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The impact of primary peristalsis, contractile reserve, and secondary peristalsis on esophageal clearance measured by timed barium esophagogram

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Abstract

Background: Primary and secondary peristalsis facilitate esophageal bolus transport; however, their relative impact for bolus clearance remains unclear. We aimed to compare primary peristalsis and contractile reserve on high-resolution manometry (HRM) and secondary peristalsis on functional lumen imaging probe (FLIP) Panometry with emptying on timed barium esophagogram (TBE) and incorporate findings into a comprehensive model of esophageal function.

Methods: Adult patients who completed HRM with multiple rapid swallows (MRS), FLIP, and TBE for esophageal motility evaluation and without abnormal esophagogastric junction outflow/opening or spasm were included. An abnormal TBE was defined as a 1-min column height >5 cm. Primary peristalsis and contractile reserve after MRS were combined into an *HRM–MRS model*. Secondary peristalsis was combined with primary peristalsis assessment to describe a complementary *neuromyogenic model*.

Key Results: Of 89 included patients, differences in rates of abnormal TBEs were observed with primary peristalsis classification (normal: 14.3%; ineffective esophageal motility: 20.0%; absent peristalsis: 54.5%; $p=0.009$), contractile reserve (present: 12.5%; absent: 29.3%; $p=0.05$), and secondary peristalsis (normal: 9.7%; borderline: 17.6%; impaired/disordered: 28.6%; absent contractile response: 50%; $p=0.039$). Logistic regression analysis (akaike information criteria, area under the receiver operating curve) demonstrated that the neuromyogenic model (80.8, 0.83) had a stronger relationship predicting abnormal TBE compared to primary peristalsis (81.5, 0.82), contractile reserve (86.8, 0.75), or secondary peristalsis (89.0, 0.78).

Conclusions and Inferences: Primary peristalsis, contractile reserve, and secondary peristalsis were associated with abnormal esophageal retention as measured by TBE.

Abbreviations: AC, absent contractility; ACR, absent contractile response; BEDQ, Brief Esophageal Dysphagia Questionnaire; CCv4, Chicago Classification version 4.0; DCI, distal contractile index; DI, distensibility index; EGJ, esophagogastric junction; FLIP, functional lumen imaging probe; GERDQ, gastroesophageal reflux disease questionnaire; HRM, high-resolution manometry; IEM, ineffective esophageal motility; IRP, integrated relaxation pressure; LA, Los Angeles; MRS, multiple rapid swallows; NM, neuromyogenic; TBE, timed barium esophagogram.

Added benefit was observed when applying comprehensive models to incorporate primary and secondary peristalsis supporting their complementary application.

KEYWORDS
achalasia, dysphagia, GERD, impedance

1 | INTRODUCTION

Esophageal high-resolution manometry (HRM) is often considered the standard to evaluate esophageal motility disorders.[1–3] According to the Chicago Classification version 4.0 (CCv4), interpretation first focuses on disorders of esophagogastric junction (EGJ) outflow, such as achalasia, by evaluating for an abnormally elevated integrated relaxation pressure (IRP).[1] Once disorders of EGJ outflow are excluded, evaluation then focuses on disorders of peristalsis.[1] Provocative tests during HRM, such as multiple rapid swallows (MRS) with assessment of contractile reserve, allow for additional assessment that may enhance the evaluation of esophageal motor function.[4] More recently, functional lumen imaging probe (FLIP) Panometry was introduced as an adjunctive tool to evaluate esophageal motility during sedated endoscopy.[5,6] FLIP Panometry uses high-resolution impedance planimetry to measure lumen dimensions along the length of the esophagus and the distensibility during volumetric distension. FLIP Panometry has shown promise to identify major esophageal motility disorders, particularly achalasia.[6] Contractile response patterns of the esophageal body on FLIP Panometry were found to parallel primary peristalsis assessed by HRM, and a classification scheme on FLIP Panometry also paralleled motility evaluation with the CCv4 on HRM.[7,8]

Although HRM and FLIP are complementary and have shared features in assessing esophageal motility, they can demonstrate discordant findings. This can be explained partly by their assessment of different components of esophageal function, primary peristalsis by HRM and secondary peristalsis in response to volumetric distension by FLIP.[7,9] Timed barium esophagogram (TBE) can also act as an objective measure of esophageal function (bolus clearance) that is independent of HRM and FLIP.[3,9–13] Previously, in a study including patients with disorders of EGJ outflow, both FLIP and HRM were shown to be good predictors of esophageal emptying on TBE, although FLIP metrics of EGJ opening were superior to the integrated relaxation pressure (IRP) on HRM.[14]

In patients without evidence of obstruction at the EGJ, but with poor bolus clearance, the impact of primary peristalsis, contractile reserve, and secondary peristalsis on esophageal emptying is less clear. Bolus clearance is the essential esophageal function and is impacted by impaired peristalsis and a lack of propulsion.[15,16] The goal of this study was to evaluate the impact of primary peristalsis (HRM), contractile reserve on multiple rapid swallows (MRS), and secondary peristalsis (FLIP) on esophageal clearance based on TBE in the context of normal EGJ function.

Key points

- Primary peristalsis and contractile reserve assessed by high-resolution manometry and secondary peristalsis assessed by the functional lumen imaging probe are all associated with esophageal emptying as measured by timed barium esophagogram.
- The predictive value of esophageal emptying improved when combining primary and secondary peristalsis into a comprehensive model of esophageal function.
- This study supports the complementary use of high-resolution manometry, the functional lumen imaging probe, and timed barium esophagogram in assessment of esophageal function.

2 | MATERIALS AND METHODS

2.1 | Subjects

Adult patients (ages 18–89 years) who presented to the Esophageal Center of Northwestern for evaluation of esophageal symptoms and motility testing between November 2012 and September 2021 were prospectively evaluated and data maintained in an esophageal motility registry. Consecutive patients who completed HRM with MRS, FLIP during sedated endoscopy, and TBE for evaluation of primary esophageal motility disorders were included. Evaluation with TBE was obtained at the discretion of the treating gastroenterologist. Patients were excluded if they had technically difficult FLIP or HRM studies. Patients with previous foregut surgery (including pneumatic dilation), esophageal mechanical obstruction such as esophageal stricture, eosinophilic esophagitis, severe reflux esophagitis defined as Los Angeles (LA) classification C or D, or hiatal hernia >3 cm were excluded because these causes are attributed to secondary esophageal motor abnormalities. As the study focus was to assess the association of primary peristalsis and contractile reserve on HRM and secondary peristalsis on FLIP with esophageal emptying on TBE independent of EGJ functional obstruction and spastic contractility disorders, only patients with CCv4 diagnoses of normal motility, ineffective esophageal motility (IEM), and absent contractility and FLIP Panometry findings of normal EGJ opening and without a spastic-reactive contractile response were included (Figure S1; Tables S1 and S2). That is, patients with CCv4 disorders of EGJ outflow (achalasia types I, II, and III, EGJ outflow obstruction), distal esophageal spasm, and hypercontractile esophagus were excluded, as were patients with reduced or borderline EGJ opening (EGJ-DI <2.0 mm^2/mm Hg or maximum EGJ diameter <16 mm). The study protocol was approved by the Northwestern University Institutional Review Board. There is overlap of this patient cohort with previous publications.[6–8,14,17]

2.2 | HRM protocol and analysis

High-resolution manometry studies were completed after a 6-h fast using a 4.2-mm outer diameter solid-state assembly with 36 circumferential pressure sensors at 1-cm intervals (Medtronic). The HRM assembly was placed transnasally and positioned to record from the hypopharynx to the stomach with approximately three intragastric pH sensors. After a 2-min baseline recording, the HRM protocol was performed with ten, 5-mL liquid swallows in a supine position and then five, 5-mL liquid swallows and two MRS sequences (five swallows of 2 mL liquid at 2–3 s intervals) in an upright, seated position.[6] High-resolution manometry studies were analyzed according to the Chicago Classification v4.0 and blinded to clinical characteristics, for example, FLIP and TBE findings (Table S1).[1] The IRP and the distal contractile integral (DCI) were measured using the commercial software (Medtronic) for the 10 supine and 5 upright swallows and the median values for each position were applied. Normal MRS augmentation ("contractile reserve") was defined when the DCI after MRS (greatest value between MRS sequences) was greater than mean DCI of the supine test swallows, that is, MRS-DCI: mean DCI ratio >1.0.

2.3 | FLIP protocol and analysis

The FLIP study was performed during sedated endoscopy using a 16-cm FLIP catheter (EndoFlip EF-322N; Medtronic) and analyzed as previously described.[6,18,19] Endoscopy was performed in the left-lateral decubitus position and generally with midazolam and fentanyl. Other medications, for example, propofol, were used with monitored anesthesia at the discretion of the performing endoscopist in some cases. Although these medications used for endoscopic sedation can alter esophageal motility, the patterns of motility during the FLIP protocol are reproducible and shown to predict motility patterns on HRM performed without these medications.[6,19–21] After withdrawal of the endoscope and calibration to atmospheric pressure, the FLIP was placed transorally and positioned in the esophagus with 1–3 impedance sensors beyond the EGJ. This positioning was maintained throughout the FLIP study. Beginning with 40 mL, stepwise 10-mL FLIP distensions were performed increasing to a target volume of 60 or 70 mL. Each stepwise distension volume was maintained for 30–60 s.

FLIP data were exported using a customized program (available open source at http://www.wklytics.com/nmgi) to generate FLIP Panometry plots for analysis. FLIP analysis was performed blinded to clinical characteristics including HRM and TBE findings.[9,22] Analysis of the EGJ specifically focused on the EGJ-distensibility index (DI) at the 60-mL FLIP fill volume and the maximum EGJ diameter achieved during the 60 or 70 mL fill volume as previously described.[18] The classification of EGJ opening with FLIP Panometry used prespecified classifications based on previous evaluation of asymptomatic volunteers and patients (Table S2).[18,19,23] Esophageal body contractility was identified by transient decreases in the luminal diameter spanning at least 3 cm in length, with distinct antegrade contractions spanning ≥6 cm in length. Studies were reviewed for specific features and patterns of contractility and then applied to a CR pattern (Table S2).[7] FLIP pressure was measured as the median of pressure values over the duration of the 60 mL fill volume.

2.4 | Integration of HRM and MRS findings into a combined model of esophageal function

To assess the combined effects of primary peristalsis measured by HRM and contractile reserve measured by MRS, the peristalsis classification by HRM (per CCv4) and presence of contractile reserve by MRS were combined into a single model described as the "HRM-MRS model" (Table 1). This model attempts to categorize esophageal function based on these two different but related studies which assess primary peristalsis and the ability of the esophagus to generate a robust contraction after sustained deglutitive inhibition (contractile reserve). The model has four categories spanning from normal

TABLE 1 Combination of HRM and FLIP contractility classifications into a *neuromyogenic model* assessing the combination of primary and secondary peristalsis.

HRM–MRS model classification	HRM CCv4 classification	MRS contractile reserve
Normal	Normal	Present
Stage 1	Normal	Absent
	IEM	Present
Stage 2	IEM	Absent
	Absent	Present
Stage 3	Absent	Absent
Neuromyogenic model classification	**HRM CCc4 classification**	**FLIP contractility classification (contractile response)**
Normal	Normal	Normal or borderline
	IEM	Normal
Ineffective-stage I (IEM/AC-I)	Normal	Impaired/disordered or absent
	IEM	Borderline
Ineffective-stage II (IEM/AC-II)	IEM	Impaired/disordered or absent
	Absent	Borderline or impaired/disordered
Stage III: Absent (AC/ACR)	Absent	Absent

Abbreviations: AC, absent contractility; ACR, absent contractile response; FLIP, functional lumen imaging probe; HRM, high-resolution manometry; IEM, ineffective esophageal motility; MRS, multiple rapid swallows.

to abnormal contractile function. "Normal" classification required normal primary peristalsis on HRM and the presence of contractile reserve on MRS, and "Stage 3" classification was characterized by absent peristalsis and the absence of contractile reserve on MRS. Two categories, "Stage 1" and "Stage 2," stratified patients with intermediate findings of primary peristalsis and contractile reserve on MRS.

2.5 | Integration of HRM and FLIP findings into a neuromyogenic model of esophageal function

To assess the combined effects of primary peristalsis measured by HRM and secondary peristalsis measured by FLIP, the HRM and FLIP peristalsis classifications were combined into a single model described as the neuromyogenic model (Table 1). This model attempts to categorize esophageal function based on the combined findings of these two independent studies. The model has four classifications, spanning the spectrum from normal primary and secondary peristalsis to abnormal. Normal contractility on the neuromyogenic model required the presence of intact primary and secondary peristalsis. "Absent" contractility (AC) on the neuromyogenic model (Stage III: absent, AC/ACR) was defined by the absence of both primary and secondary peristalsis. Two categories, ineffective-stage I (IEM/AC-I) and ineffective-stage II (IEM/AC-II), further stratified patients with intermediate findings of primary and secondary peristalsis.

2.6 | TBE protocol and analysis

During timed barium esophagogram, patients were in the upright position and consumed 200 mL of low-density barium sulfate with images obtained at 1 and 5 min.[24] The height of the barium column was measured vertically from the EGJ. Abnormal TBE was defined by a column height >5 cm at 1-min.[12] Patients with abnormal TBE were further categorized by a 5-min column height >5 cm.[12,25]

2.7 | Patient-reported outcomes

Most subjects completed validated self-reported symptom scores at the time of baseline testing with FLIP and HRM including the Brief Esophageal Dysphagia Questionnaire (BEDQ) and the gastroesophageal reflux disease questionnaire (GerdQ).[26,27] Because some patients chose not to complete the symptom questionnaires, these were not available for all subjects. The BEDQ included eight 6-point Likert scale questions (scored 0–5) that assessed the frequency and severity of dysphagia over the preceding 14 days; items were summed to yield scores ranging from 0 (asymptomatic) to 40, with greater scores indicating greater dysphagia severity.[26] The GerdQ is a 6-item self-report measure used to support GERD diagnosis. The items assess the frequency of symptoms and medication use over the preceding 7 days and the GerdQ score is generated by summing four graded Likert scale items of four positive predictors (scored 0–3) and two reverse Likert scale items of negative predictors (scored 3–0).[27]

2.8 | Statistical analysis

Results were reported as mean (SD) or median (interquartile range) depending on the data distribution. Groups were compared with the chi-square (χ^2) test for categorical variables and ANOVA/*t* tests or Kruskal–Wallis/Mann–Whitney *U* for continuous variables, depending on the data distribution. Binary logistic regression was used to assess prediction of an abnormal TBE defined by a TBE column height >5 cm at 1 min. The TBE outcome of column height >5 cm at 5 min was not applied as an independent outcome for regression analysis based on the sample size of $n=7$. Because of the correlation between CCv4 classifications, presence of contractile reserve on MRS, contractile response (CR) pattern on FLIP, and the HRM–MRS and neuromyogenic model classes, we fit separate logistic regression models for each set of variables; these models additionally adjusted for age, sex, and presence of hiatal hernia (HH). We compared the akaike information criteria (AIC) of these models, as well as the within-sample areas under the receiver operating characteristic curve (AUROC) for each model. Akaike information criteria is an information-theoretic measure of prediction error for statistical models. AIC quantifies the relative information loss of statistical models, and hence models with smaller AIC values are interpreted as fitting the data better than models with larger AIC. Unless otherwise specified, a two-tailed *p* value <0.05 was considered to meet statistical significance.

3 | RESULTS

3.1 | Subjects

Eighty-nine patients with a mean age (SD) of 49.5 (16.5) years and 73% female were included (Table 2; Figure S1). Of the 89 patients, 71 (80%) had a normal TBE and 18 (20%) had an abnormal TBE with 1-min TBE column height >5 cm. Of the 18 abnormal TBEs, 7 (39%) patients also had a 5-min TBE column height >5 cm. Among the 71 patients with a normal esophagogram, there were 5 patients with a column height >0 cm but <5 cm at 1-min and the remainder had no barium retention (0 cm). Seventy-two patients completed the BEDQ, 74 patients completed the GerdQ, and 67 patients completed both surveys. Symptoms as measured by the BEDQ and GerdQ were similar between patients with a normal and abnormal TBE (Table 2). The presence of a small hiatal hernia was more common in patients with TBE column height >5 cm at 5 min ($p=0.016$, Table 2).

3.2 | Primary peristalsis (high-resolution manometry) and association with TBE results

The most common classifications by CCv4 were normal in 63 (70.8%) patients, IEM in 15 (16.9%) patients, and absent in 11 (12.4%) patients (Figure 1). A significantly higher proportion of patients with a normal TBE had normal contractility on HRM compared to an abnormal TBE ($p=0.03$) and a significantly greater proportion of patients with an abnormal TBE had absent peristalsis on HRM

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TABLE 2 Cohort characteristics by timed barium esophagogram (TBE) findings.

Characteristics	All patients	Normal TBE	Abnormal TBE (1-min >5 cm)	Abnormal TBE (5-min >5 cm)
N, *n* (%)	89 (100)	71 (79.8)	11 (12.4)	7 (7.9)
Age, mean (SD), years[a]	49.5 (16.5)	46.7 (16.1)	57.3 (16.0)[b]	64.7 (9.1)[b]
Sex, female, *n* (%)	65 (73.0)	51 (71.8)	8 (72.7)	6 (85.7)
Symptoms				
BEDQ score, median (IQR) 72 patients	11.0 (6.0–17.0)	11 (6–17)	8 (6.5–12.0)	15 (11–27)
GerdQ score, median (IQR) 74 patients	6.0 (6.0–9.0)	6 (6–9)	8 (6–11)	9 (6–12)
Endoscopic findings, *n* (%)				
Erosive esophagitis: LA-A/LA-B	6 (7) / 3 (3)	3 (4.3)/ 3 (4.3)	1 (9.1)/ 0 (0)	2 (28.6)/ 0 (0)
Small hiatal hernia[a]	25 (28.4)	19 (27.1)	1 (9.1)	5 (71.4)[b]
HRM characteristics				
DCI, mmHg·s·cm, median (IQR)[a]	1128 (383–2104)	1286 (497–2213)	865 (366–1861)	35 (0–334)[b]
FLIP characteristics				
Pressure 60 mL, mmHg (SD)[a]	42.1 (12.5)	43.4 (12.1)	42.0 (12.0)	28.7 (9.68)[b]

Note: An abnormal TBE was defined and categorized as a 1-min column height >5 cm or a 5-min column height >5 cm. Percentages represent percent across columns.

Abbreviations: BEDQ, brief esophageal dysphagia questionnaire; DCI, distal contractile integral; FLIP, functional lumen imaging probe; GERDQ, gastroesophageal reflux disease questionnaire; LA, Los Angeles grade; MRS, multiple rapid swallows.

[a]*p*-value <0.05 on comparison across three TBE categories.

[b]*p* < 0.05 on pairwise comparison with normal TBE.

compared to a normal TBE ($p=0.002$). Pairwise differences in normal HRM and absent contractility on HRM were observed between normal TBE and abnormal TBE with 5-min column height >5 cm. There were two patients with a normal HRM and a TBE with 5-min column height >5 cm (one had contractile reserve after MRS and impaired/disordered contractile response on FLIP, the other had absent contractile reserve after MRS and borderline contractile response on FLIP). The median DCI was not significantly different between patients with a normal and abnormal TBE ($p=0.058$), although pairwise differences in median DCI were observed between normal TBE and abnormal TBE with 5-min column height >5 cm (Table 2). There were not differences in the presence of a HH or IRP (supine or upright swallows) on HRM and findings of a normal or abnormal TBE (Table S3). BEDQ score did not differ between the CC HRM classifications (Figure S2).

3.3 | Multiple rapid swallows and association with TBE results

When assessing the presence of contractile reserve on MRS, 48 (53.9%) patients had contractile reserve and 41 (46.1%) did not. More patients with a normal TBE had contractile reserve compared to patients with an abnormal TBE ($p=0.05$, Figure 1). There was a stepwise increase in the presence of contractile reserve when assessing relative to primary peristalsis by HRM Chicago Classification version 4.0, secondary peristalsis by FLIP, and esophageal emptying by TBE (Figures 1 and 2). BEDQ score did not differ between patients with or without contractile reserve (Figure S2)

3.4 | Model combining primary peristalsis (high-resolution manometry) and contractile reserve

When assessing esophageal function by the *HRM–MRS model*, 38 (42.7%) patients were classified as normal, 34 (38.2%) as Stage 1, 7 (7.9%) as Stage 2, and 10 (11.2%) as Stage 3. There was a difference in rates of abnormal TBE between the HRM-MRS stages ($p=0.008$), with pairwise differences between Stage 3 and Normal and Stage 3 and Stage 1, Figure 1 and Figure S3. BEDQ score did not differ between the HRM-MRS-stages (Figure S2)

3.5 | Secondary peristalsis (FLIP Panometry contractile response) and association with TBE results

Contractile response patterns were normal in 31 (34.8%) patients, borderline in 34 (38.2%) patients, impaired/disordered in 14 (15.7%) patients, and absent in 10 (11.2%) patients (Figure 1). There were differences in rates of abnormal TBE between the FLIP contractile response patterns ($p=0.039$): 90% of patients with a normal contractile response had a normal TBE (and zero patients with normal contractile response had a TBE with 5-min column height >5 cm), while 50% of patients (5/10 patients) with an absent contractile

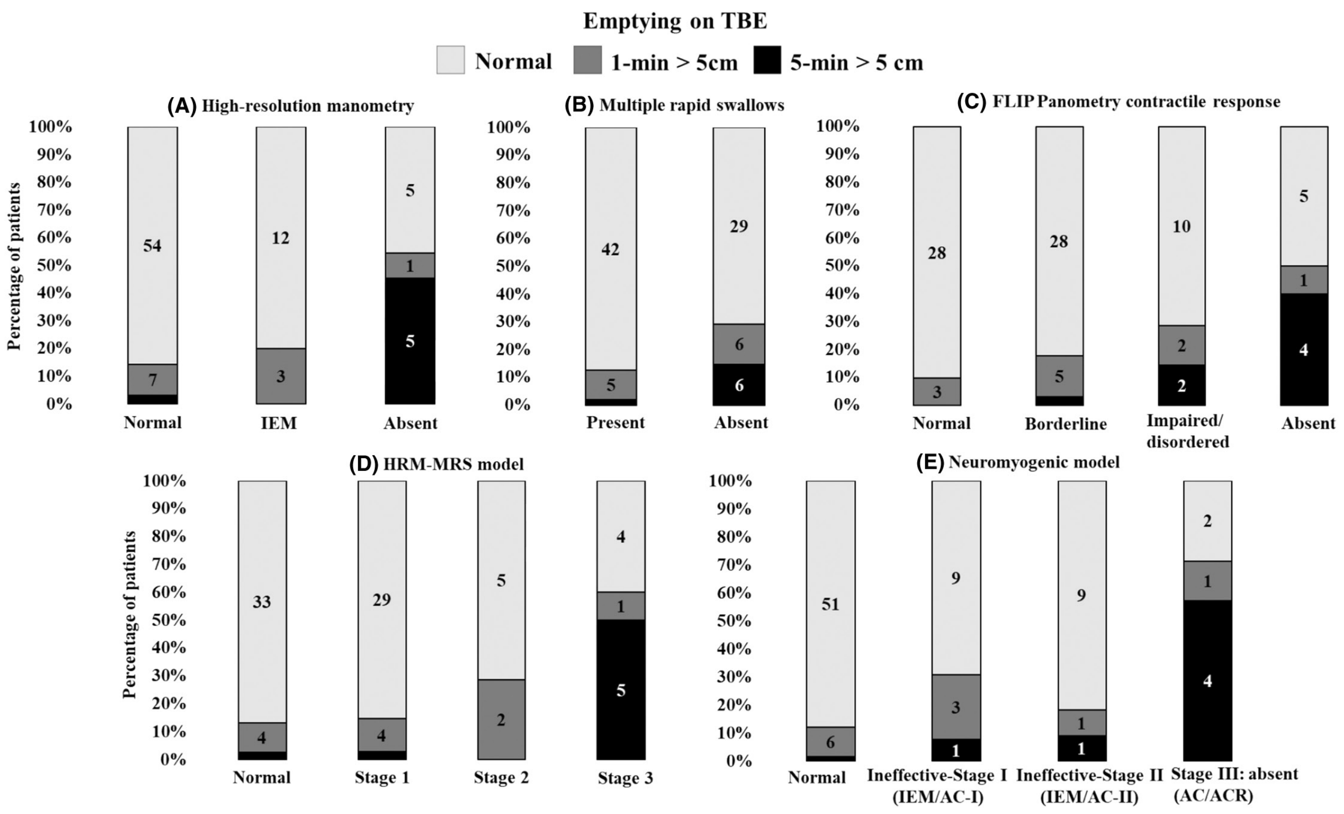

FIGURE 1 Association of esophageal retention with esophageal peristalsis. Emptying on TBE is assessed by HRM CCv4 classification (A), contractile reserve on multiple rapid swallows (B), FLIP Panometry contractile response classification (C), the HRM–MRS model (D), and the neuromyogenic (NM) model (E). Patients were stratified by abnormal TBE emptying at 1 min and abnormal emptying at 5 min.

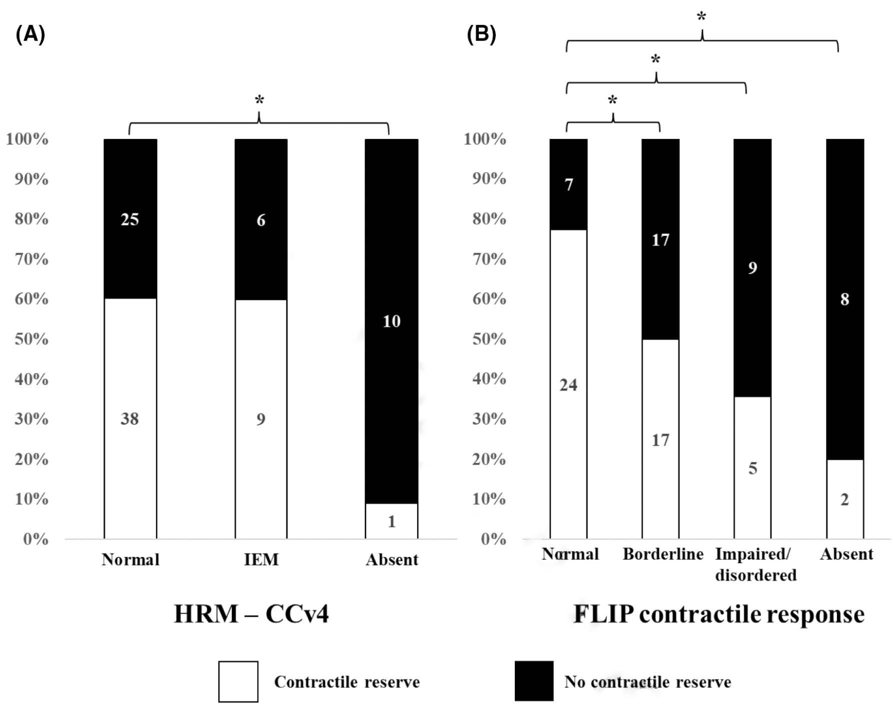

FIGURE 2 Association of contractile reserve on MRS with HRM Chicago classification version 4.0 (A) and FLIP contractile classification (B). There was stepwise increase in the presence of contractile reserve by HRM and FLIP classifications. *$p < 0.05$ on pairwise comparison. FLIP, functional lumen imaging probe; HRM, high-resolution manometry; IEM, ineffective esophageal motility; MRS, multiple rapid swallows.

response had an abnormal TBE (including 4/5 with a 5-min column height >5 cm).

The mean FLIP pressure at 60 mL balloon volume was greater in patients with a normal TBE ($p = 0.043$) compared to an abnormal TBE (Table 2) and there were no differences in maximum EGJ diameter or the EGJ distensibility index, between groups with normal and abnormal TBE (Table S3). BEDQ score did not differ between the FLIP contractile response patterns (Figure S2)

3.6 | Neuromyogenic model and association with TBE results

When assessing esophageal contractility by the neuromyogenic model, 58 (65.2%) patients were classified as normal, 13 (14.6%) patients as ineffective-stage I (IEM-AC-1), 11 (12.4%) patients as ineffective-stage II (IEM-AC-2), and 7 (7.9%) patients as Stage III: absent (AC/ACR). There was a difference in rates of abnormal TBE between the HRM–MRS stages ($p=0.002$), with pairwise differences between Stage III: absent and normal, Figure 1. More patients with a normal TBE had a normal classification compared to an abnormal TBE ($p=0.009$) and more patients with an abnormal TBE had Stage III: Absent classification compared to a normal TBE ($p<0.001$); Figure 1. Pairwise differences were detected by neuromyogenic model classifications normal and Stage III: absent between normal TBE and abnormal TBE with 5-min column height >5 cm. BEDQ score did not differ between the neuromyogenic model classifications (Figure S2).

3.7 | Predictors of esophageal emptying on TBE

Across the five logistic regression models, the regression that incorporated the neuromyogenic model exhibited the lowest AIC (80.8) and highest AUROC (AUROC = 0.83, 95%CI = [0.71, 0.95]) relative to the models for CCv4 (AIC = 81.5; AUROC = 0.82 [0.70, 0.95]), contractile reserve on MRS (AIC = 86.8, AUROC = 0.75, [0.61, 0.89]), HRM-MRS model (AIC = 82.1, AUROC = 0.83, [0.70, 0.95]), and FLIP Panometry contractile response classification (AIC = 89.0, AUROC = 0.78, [0.65, 0.92], Table 3).

4 | DISCUSSION

The main findings of this study focused on the relationships of primary peristalsis, contractile reserve, and secondary peristalsis with esophageal clearance on TBE was that each of these distinct, yet related, components of esophageal function were associated with abnormal esophageal emptying. Furthermore, when incorporating assessment of primary and secondary peristalsis into a comprehensive model of esophageal function, that is, the *neuromyogenic model*, this outperformed the individual assessments and the HRM–MRS model and supports the complementary use of HRM and FLIP in evaluation of patients with esophageal symptoms. By only including patients with normal EGJ outflow/opening metrics and without spasm on HRM or FLIP, this study uniquely isolated the impact of peristalsis on esophageal emptying. Esophageal retention on TBE was observed among this non-achalasia/non-spasm patient cohort, including even in patients with normal HRM. These patients, however, had abnormal findings on MRS and/or FLIP, suggesting that perhaps functional dysphagia (Rome IV) should not be defined by a normal EGD and HRM, but also incorporate FLIP and/or TBE to provide a comprehensive evaluation of esophageal function.[28]

Esophageal peristalsis is important in esophageal bolus clearance and emptying. Previous studies evaluating the association of esophageal peristalsis on conventional manometry and esophagogram have shown good agreement and their complementary features.[29,30] In a study of patients with nonobstructive dysphagia and heartburn, a normal peristaltic wave on manometry resulted in 100% clearance of barium from the esophagus, whereas absent, incomplete, or hypotensive peristaltic complexes were associated with poor volume clearance and retrograde escape.[31] Studies have also compared esophageal motility on HRM with intraluminal impedance and bolus clearance. There was a stepwise improvement in complete bolus transit between the HRM classifications absent contractility, IEM, and normal motility.[32] Thus while our findings corroborate these studies by similarly demonstrating an association between peristalsis on manometry and bolus clearance on esophagogram, our study is novel and rigorous in that it incorporates multiple measures of esophageal function (primary peristalsis and contractile reserve on HRM, secondary peristalsis on FLIP), as well as using the barium column height on TBE, an additional measure of esophageal retention, as an endpoint of bolus transit.

Primary peristalsis provides the primary mechanism for esophageal emptying with ingestion, and appropriately was the stronger predictor of esophageal emptying compared to secondary peristalsis in this study. Hence, as esophagogram is a measure of esophageal clearance associated with swallowing (i.e., primary peristalsis), this was not an unexpected finding. However, secondary peristalsis plays an important protective role, such as when primary peristalsis is ineffective and/or for clearance of gastroesophageal reflux.[33] Studies by Schoeman and Holloway using conventional manometry and focal esophageal distension demonstrated that in patients with reflux disease and dysphagia (as well as in healthy controls), secondary peristalsis was triggered less frequently than primary peristalsis.[34–36] Primary peristalsis contributes to esophageal emptying on timed barium esophagogram through clearance of the swallowed bolus with a primary peristaltic wave and secondary peristalsis contributes through clearance of escaped bolus or refluxed contrast. Contractile reserve, that is, the ability of the esophagus to generate a robust contraction after the MRS sequence, also appears to represent an important aspect of esophageal function with the absence of contractile reserve being associated with late postoperative dysphagia and with the new development of or persistence of IEM after anti-reflux surgery.[4,37,38]

Primary peristalsis assessed during HRM is mediated by vagal innervation in response to a swallow and secondary peristalsis during FLIP is mediated by distension-induced signaling in response to distension of the FLIP balloon. Although these processes have overlapping neural pathways, disorders can occur in one without affecting the other.[39] In addition to impaired neural triggering, weak/impaired contractions may also indicate impaired *myogenic* function of the esophagus, with absent neural and myogenic function indicating severe dysfunction. C*ontractile reserve*, that is, the ability of the esophagus to generate a robust contraction after the MRS sequence, is indicative of intact myogenic

TABLE 3 Logistic regression models for prediction of esophageal emptying on timed barium esophagogram.

	HRM-CCv4 Model	Contractile reserve model	FLIP contractile response model	HRM–MRS model	Neuromyogenic model
Variable					
Age	0.07 (0.02)	0.06 (0.02)	0.05 (0.02)	0.07 (0.02)	0.06 (0.03)
Sex (male)	−0.32 (0.76)	−0.09 (0.68)	−0.32 (0.71)	−0.25 (0.78)	−0.03 (0.77)
Small hiatal hernia (present)	−1.26 (0.96)	0.02 (0.63)	−0.43 (0.75)	−1.30 (0.95)	−1.43 (1.11)
HRM Chicago Classification v4.0					
Normal [reference]					
Ineffective	0.50 (0.86)				
Absent	2.94 (1.05)				
MRS contractile reserve					
Present [reference]					
Absent		0.90 (0.60)			
FLIP Panometry contractile response					
Normal [reference]					
Borderline			0.12 (0.81)		
Impaired/disordered			0.70 (093)		
Absent			1.83 (1.05)		
HRM–MRS model					
Normal [reference]					
Stage 1				0.77 (0.74)	
Stage 2				1.04 (1.13)	
Stage 3				3.15 (1.12)	
Neuromyogenic model					
Normal [reference]					
Stage I					1.28 (0.81)
Stage II					0.19 (1.01)
Stage III					3.84 (1.38)
AIC	81.5	86.8	89.0	82.1	80.8
AUROC (95% CI)	0.82 (0.70,0.95)	0.75 (0.61, 0.89)	0.78 (0.65, 0.92)	0.83 (0.70, 0.95)	0.83 (0.71, 0.95)

Note: Values reflect B (SE), unless otherwise stated. Separate logistic regression models were created for each variable, that is, primary peristalsis (high-resolution manometry [HRM]—Chicago Classification v4.0 [CCv4.0]), contractile reserve on multiple rapid swallows (MRS), secondary peristalsis/contractile response (functional lumen imaging probe, FLIP), the HRM–MRS model, and the neuromyogenic model. Multivariable models adjusted for age, sex, and presence of hiatal hernia (on HRM) and the akaike information criteria (AIC) and the within-sample areas under the receiver operating characteristic curve (AUROC) were compared.

function when observed.[4,40] The presence of secondary peristalsis supports both intact triggering and myogenic function in the presence or absence of primary peristalsis on HRM. Overall, this study demonstrates the potential value that arises from combined utilization of HRM (standard test swallows and MRS) and FLIP Panometry to provide a comprehensive, complementary evaluation of peristaltic function.

An initial iteration of a neuromyogenic model based on findings from HRM (including MRS) and FLIP was recently described in a study of 32 patients with systemic sclerosis (SSc).[17] The model aimed to reflect the pathogenesis of scleroderma involving progressive neural and myogenic dysfunction, with the most severe form demonstrating loss of both primary and secondary peristalsis which was associated with poor esophageal clearance (assessed using manometric impedance bolus height).[17] Thus, when both primary and secondary peristalsis are impaired, the patient is at greatest risk of impaired esophageal clearance.

Significant retention of barium on TBE (5-min column height >5 cm), a finding associated with achalasia, occurred in the absence of significant esophagogastric junction outflow obstruction among this study cohort demonstrating the importance of peristalsis as an independent factor in esophageal clearance. The severe esophageal retention was significantly more likely among patients with absent peristalsis on HRM, absence of contractile reserve, and absent contractile response on FLIP Panometry, and in particular when two or more were absent (Stage 3 HRM–MRS and Stage III of neuromyogenic model). This may also have implications in evaluating treatment outcomes (and need for subsequent treatment) in achalasia noting that esophageal retention can occur related to peristaltic dysfunction in the absence of EGJ obstruction. Thus, objective evaluation of EGJ function beyond TBE should be utilized to direct subsequent treatment in achalasia.[41]

While the primary aim of the study was to evaluate objective esophageal function using retention on TBE, it was also noted that dysphagia severity did not differ relative to the peristaltic classification models assessed. This is similar to the discordance observed between symptoms and objective measures of esophageal function, including those observed with achalasia and TBE.[13] This also reflects the complexity of esophageal symptom generation in which other factors such as hypervigilance and anxiety play a large role and will be necessary to incorporate into future analysis focused on symptom severity.[42]

This study also suggests that a normal EGD and HRM should not necessarily define functional dysphagia (Rome IV).[28] There were two patients with normal primary peristalsis, but that had varying defects in contractile reserve or secondary peristalsis (abnormal contractile responses) that had significant barium retention on TBE (>5 cm at 5 min). Thus, despite the standard 'normal' HRM, severe bolus retention found on TBE may be driving symptoms in these patients, which may be related to other defects in esophageal function. While isolated esophageal barium retention could warrant consideration as a false positive finding, this instead likely supports that a comprehensive evaluation with adjunctive testing including TBE and/or FLIP might identify other abnormalities to explain symptoms. Notably, no patients with a normal contractile response on FLIP had absent contractility on HRM or significant barium retention on TBE (>5 cm at 5 min), lending support to FLIP as a screening tool during index endoscopy for severe esophageal dysmotility. While the use of HRM, EGD with FLIP, and TBE is not necessary in all patients with esophageal symptoms, the study findings support the complementary nature of these tests. This may be particularly relevant in cases in which findings from one test are of uncertain clinical relevance (e.g., IEM on HRM) or can be helpful in select patients in which the etiology of symptoms remains unclear.

This study demonstrates multiple strengths related to the comprehensive evaluation involving HRM with MRS, FLIP, and TBE among a "pure cohort" (i.e., with EGJ/LES dysfunction or spasm excluded) to assess the impact of primary peristalsis, contractile reserve, and secondary peristalsis on esophageal emptying. However, the study also has limitations, with the main limitation likely being the application of retention on TBE as the primary outcome. While TBE offers the distinct advantage of being a measure of esophageal clearance that is independent of both HRM and FLIP, we recognize it is not a perfect "gold standard" tool to assess esophageal function. Further, there are other factors on esophagogram that may contribute to emptying, such as esophageal anatomy (e.g., tortuosity or dilatation) that were not directly accounted for in the present analysis, and thus future study is warranted to address these aspects. Another limitation is the relatively small number of patients with an abnormal esophagogram, which limits the power for comparative analysis between subgroups. Nevertheless, this is the largest study cohort to date describing patients with HRM and MRS, FLIP, and TBE with a specific focus on the impact of primary peristalsis, contractile reserve, and secondary peristalsis. Also, the patient population is one of a tertiary referral center and may somewhat limit generalizability to patients with esophageal symptoms in the community setting.

In conclusion, in this study of patients with normal EGJ opening metrics on HRM and FLIP and without spasm, we demonstrated the impact of primary peristalsis (HRM), contractile reserve (MRS), and secondary peristalsis (FLIP Panometry) on abnormal esophageal emptying defined by TBE. While each of these studies were associated with esophageal retention on TBE, we found that a complementary neuromyogenic model that incorporated both primary and secondary peristalsis improved predictive value for an abnormal esophagogram. This demonstrated the importance of primary peristalsis, contractile reserve, and secondary peristalsis in the physiology of esophageal emptying and bolus transit and supports the adjunctive use of complementary tools to assess esophageal function.

AUTHOR CONTRIBUTIONS

Andree H. Koop: study analysis, data interpretation, drafting the work, revising it critically for important intellectual content, final approval of the version to be published. Peter J. Kahrilas: data interpretation, critical revision, final approval of the version to be published. Jacob Schauer: study analysis, drafting the work, final approval of the version to be published. John E. Pandolfino: study conception and design, data interpretation, critical revision, final approval of the version to be published. Dustin A. Carlson: study conception and design, study analysis, data interpretation, drafting the work, revising it critically for important intellectual content, final approval of the version to be published.

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CONFLICT OF INTEREST STATEMENT

No competing interests declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request and completion of necessary privacy and ethical approvals.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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