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ORIGINAL ARTICLE

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# Fragmented and failed swallows on esophageal high-resolution manometry associate with abnormal reflux burden better than weak swallows

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## Abstract

**Background:** Association between proportions of hypomotile swallows on esophageal high-resolution manometry (HRM) and esophageal reflux burden remains incompletely understood. We investigated relationships between hypomotility, acid exposure time (AET), and mean nocturnal baseline impedance (MNBI) on ambulatory reflux monitoring.

**Methods:** Clinical data, HRM, and ambulatory pH-impedance studies (performed off acid suppression) from patients with persisting reflux symptoms were reviewed from five international centers. AET (abnormal > 6%) and MNBI (abnormal < 2292 ohms) were extracted from pH-impedance studies. Distal contractile integral (DCI) designated esophageal peristalsis into normal (DCI > 450 mmHg.cm.s), fragmented (DCI > 450 mmHg.cm.s with breaks > 5 cm), weak (DCI 100-450 mmHg.cm.s), and failed (DCI < 100 mmHg.cm.s) sequences. Univariate and multivariate analyses were performed to identify motor associations of abnormal reflux burden.

**Key Results:** Of 351 patients (52.1 ± 0.8 years, 67%F), 29.3% had AET > 6% and 61.8% had MNBI < 2292 ohms. On univariate analysis, both fragmented peristalsis and IEM associated with abnormal AET ($P \leq .01$) and MNBI ($P \leq .03$); reflux burden was more profound with >70% fragmented as well as ineffective sequences compared to ≤70% for each ($P < .05$ for each comparison). When weak and failed sequences within IEM were separately analyzed, ≥50% failed sequences predicted abnormal AET ($P \leq .009$), and ≥50% weak sequences did not ($P = .14$). On multivariate regression, ≥50% failed sequences predicted abnormal AET ($P = .02$), and >70% ineffective sequences trended strongly ($P = .069$); >70% ineffective sequences predicted abnormal MNBI ($P = .046$), and >70% fragmented sequences trended strongly ($P = .076$).

**Conclusions and Inferences:** Breaks in esophageal peristaltic integrity seen with fragmented and failed sequences are more relevant to abnormal esophageal acid burden than weak sequences.

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**KEYWORDS**
acid exposure time, ambulatory pH-impedance monitoring, failed swallows, fragmented peristalsis, ineffective esophageal motility, mean nocturnal baseline impedance

## 1 | INTRODUCTION

Retrograde movement of gastric content into the esophagus is a common occurrence and can be physiological.[1] An increase in frequency, duration and amount of reflux, and/or an inability to clear refluxed content can lead to gastroesophageal reflux disease (GERD).[2] Inadequate refluxate clearance can involve various elements of esophageal motor function, including inability to initiate primary or secondary peristalsis, impaired or absent peristaltic sequences, and abnormal esophagogastric junction (EGJ) morphology.[3-6] Since the advent of high-resolution manometry (HRM), enhanced recognition of esophageal body motor patterns and esophagogastric junction (EGJ) morphology has improved our understanding of the relationship between motor abnormalities and gastroesophageal reflux disease (GERD).[7,8]

Hypomotility patterns on esophageal HRM, including fragmented peristalsis, ineffective esophageal motility (IEM), and absent contractility, have been linked to abnormal reflux clearance.[9] Profound motor impairment can be encountered in Barrett's esophagus,[10] and bolus clearance can be significantly abnormal when swallows fail.[11] However, reflux clearance can be abnormal even when peristalsis is intact, especially when there are breaks in peristaltic integrity in the esophageal body.[12]

In this multicenter, retrospective observational study, our primary aim was to understand the relationships between esophageal body motor performance and peristaltic integrity on one hand, and esophageal reflux burden on the other. Using esophageal acid exposure time (AET) and mean nocturnal baseline impedance (MNBI) as metrics defining esophageal reflux burden,[8] we compared the reflux implications of various proportions of fragmented, weak, and failed peristalsis as part of the standard HRM swallow protocol.

**Key Points**

- The association between type and proportions of hypomotile esophageal peristaltic sequences and esophageal reflux burden is not fully understood
- Breaks in esophageal body contraction vigor on standard water swallows performed during esophageal high resolution manometry (fragmented swallows, failed swallows) associate with either cross-sectional or longitudinal reflux burden on ambulatory reflux monitoring.
- A gradient of increasing reflux burden is noted with higher proportions of sequences with breaks. Weak sequences without breaks do not demonstrate a similar association.
- Assessment of swallow patterns on esophageal high resolution manometry complements measurement of reflux burden using ambulatory pH-impedance monitoring in patients with persisting reflux symptoms.

## 2 | METHODS

Adults (age > 18 years) referred for esophageal physiologic testing for persisting typical and atypical reflux symptoms despite double-dose acid-suppressive therapy for at least 8 weeks at five centers (4 in Europe and one in the United States) were eligible for inclusion in this retrospective observational cohort study. Patients were included if alternate esophageal mechanisms for symptoms had been excluded with endoscopy, if they underwent ambulatory pH-impedance studies off acid-suppressive therapy, and if 10 acceptable supine water swallows were available for HRM analysis using Chicago Classification version 3.0 (CCv3.0).[13] Exclusion criteria consisted of inadequate studies (equipment malfunction, poor study quality, artifacts) and incomplete studies (fewer than ten swallows). Patients with achalasia spectrum disorders (integrated relaxation pressure, IRP > 15 mm Hg), hypercontractile disorders, distal esophageal spasm, connective tissue disorders, neoplasia, and previous foregut surgery were also excluded. The study protocol was approved by the Human Research Protection Office (Institutional Review Board) at Washington University in St. Louis, and each collaborating institution completed data sharing agreements for analysis of de-identified clinical, pH-impedance, and HRM data.

### 2.1 | High-resolution manometry

Following an overnight fast, an HRM catheter system (Sierra vintage, Medtronic) with high-fidelity circumferential sensors 1 cm apart was inserted through the nasal canal by an experienced nurse using previously described methodology.[14,15] The HRM catheter was advanced such that the three distal-most sensors registered an intragastric location. All studies were performed in a semi-recumbent position, with the head tilted slightly to the left to facilitate swallowing. Five mL of ambient temperature water was administered using a syringe every 20-30 seconds until 10 swallows were performed. A 20- to 30-seconds landmark phase of quiet rest was recorded, either before or after the 10-swallow protocol.[14,15]

All HRM studies were analyzed using dedicated computerized HRM acquisition, display, and analysis software. HRM studies were analyzed and interpreted independent of pH-impedance studies at each center. Each HRM study was categorized by one of the authors using the following CCv3.0 criteria: (a) intact swallow: distal contractile integral (DCI) > 450 mmHg.cm.s; (b) fragmented swallow: DCI > 450 mmHg.cm.s with > 5 cm breaks; (c) weak swallow: DCI

100-450 mmHg.cm.s; (d) failed swallow: DCI < 100 mm Hg.cm.s. CCv3.0 diagnoses consisted of the following: (a) fragmented peristalsis: ≥50% fragmented swallows; (b) IEM: ≥50% of any combination of weak or failed swallows; (c) absent contractility: 100% failed swallows. Individual proportions of fragmented, weak, and failed swallows were separately recorded; >70% ineffective sequences constituted severe IEM.[16]

In addition to CCv3.0 criteria, EGJ barrier function and morphology were recorded. EGJ contractile integral (EGJ-CI) was evaluated by recording the EGJ barrier vigor (using a DCI like tool) during a period of quiet rest over exactly three respiratory cycles, and divided by the duration of the respiratory cycles to make the metric independent of respiration.[13,17] EGJ-CI was considered low when <39.1 mmHg.cm.[17,18] EGJ morphology was determined by the relationship between LES and crural diaphragm (CD); type 1 when LES and CD were superimposed, type 2 when separated <3 cm, and type 3 when separated ≥3 cm. Types 2 and 3 together constituted abnormal EGJ morphology, while type 1 morphology was considered normal.[8,13]

**TABLE 1** Demographic and Clinical Characteristics of Study Patients

| | N = 351 |
|---|---|
| Age (y) | 52.1 ± 0.8 y |
| Gender (female) | 235, 67.0% |
| Indications for testing | |
| Heartburn | 183, 52.1% |
| Chest pain | 36, 10.3% |
| Regurgitation | 33, 9.4% |
| Cough | 30, 8.5% |
| ENT symptoms | 12, 3.4% |
| Other | 57, 16.2% |
| High-resolution manometry | |
| Fragmented peristalsis | 20, 5.7% |
| Ineffective esophageal motility | 99, 28.2% |
| Absent contractility | 13, 3.7% |
| Intact peristalsis (100% intact) | 102, 29.1% |
| Mean EGJ-CI (mmHg.cm) | 45.0 ± 6.2 |
| Type 1 EGJ morphology | 159, 45.3% |
| Type 2 EGJ morphology | 119, 33.9% |
| Type 3 EGJ morphology | 73, 20.8% |
| pH-impedance monitoring | |
| Total AET >6% | 103, 29.3% |
| Upright AET >6% | 134, 38.2% |
| Supine AET >2% | 137, 39.0% |
| MNBI <2292 ohms (3 cm) | 227, 64.7% |
| MNBI <2292 ohms (5 cm) | 217, 61.8% |

Abbreviations: AET, acid exposure time; EGJ, esophagogastric junction; EGJ-CI, EGJ contractile integral; ENT, ear, nose, and throat; MNBI, mean nocturnal baseline impedance.

## 2.2 | Ambulatory pH-impedance testing

All pH-impedance studies were performed after patients were directed to stop proton pump inhibitor therapy at least seven days prior to the study and anti-histamine-2 receptor antagonists, prokinetics, and antacids three days prior to the study.[1] The distal pH sensor was positioned 5 cm proximal to the upper border of the HRM-identified lower esophageal sphincter (LES). Patients reported meals, activities, and symptoms using event logger buttons on the recorder, and on separate diaries for corroboration.

Abnormal acid exposure was defined as total AET > 6%; values between 4% and 6% were considered borderline, while AET < 4% was considered physiologic acid exposure.[8] Mean nocturnal baseline impedance (MNBI) was the averaged baseline impedance calculated at the 3-cm and 5-cm channels at three stable nocturnal time periods (1, 2, and 3 AM) to avoid artifacts and swallows; values <2292 ohms defined abnormal studies.[19]

## 2.3 | Data analysis

Data are reported as mean ± standard error of the mean (SEM) unless indicated otherwise. Categorical data alone were compared using the $\chi$-squared test, and continuous data were analyzed using the 2-tailed Student's *t* test. Univariate and multivariate analyses were performed to identify predictors of esophageal reflux. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated to determine the likelihood of abnormal reflux metrics with varying proportions of fragmented, weak, and failed sequences, using normal HRM studies (10 intact sequences with DCI > 450 mm Hg.cm.s) for comparison. Multivariate regression models were generated to evaluate whether hypomotility parameters and thresholds identified on univariate analyses were independent predictors for abnormal AET while controlling for EGJ morphology and barrier function. In all cases, $P < .05$ was required for statistical significance. All statistical analyses were performed using Microsoft Excel and RStudio (v2.11).

# 3 | RESULTS

Between the five study centers, a total of 351 patients (mean age 52.1 ± 0.8 years, 67% female) with typical and atypical presentations were included in the analysis (Table 1). The breakdown of patients between the centers was as follows: Milan: 19, Padua: 100, Pisa: 30, Rome: 85, and St. Louis: 117. Abnormal AET was noted in 103 (29.3%) patients, while MNBI was low in 217 (61.8%) patients; proportions were similar between female and male patients ($P \geq .16$ for each comparison). EGJ morphology was abnormal in 54.7%, and EGJ-CI was low in 81.1%; more males had abnormal EGJ morphology (25.0% vs 14.0%, $P = .054$) and low EGJ-CI (89.0% vs 79.3%, $P = .03$). Esophageal body motor patterns were similar between genders, except for IEM with > 70% ineffective sequences, which was seen more often in males (25.0% vs 14.0%, $P = .02$). On univariate analysis, a low EGJ-CI was associated with

**TABLE 2** Univariate and Multivariate Logistic Regression Analysis of Predictors of Reflux Burden

| | Total AET > 6% | MNBI < 2292 ohms |
|---|---|---|
| | Odds ratio (95% confidence intervals) | Odds ratio (95% confidence intervals) |
| Univariate analysis | | |
| ≥50% fragmented | 3.6 (1.3-9.8) *P* = .01 | 3.7 (1.2-11.8) *P* = .03 |
| ≥50% ineffective (IEM) | 2.4 (1.3-4.4) *P* = .009 | 2.3 (1.3-4.2) *P* = .006 |
| ≥50% weak | 1.9 (0.8-4.2) *P* = .14 | 3.8 (1.6-9.1) *P* = .002 |
| ≥50% failed | 3.3 (1.5-7.2) *P* = .004 | 1.8 (0.8-3.9) *P* = .18 |
| >70% fragmented | 3.6 (0.7-19.3) *P* = .135 | 1.9 (1.6-2.3) *P* = .031 |
| >70% ineffective | 2.5 (1.2-4.9) *P* = .013 | 2.7 (1.3-5.3) *P* = .005 |
| 100% failed | 8.2 (2.3-29.1) *P* = .0009 | 2.1 (0.6-7.2) *P* = .376 |
| Multivariate logistic regression[a] | | |
| ≥50% failed | 1.2 (1.03-1.40) *P* = .022 | 1.05 (0.89-1.23) *P* = .58 |
| >70% fragmented | 1.20 (0.83-1.73) *P* = .34 | 1.14 (0.96-2.1) 0.076 |
| >70% ineffective | 1.12 (0.99-1.27) *P* = .069 | 1.15 (1.00-1.31) *P* = .046 |

Abbreviations: AET, acid exposure time; MNBI, mean nocturnal baseline impedance.
[a]Controlling for esophagogastric junction (EGJ) barrier function and EGJ morphology.

AET > 6% (OR 1.14, 95% CI 1.01-1.29, *P* = .027) but not MNBI (OR 0.99, 95% CI 0.87-1.12, *P* = .84). Although abnormal EGJ morphology was associated with abnormal MNBI (OR 1.17, 95% CI 1.05-1.29, *P* = .003), this did not associate with abnormal AET (OR 1.03, 95% CI 0.94-1.14, *P* = .53).

The presence of fragmented peristalsis was associated with abnormal AET (*P* = .01) and abnormal MNBI (*P* = .03) compared to normal peristalsis (Table 2). Additionally, when fragmented sequences comprised >70% of swallows (n = 6), AET and MNBI were more markedly abnormal (AET 8.8 ± 1.5% vs 4.5 ± 0.6%, *P* = .03, MNBI 1225 ± 193 vs 2232 ± 87 ohms, *P* = .002, Figure 1A). Both AET and MNBI followed a linear relationship with increased numbers of fragmented swallows (Figure 2A). On multivariate logistic regression, >70% fragmented sequences was not independently predictive of abnormal AET (*P* = .34), but abnormal MNBI trended toward significance (*P* = .076, Table 2).

The presence of IEM also associated with abnormal AET (*P* = .009) and abnormal MNBI (*P* = .006) on univariate analysis (Table 2). With >70% ineffective sequences (n = 62), total AET was 7.53 ± 1.16%, compared to 5.04 ± 0.4% with ≤70% ineffective sequences (*P* = .048), and 4.05 ± 0.6% with normal manometry (*P* = .01, Figure 1B). MNBI demonstrated a decreasing gradient from 2239.53 ± 101.86 ohms (normal manometry), to 2061 ± 62.26 ohms (≤70% ineffective sequences) and 1656 ± 120.35 ohms (>70% ineffective sequences, *P* < .004 for each comparison, Figure 1B). On multivariate analysis, >70% ineffective sequences were independently predictive of abnormal MNBI (*P* = .046) and trended toward significance for abnormal AET (*P* = .069).

When weak sequences within IEM were separately examined, the presence of ≥50% weak sequences was not associated with abnormal AET (*P* = .14, Figure 2C) but did identify abnormal MNBI (*P* = .002, Table 2). In contrast, there was an increasing prevalence of abnormal AET as proportion of fragmented swallows and failed swallows increased (Figure 1A,D). A threshold of ≥50% failed peristalsis (n = 38) was discriminative of higher AET and lower MNBI vs normal manometry (*P* ≤ .02, Figure 2C). MNBI was consistently low with failed sequences (1815 ± 151 ohms) and therefore not discriminative when compared between <50% and ≥50% sequences (*P* ≥ .2). On multivariate analysis, ≥50% failed peristalsis was independently predictive of abnormal AET (*P* = .022), but not abnormal MNBI (*P* = .58, Table 2).

The study cohort was further interrogated in terms of abnormal reflux physiology (presence of all of the following: abnormal AET > 6%, abnormal MNBI < 2292 ohms, and presence of a hiatus hernia) and normal physiology (absence of all of these metrics). There were higher proportions of patients with IEM in the subset with abnormal physiology (*P* ≤ .02, Table 3) compared to those with normal physiology; ≥50% failed peristalsis and fragmented trended toward significance (*P* = .1). In contrast, proportions with intact esophageal motor function were higher in those with normal physiology (*P* = .01).

## 4 | DISCUSSION

In this retrospective multicenter cohort study, we report that both fragmented peristalsis and IEM as currently defined are associated with higher esophageal acid burden compared to normal manometry. There is a gradient of abnormal acid burden, with highest burden when >70% sequences are ineffective, designating a "severe" version of this motor diagnosis. Further, within the IEM category, we demonstrate that failed swallows are more relevant to abnormal reflux burden than weak sequences, and a threshold of 50% failed sequences is discriminative of higher reflux burden. On multivariate analysis, these thresholds are independently predictive of higher esophageal reflux burden (abnormal AET and/or low MNBI), when controlling for EGJ morphology and barrier function. Our data are consistent with existing reports that have linked hypomotile esophageal peristalsis to increased acid burden, measured using AET[3,6] and MNBI.[18,20,21] Thus, evaluation of swallow patterns on esophageal HRM complements measurement of reflux burden on pH-impedance monitoring in patients with persisting reflux symptoms.

Our findings indicate the existence of a spectrum of esophageal body peristaltic aberration whereby reduced vigor impairs

refluxate clearance in a cumulative fashion. Thus, weak swallows are associated with less impairment of clearance than failure of peristalsis. Our data also suggest that breaks in peristaltic integrity—partial in fragmented peristalsis, or the entire length of the esophagus in failed peristalsis—are more relevant to abnormal refluxate clearance than weak swallows by themselves. When weak and failed swallows are combined, there is a gradient of abnormal reflux burden, with higher burden when >70% sequences are ineffective. Therefore, the current paradigm that combines weak and failed sequences in defining IEM may be suboptimal in characterizing mechanism of abnormal esophageal acid burden in GERD, and recognition of failed peristalsis as a unique entity may be relevant in the context of reflux disease. Interestingly, a hypotensive EGJ (low EGJ-CI) does not appear to be enough on its own to result in low MNBI, but abnormal EGJ morphology does associate with low MNBI, potentially because this also associates with hypotensive esophageal body peristalsis.[22] This may be related to the fact that AET assesses cross-sectional acid burden accurate for the day of the study, while MNBI reflects longitudinal reflux burden impairing mucosal integrity; while the two do not always correlate with each other, both predict symptom improvement from antireflux therapy.[23-25]

There is existing evidence for association of increased reflux exposure with failure of peristalsis.[11] Similar to our results, others have demonstrated failed peristalsis to impair refluxate clearance more than weak swallows,[26] with clinically relevant end-organ damage.[27] Prior evidence has also linked inadequate contraction vigor to poor bolus transit within the esophagus, with aperistalsis being more relevant that partial losses in function.[12] Further, breaks in peristalsis, whether partial or complete, correlate with impaired bolus transit more so than weak swallows, and the degree of impairment associates with reflux symptom severity.[28,29] Other studies have linked abnormal bolus clearance with symptoms of dysphagia [12] and cough.[29,30] Our findings are consistent with this existing literature and support the notion that breaks in peristaltic integrity contribute to prolonged bolus retention, abnormal clearance, and elevated reflux burden. Further, patients with consistently abnormal reflux physiology had higher proportions of patients with IEM, failed and fragmented peristalsis, further supporting these concepts.

Data from animal studies and observations from GERD patients are inconclusive in determining whether defective peristalsis is the consequence of reflux-related mucosal injury or a causative factor predisposing to increased reflux burden,[31,32] However, it is known that weakness or delay in initiation of proximal of the two smooth

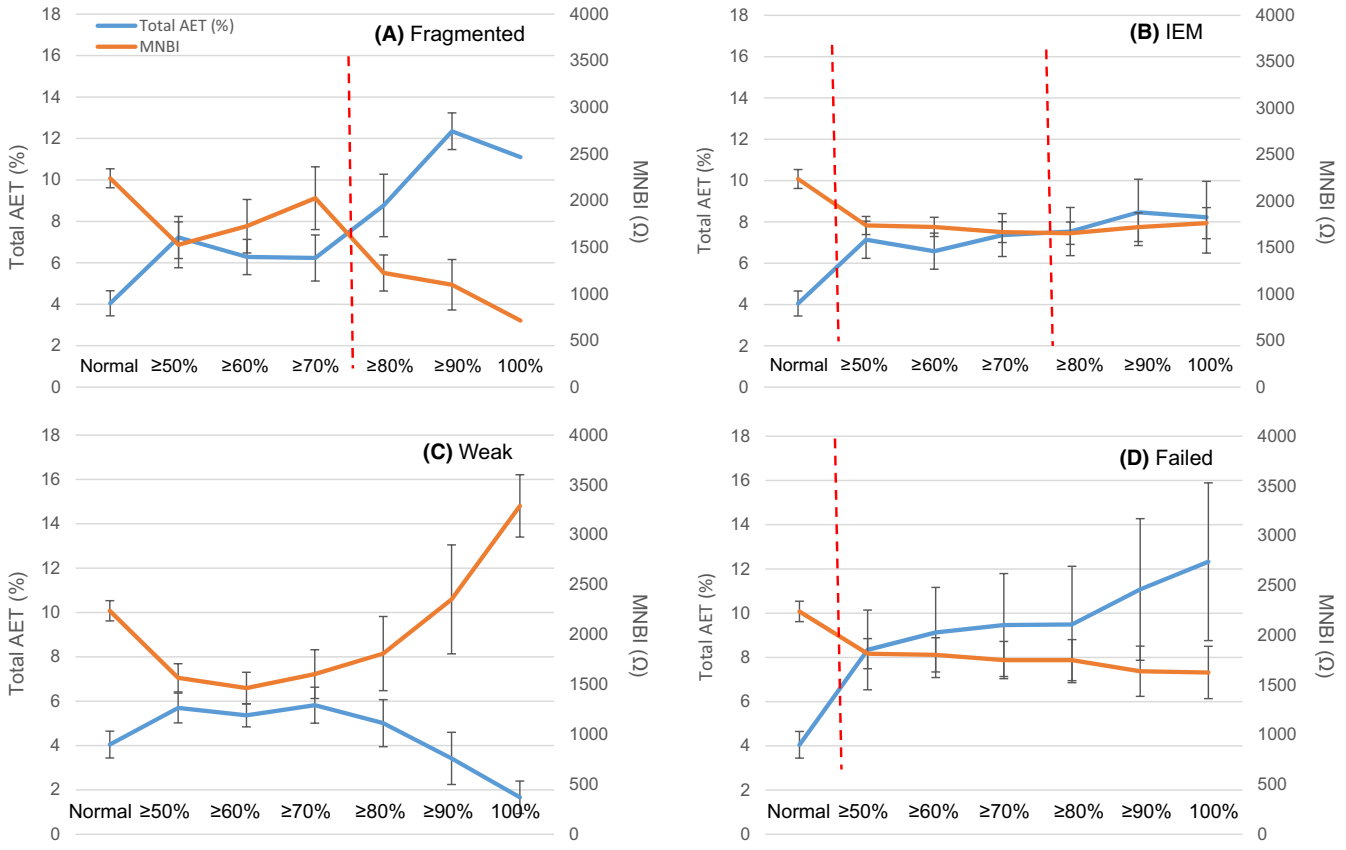


**FIGURE 1** Comparison of total acid exposure time (AET) and mean nocturnal baseline impedance (MNBI) across varying thresholds of fragmented (A), ineffective (B), weak (C), and failed (D) sequences. As proportions of fragmented, ineffective and failed sequences increased, AET correspondingly increased, while MNBI decreased. Finite thresholds (dashed vertical lines) could be identified designating severe fragmentation (>70%, A), severe ineffective esophageal motility (>70%, B), and failed sequences (≥50%, D), manifesting significantly higher AET and low MNBI. Similar thresholds could not be identified for weak sequences (C)

muscle contraction segments is a cholinergic dominant process,[33] which can be related to GERD[34] and may be associated with reduced reflux bolus clearance.[35]

Our study suffers from limitations inherent to retrospective data collection. Individual numbers of patients with each category of fragmented, weak, failed, and ineffective sequences were small, and a bigger patient cohort would have further solidified our findings. We were not able to examine the impact of break location in predicting reflux burden and were not able to confirm consistent marking of breaks across the centers: We relied on individual site interpretation for motor metrics. We did not study the impact of contraction reserve in altering reflux burden in the esophagus. We did not follow patients to determine whether our findings impacted decision making. We evaluated MNBI at both the 3-cm and 5-cm locations above the LES; most existing MNBI data relates to the 3-cm location,[19,36] although the 5-cm location could correlate better with AET measured at the same location.[25] Finally, the patients included in this study were evaluated at tertiary care centers and may not necessarily be generalizable to non-tertiary care settings. Despite these limitations, we report that there is a gradient of severity of both fragmented peristalsis and IEM, with >70% abnormal peristalsis associating with higher reflux burden.

In conclusion, our analysis corroborates prior studies that have suggested that esophageal body hypomotility demonstrates a

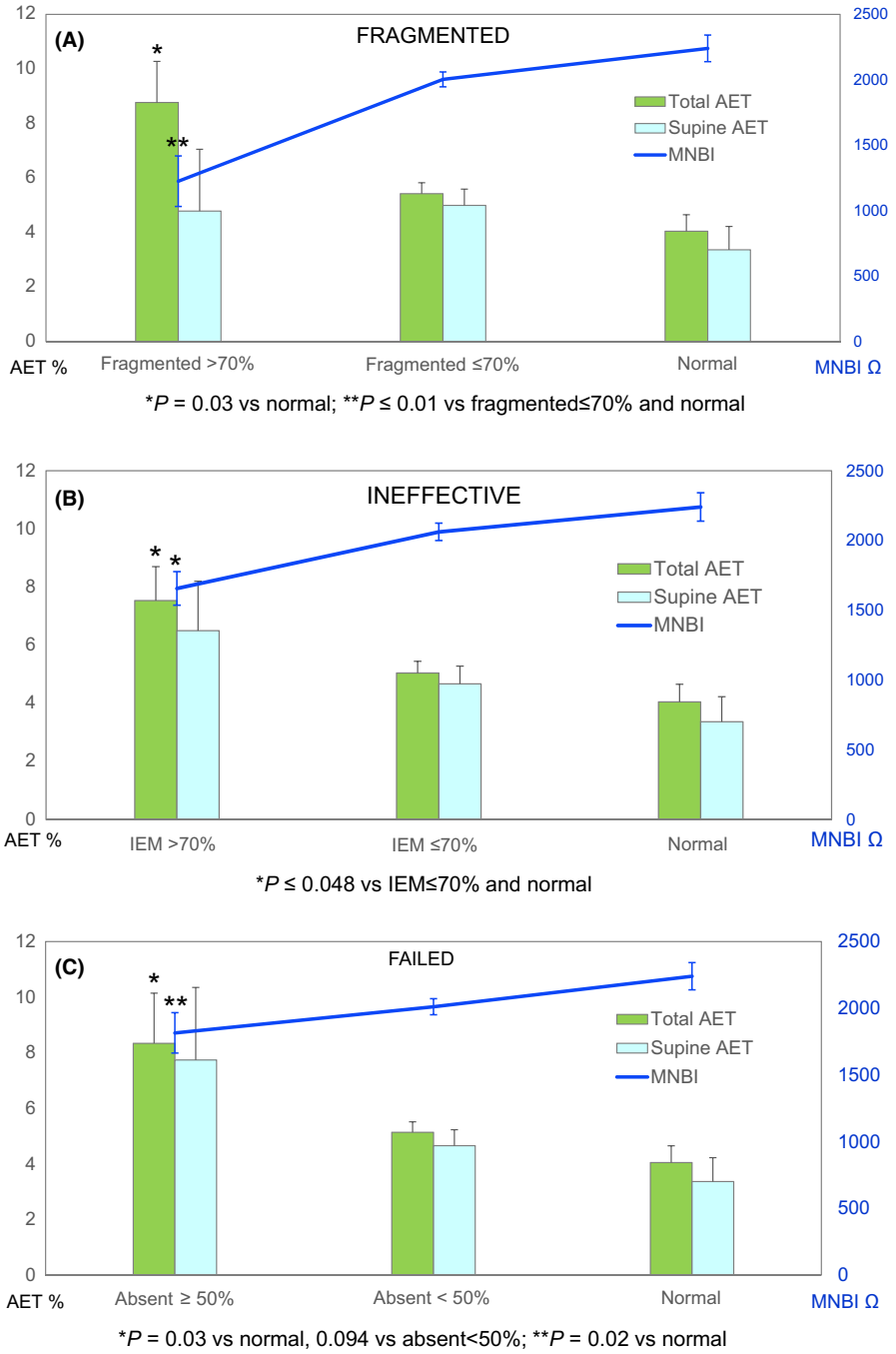


**FIGURE 2** Comparison of mean total acid exposure time (AET), supine AET, and mean nocturnal baseline impedance (MNBI) between threshold proportions of fragmented, ineffective, and failed sequences, compared to normal: A, fragmented sequences, where >70% fragmentation was associated with higher reflux burden compared to normal manometry; B, ineffective sequences, where >70% ineffective sequences (severe IEM) was associated with higher reflux burden compared to both ≤70% ineffective sequences and normal manometry; and C, failed sequences, where ≥50% failed sequences were associated with higher reflux burden compared to normal manometry

**TABLE 3** Comparison of motor parameters between patients with abnormal and normal reflux physiology

| | Abnormal physiology | Normal physiology | |
|---|---|---|---|
| | n = 59 | n = 72 | *P* value |
| Fragmented (≥50%) | 6 (10.3%) | 2 (2.8%) | .14 |
| Fragmented (>70%) | 2 (3.4%) | 0 | .20 |
| Weak (≥50%) | 7 (11.9%) | 4 (4.6%) | .22 |
| IEM (≥50%) | 23 (39.0%) | 13 (18.1%) | .01 |
| IEM (>70%) | 15 (25.4%) | 6 (8.3%) | .02 |
| Failed (≥50%) | 11 (18.6%) | 6 (8.3%) | .12 |
| Absent (100%) | 5 (8.5%) | 2 (2.8%) | .24 |
| Intact | 12 (21.3%) | 30 (41.7%) | .01 |

*Note:* Abnormal physiology includes all of acid exposure time >6%; mean nocturnal baseline impedance <2292 ohms and the presence of either type 2 or type 3 esophagogastric junction morphology. Normal physiology includes the absence of all of these same parameters.
Abbreviation: IEM, ineffective esophageal motility.

spectrum where degree of peristaltic dysfunction correlates with abnormal reflux burden. We demonstrate that failed peristalsis is a category distinct from weak peristalsis, wherein ≥50% peristaltic failure associates with higher reflux burden, and absent contractility represents the most severe form. Using a > 70% threshold, categorization of fragmented peristalsis and IEM into "mild" and "severe" is clinically relevant, and these findings may have implications on the next versions of the Chicago Classification and classification of motor findings in GERD. Finally, these findings show how assessment of esophageal motor patterns can complement measurement of both cross-sectional and longitudinal reflux burden on esophageal pH-impedance monitoring, and demonstrate the need for further research.

## CONFLICTS OF INTEREST

No conflicts of interest exist. There was no funding for this study.

## DISCLOSURES

BR, AR, AM, MG, RP, MR, MC, NdB have no disclosures; received consulting fees from ES Abbvie, Allergan, MSD, Takeda, Sofar, and Janssen; speaking and teaching fees from Medtronic, Reckitt-Benckiser, Malesci, and Zambon; teaching and consulting fees from CPG: Medtronic, Diversatek; consulting fees from Ironwood, Quintiles.

## AUTHOR CONTRIBUTION

BR, AR, AM, MG, RP, MR, MC, NdB: no disclosures; ES Abbvie, Allergan, MSD, Takeda, Sofar, and Janssen (consulting); Medtronic, Reckitt-Benckiser, Malesci, and Zambon (speaking and teaching); CPG: Medtronic, Diversatek (teaching and consulting), Ironwood, Quintiles (consulting).

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