosa.

Comparing BE patients who had previously undergone ablative therapy with those who had not; the degree of contractile vigor (whether assessed by water swallows, RDC or solid swallows), the total amount of acid reflux, as well as bolus clearance time and total bolus exposure time were all similar between groups. There was a trend towards stronger symptom association in BE patients post-endotherapy, though the numbers were small and did not reach significance (Supplementary Table 1).

There was no difference in motility when comparing BE patients who were studied whilst on or off acid suppression therapy (Supplementary Table 2)

Discussion

Using HRM, we demonstrated how patients with BE exhibit a greater degree of impairment in esophageal motility compared to ENRD patients and control subjects with functional heartburn. The use of adjunctive HRM testing in addition to standard 5mL water swallows aided in differentiating the motility abnormalities between patient groups. Specifically in BE, motility is reduced compared to ENRD and FHC, is most pronounced with the increased oesophageal workload of swallowing solids, and is likely to be related to problems with clearance than simply a greater amount of reflux events which in fact was similar to ENRD. In particular, ENRD subjects who appeared to have significantly worse motility than the control group with water swallows, demonstrated motility patterns similar to that seen in FHC when the more physiologically representative challenges of solid swallows or high volume water swallows were administered. In contrast, the motility abnormalities found in BE patients during small volume water swallows persisted throughout the adjunctive tests (Figure 2).

While these findings are observational and do not prove causality, they are compatible with the hypothesis that esophageal dysmotility contributes to the pathogenesis of BE by allowing prolonged mucosal exposure to noxious refluxate.[5, 21] Historical studies support this concept and showed that treatment-induced healing of erosive esophagitis is not always followed by recovery of esophageal dysmotility,[22] suggesting that that the esophageal motor abnormalities might be at least a significant contributing factor to worsening reflux and BE. The present study expands on this concept by intimating that differences in motility contribute to the different phenotypic manifestations of GERD.

Increasing workload on the esophagus with solids is more representative of normal physiological swallowing behavior. Prior studies have demonstrated that in health, solid swallows improve contractility and coordination of peristalsis compared to small volume water swallows.[9, 10, 14] A better-coordinated and more vigorous peristaltic wave often ensues in response to the greater workload on the esophagus. In a similar fashion to the present study, others also demonstrated that using solid swallows and RDC, peristaltic dysfunction was reduced in subjects with ENRD as well as those with dysphagia symptoms, despite dysmotility being demonstrated when using water swallows alone; demonstrating the concept of contractile reserve.[12, 14] The present study exemplifies the value of performing adjunctive tests when assessing the motility of GERD patients, and highlights the non-specific nature of manometric findings based on small volume water swallows alone.

We found that the number of reflux events was not greater in BE compared to ENRD, but reflux events lasted longer, especially while supine (bolus exposure and bolus clearance time). Despite this, the correlation of symptoms to reflux events in BE was poor; symptom index for both acid reflux and impedance-detected reflux events were similar to that seen in FHC while the symptom index in ENRD was significantly higher. The implication is that esophageal sensory dysfunction is likely to also play a crucial role, as patients with BE differed in the duration of reflux events and their ability to sense them. Taken cumulatively, these findings support the concept that impairment in esophageal sensory capacity contributes to less frequent primary peristaltic clearing contractions, which if inherently hypomotile, will culminate in the prolongation of mucosal exposure to noxious refluxate and thus predispose to BE.[23]

The relatively high incidence of poor contractile vigor in the FHC group (27% of these subjects had a mean DCI of less than 450 mmHg.s.cm with 5mL water swallows) is also of interest, as little data is available regarding normal values for HRM metrics using water-perfused catheters. Kessing et al. reported a median DCI in healthy volunteers of 970 mmHg.s.cm,[24] while Tseng et al., in a Chinese population reported median DCI (IQR) of 799 (438 – 1380) mmHg.s.cm,[25] which compares to corresponding values of 602 (362 – 1048) mmHg.s.cm we observed in the FHC group. The main caveat to making a direct comparison here is that those with functional heartburn and healthy subjects cannot be considered completely identical groups. Still, these figures are very similar to some other studies that looked at normal values using solid state catheters while in the upright position; for example in one study of 23 healthy subjects the DCI (IQR) was 734 (478-1366).[9] Aside from highlighting the importance of determining device and population specific normal values for HRM parameters, this again emphasizes the value of performing the adjunctive tests, since almost all FHC subjects had adequate contractility when tested with solids and RDC, as one would expect of those with normal esophageal motor function.

Limitations of the study mainly relate to its observational nature. Despite that, the study benefited from designation into discrete, homogenous and well-defined study groups, based upon objective findings on endoscopy and 24-hour pH-impedance monitoring. While the study lacked a true healthy control group, the use of functional heartburn as a surrogate patient-control is valid in this context, given that these subjects by definition have normal esophageal motility and acid exposure. Furthermore, the use of functional heartburn patients rather than healthy controls conferred a significant benefit to the study by allowing a meaningful comparison of symptoms to be performed. Another limitation relating to the study's observational nature is the discordance in PPI use between the groups, with approximately half the BE patients using acid suppression therapy during the time of testing compared to the other groups, all of whom were tested treatment-free. However, while this may confound the comparison of 24h esophageal acid exposure measurement between the groups, PPI use should not have had significant bearing on the number of impedance-detected reflux events, nor on the manometric findings.[26] Furthermore, there was no difference in the motility patterns nor the number of impedance-detected reflux events between the BE patients who were on PPI compared to those who were not (Supplementary Table 2). Lastly, we acknowledge that the findings of the ENRD cohort may not be generalizable, since HRM and pH-impedance testing was only performed for ENRD patients with refractory symptoms and/or as part of workup for surgery.

In conclusion, this study demonstrated the presence of significant impairments in esophageal contractility in patients with BE. The use of adjunctive HRM testing with solid swallows and free drinking elucidated these abnormalities and helped to differentiate dysmotility within the BE cohort from those with ENRD in whom motility was found to be similar to the normal contractile patterns of the control group with functional heartburn. In addition, patients with BE had sensory impairment and poor clearance of refluxate which together are likely strong contributors to the genesis of this disease. These data advance our understanding of the pathogenesis of BE and provide important groundwork for future research.

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Abbreviations: AET, acid exposure time; BE, Barrett's esophagus; DCI, distal contractile integral; ENRD, endoscopy-negative reflux disease FHC, functional heartburn patient-controls; GERD, gastro-esophageal reflux disease; HRM, high-resolution manometry; PPI, proton pump inhibitor; RDC, rapid drink challenge

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Table 1: Baseline patient characteristics

	Barrett's esophagus	Endoscopy negative reflux disease	Functional heartburn	*P*
N	25	27	26	
Females (%)	6 (24%)	17 (63%)	20 (77%)	<0.01
Mean age ± S.D. (years)	57 ± 13	48 ± 14	44 ± 14	<0.01
Acid suppressing medication use at time of studies (%)	13 (52%)	0	0	
Median circumferential length of Barrett's segment, cm (range)	3 (0-11)	-	-	
Median maximal length of Barrett's segment, cm (range)	6 (2-14)	-	-	
Previous endoscopic therapy for Barrett's, *N* (%)	8 (32%)	-	-	

Table 2: Comparison of manometric parameters of interest by 5mL water swallows, solid swallow and rapid drink challenge

	BE	P vs. FHC	ENRD	P vs. FHC	FHC
LES pressure, mmHg, Median (IQR)^	8 (4-11)	<0.001	14 (6-21)	0.60	14 (10-19)
*DCI, mmHg.cm.s, Median (IQR)^*					
5mL water	87 (25 – 423)	<0.001	442 (288 – 826)	0.04	602 (362 – 1048)
Solids	818 (406.5-1423)	<0.01	1732 (1080-2213)	0.93	1242 (808-2885)
RDC	552 (263-1303)	<0.001	1080 (271-2760)	0.06	2308 (619-3800)
Adequate mean DCI, % of subjects~					
5mL water DCI > 450 mmHg.s.cm	24%	0.001	48%	0.09	73%
Solids DCI > 450 mmHg.s.cm	73%	<0.01	96%	>0.99	100%
Solids DCI > 500	73%	<0.01	96%	>0.99	100%

mmHg.s.cm					
RDC DCI > 450 mmHg.s.cm	55%	0.01	65%	0.09	88%
RDC DCI > 500 mmHg.s.cm	55%	0.01	65%	0.09	88%
*Intact contractile front, % of swallows, Median (IQR)**					
5mL water	10 (0 – 60)	<0.001	40 (10 – 70)	<0.001	65 (40 – 100)
Solids	40 (20 – 75)	<0.001	75 (40 – 80)	0.65	60 (40-100)
RDC	32	0.02	65	0.95	69

BE, Barrett's esophagus; DCI, distal contractile integral; ENRD, endoscopy-negative reflux disease; FHC, functional heartburn controls; LES, lower esophageal sphincter RDC, rapid drink challenge; ^*P* from Wilcoxon rank sum test; ~*P* from Fisher's exact test/ chi-square test; **P* is from a random effects logistic model comparing the percentage of swallows with intact contractile front

Table 3: Comparison of findings on 24h pH-impedance testing

	BE	*P* vs. FHC[#]	ENRD	*P* vs. FHC[#]	FHC
Acid reflux by pH-metry					
Distal esophageal AET, % time pH<4	11.2 (2.6-18.7)	<0.001	8.1 (5.5-12.9)	<0.001	2.0 (0.9-2.7)
Upright reflux, % upright time pH<4	8.8 (3.5-17.1)	<0.001	9.6 (4.6-14.8)	<0.001	2.2 (1.2-4.0)
Supine reflux, % supine time pH<4	3.6 (0.9-29.0)	<0.001	1.9 (0.1-11.2)	<0.001	0 (0-0.5)
Prolonged reflux episodes, n	6 (1-12)	<0.0001	3 (1-7)	<0.0001	0 (0-1)
Impedance-based reflux parameters					
Total no. reflux episodes/ 24h, n	67 (37-106)	<0.001	57 (33-91)	<0.001	22 (12-34)

Bolus clearance time, s	11.5 (9.5-15.25)	0.02	11 (9-12)	0.15	10 (9-11)
Upright BCT, s	11 (7.3-13.5)	0.23	12 (7.5-13.5)	0.07	10 (8.3-11)
Supine BCT, s	13 (9-15.5)	0.03	10 (7-12)	0.62	9.5 (6-12)
Bolus exposure time, %	1.8 (0.7-2.6)	<0.001	1.2 (0.6-1.7)	<0.001	0.5 (0.3-0.6)
Upright BET, %	1.8 (0.6-4.7)	0.001	1.7 (1.0-2.7)	<0.001	0.7 (0.5-1.0)
Supine BET, %	0.3 (0.1-1.1)	0.01	0.1 (0-0.3)	0.16	0.1 (0-0.2)

Values are median (IQR). AET, acid exposure time; BCT, bolus clearance time; BE, Barrett's esophagus; BET, bolus exposure time; ENRD, endoscopy-negative reflux disease; FHC, functional heartburn controls; SI, symptom index; [#]Wilcoxon rank sum test

Figure 1: Symptom association for pH and impedance-detected reflux events. X: *P* non-significant c.f. FHC; ** *P*<0.001 c.f. FHC; * *P*<0.01 c.f. FHC

Figure 2: Esophageal body contractile patterns demonstrating contractile reserve in ENRD, but not in BE, when challenged with solid swallows and RDC. Representative swallows from BE (upper panel) are compared with those in ENRD (lower panel). (A) During single 5mL water swallows, esophageal body contractility was similarly poor in both BE and ENRD. (B) However following solid swallows, significant improvement in contractility was seen in ENRD, where a normal peristaltic contraction occurs; yet, contractility remains poor in BE. (C) Following RDC, similar findings are seen. There is no peristaltic after-contraction observed in BE. This is in contrast to ENRD, where a normal, effective after-contraction is seen following RDC.