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Multiple Rapid Swallow Maneuver Enhances the Clinical Utility of High-Resolution Manometry in Patients Showing Ineffective Esophageal Motility

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Abstract: The clinical significance of ineffective esophageal motility (IEM) together with multiple rapid swallow (MRS) has not been yet evaluated in the Chicago Classification v3.0. This study evaluated the adjunctive role of MRS in IEM and determined the criteria of abnormal MRS to maximize the utility of IEM. We analyzed 186 patients showing IEM or normal esophageal motility (NEM), who underwent esophageal high-resolution impedance–manometry for esophageal symptoms. Two different criteria for abnormal MRS were applied to IEM subjects, resulting in 2 corresponding subgroups: IEM-A when distal contractile integral (DCI) ratio between an average wet swallows and MRS contraction was <1 and IEM-B when MRS contraction DCI was <450 mm Hg-s-cm. One IEM subject inadequately performed MRS. Among the remaining 52 IEM subjects, 18 (34.6%) were classified into IEM-A and 23 (44.2%) into IEM-B. IEM subjects showed less complete bolus transit (median 0.0%, interquartile range 0.0–20.0% vs 60.0%, 30.0–80.0; $P < 0.001$) resulting in higher impaired bolus transit than NEM subjects (98.1% vs 66.9%, $P = 0.001$). IEM-B subjects showed additionally higher pathologic bolus exposure than NEM subjects (55.6% vs 29.3%, $P = 0.001$), whereas IEM-A subjects could not. Although IEM-B subjects had the highest prevalence of gastroesophageal reflux disease among the subjects groups, it did not reach statistical significance. In conclusion, IEM patients with abnormal MRS contraction have an increased risk of prolonged bolus clearance, poor bolus transit, and pathologic bolus exposure. IEM patients need to be assessed concerning whether MRS contraction DCI is <450 mm Hg-s-cm to segregate clinically relevant patients.

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Abbreviations: CC = Chicago Classification, DCI = distal contractile integral, GERD = gastroesophageal reflux disease, HRIM = high-resolution impedance-manometry, HRM = high-resolution manometry, IBT = impaired bolus transit, IEM = ineffective esophageal motility, IQR = interquartile range, IRP = integrated relaxation pressure, MRS = multiple rapid swallow, NEM = normal esophageal motility, PAE = pathologic acid exposure, PBE = pathologic bolus exposure, RE = reflux esophagitis.

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INTRODUCTION

High-resolution manometry (HRM) has been widely utilized for the clinical evaluation of esophageal motility.[1] The classification scheme for HRM, termed the Chicago Classification (CC), has evolved from conventional criteria and has improved the ability to make manometric diagnoses.[2,3] Subsequent researches have improved the diagnostic accuracy and utility of classification, resulting in the CC v3.0 update.[4,5] CC v3.0 adopted the term ineffective esophageal motility (IEM) popularized in conventional manometry, to replace the previous weak peristaltic abnormalities.

Traditionally, IEM was defined by distal esophageal contractions amplitude <30 mm Hg (ineffective swallows) in >30% of wet swallows.[6] The new definition of IEM (≥50% ineffective liquid swallows in the distal esophagus swallows) has a stronger association with bolus transit abnormalities and esophageal symptoms.[7] In HRM, the distal contractile integral (DCI) value <450 mm Hg-s-cm predicts ineffective swallow.[8] Accordingly, ineffective swallows in the CC v3.0 is defined as a DCI <450 mm Hg-s-cm with ≥50% ineffective swallows constituting IEM.[5] Although IEM is associated with ineffective bolus movement, its clinical significance remains unclear.[9] Thus, the HRM working group acknowledged the potential utility of multiple repetitive swallow assessment in patients with IEM to evaluate peristaltic reserve.[5]

Repetitive and rapid swallow results in inhibition of the progression of peristalsis by a subsequent swallow, after which a high-amplitude peristaltic wave propagates along the esophagus.[10,11] Understanding the physiology of esophageal peristalsis led to development of a simple multiple rapid swallow (MRS) maneuver to detect abnormalities in inhibitory and excitatory esophageal motor function.[12–14] When the contraction following the last swallow is weak in MRS, an impaired integrity of neural excitation and muscle is predicted. Postoperative dysphagia in patients undergoing antireflux surgery has been predicted according to the DCI ratio between average single swallow and MRS.[15] Strictly speaking, however, the DCI ratio would not predict effective swallow, but could reflect the peristaltic reserve. The optimal criteria of abnormal MRS in IEM need to be determined. Furthermore, the clinical utility of IEM together with MRS has not yet been evaluated in the CC v3.0. The present study was undertaken to evaluate the adjunctive role of MRS in IEM and to determine the criteria of abnormal MRS for maximizing the clinical utility of IEM.

MATERIALS AND METHODS

Subjects

We analyzed 186 consecutive patients showing IEM or normal esophageal motility (NEM) on HRM, who underwent esophageal high-resolution impedance-manometry (HRIM) for esophageal symptoms at Samsung Medical Center between November 2013 and February 2015. Patients who received upper gastrointestinal surgery were excluded. This study protocol was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board at Samsung Medical Center on June 29, 2015 (No. 2015–06–141). The institutional review board also plays a role as an ethical committee. As MRS is part of the standard esophageal HRM protocol for symptomatic patients in our motility laboratory, the informed consents from participants were not given in this retrospective observational study.

HRM Protocol

HRM was performed in the standard fashion with a series of 10 swallows of 5 mL normal saline with the subject in the supine position, using the HRIM system (Sandhill Scientific, Highlands Ranch, CO). The probe has 32 circumferential pressure sensors spaced 1 cm apart and 16 impedance channels with 2-cm spacing. Following a series of single swallows, rapid 5 swallows of 2 mL normal saline within 10 seconds were done also while in the supine position. All measurements were analyzed by using BioVIEW Analysis software (Sandhill Scientific) and were also reviewed manually. IEM and NEM were defined according to the CC v3.0.[5]

Twenty-Four-Hour Multichannel Intraluminal Impedance-pH Monitoring

For 24-hour impedance-pH monitoring, a single-use combined impedance and pH probe (Sandhill Scientific) was used. It consisted of a 2.1 mm polyurethane catheter with 6 impedance-measuring sites (3, 5, 7, 9, 15, and 17 cm above the manometrically determined upper margin of the lower esophageal sphincter) and a built-in pH probe positioned 5 cm above the upper margin of the lower esophageal sphincter. Patients were instructed to eat 3 meals per day and no liquids were allowed between meals. Patients were asked to keep a diary with the exact details of meals and of the supine and erect phases for the measurements. After completion of the measurements, probes were withdrawn from the subjects and data were stored via an interface on an IBM compatible computer. Data analysis was performed using the BioView MII software (Sandhill Scientific) and was also reviewed manually.

DEFINITIONS

Abnormal MRS contraction was defined when post-MRS contraction was weak. Two different criteria for weak MRS contraction were applied to IEM subjects, resulting in 2 corresponding IEM subgroups: IEM-A when DCI ratio between average 10 wet swallows and post-MRS contraction was <1 and IEM-B when DCI of post-MRS contraction was <450 mm Hg-s-cm (Figures 1 and 2). According to the 2 different criteria, some subjects showed the same MRS results and others did not (Figure 3).

Pathologic acid exposure (PAE) was defined as an intraesophageal pH of <4 for >4.2% of the recording time.[16] Pathologic bolus exposure (PBE) was defined as refluxate in contact with distal impedance electrodes for >1.4% of the recording time.[16] Impaired bolus transit (IBT) was defined as >20% liquid swallows with incomplete bolus transit.[17,18] Gastroesophageal reflux disease (GERD) was defined as the presence of PAE or reflux esophagitis (RE, at least grade A according to the Los Angeles classification[19]) on upper endoscopy. All endoscopic images were reviewed in consensus by 2 experienced endoscopists (Y.W.M. and I.S.).

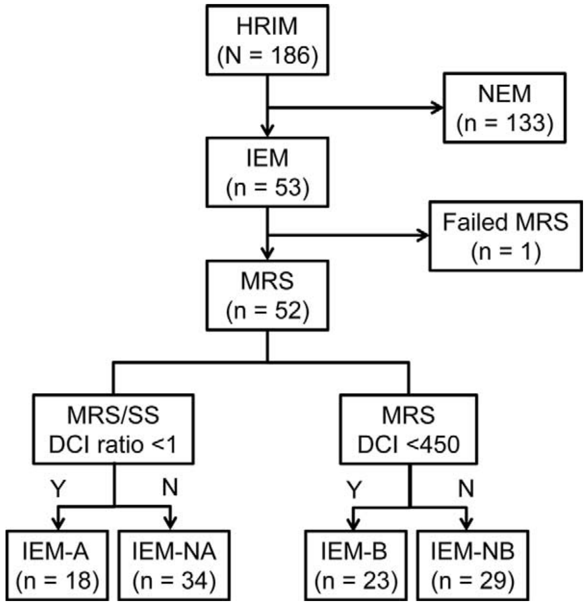

FIGURE 1. Subject flow. Three different criteria for abnormal MRS contraction was applied to IEM subjects, resulting in 2 corresponding IEM subgroups: IEM-A when DCI ratio between average 10 single swallows and MRS contraction was <1 and IEM-B when DCI of MRS contraction was <450 mm Hg-s-cm. IEM-NA and NB indicates IEM subjects who are not classified into IEM-A and B, respectively. DCI = distal contractile integral, HRIM = high-resolution impedance-manometry, IEM = ineffective esophageal motility, MRS = multiple rapid swallow.

Statistical Analyses

The statistical results are presented as the median with interquartile range (IQR) or number (percentages). Continuous variables were compared nonparametrically using the Mann–Whitney *U* test. Categorical variables were compared using the χ^2 test or Fisher exact test as appropriate. Wilcoxon signed-rank test was used to evaluate changes between DCI of single swallow and of MRS. A two-sided P value < 0.05 was considered statistically significant. Statistical analyses were conducted using the IBM SPSS statistical package 20.0 (IBM, Armonk, NY).

RESULTS

Subjects

In the study population of 186 subjects, 53 (28.5%) had IEM and 133 (71.5%) had NEM. Among the 53 IEM subjects, 1 (1.9%) inadequately performed MRS and was excluded from the analysis of MRS. According to the 2 different criteria for abnormal MRS contraction, 18 IEM subjects (34.6%) were classified into IEM-A and 23 (44.2%) into IEM-B (Figure 1). A total of 175 subjects (94.1%) had available

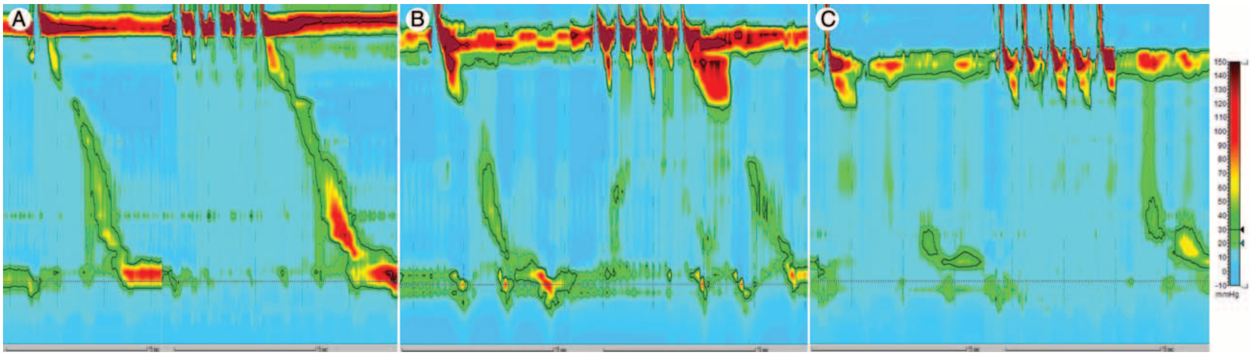

FIGURE 2. Typical manometric patterns of MRS in subjects with IEM. (A) Normal MRS. DCI ratio between average 10 single swallows and MRS contraction is 6.3 and DCI of MRS contraction is 1365 mm Hg-s-cm. (B) Abnormal MRS meeting both IEM-A and IEM-B. DCI ratio is 0.49 and DCI of MRS contraction is 133 mm Hg-s-cm. (C) Abnormal MRS meeting IEM-B but not IEM-A. DCI of MRS contraction is 365 mm Hg-s-cm, whereas DCI ratio is 6. DCI = distal contractile integral, IEM = ineffective esophageal motility, MRS = multiple rapid swallow.

endoscopic data and 138 (74.2%) underwent 24-hour multichannel intraluminal impedance (MII)-pH. No subject lacked both endoscopic and 24-hour MII-pH data Figure 4.

Demographics and Clinical Characteristics

There were no significant differences between subjects with NEM and subjects with IEM, and IEM with abnormal MRS in age, sex, height, weight, body mass index, and presence of diabetes and hypertension (Table 1). Chest pain/discomfort and globus were the most common reasons for request of HRM in all subjects. The prevalence of RE on endoscopy in subjects with IEM (12.0%) did not significantly differ from that in subjects with NEM (5.6%). Even IEM subjects with abnormal MRS (6.3% and 14.3% for IEM-A and B, respectively) did not show significantly different prevalence of RE compared with subjects with NEM.

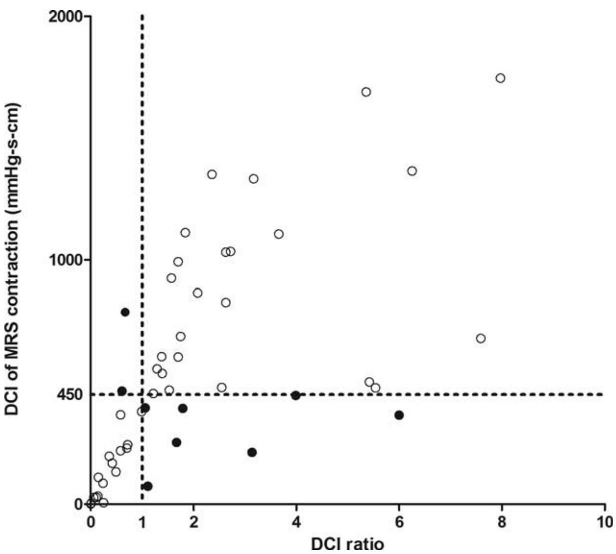

FIGURE 3. Scattergram of the relationship between DCI ratio between an average of 10 wet swallows and MRS contraction and DCI of MRS contraction in subjects with ineffective esophageal motility. Open circles indicate subjects who show agreement in the MRS result by DCI ratio and DCI value. Closed circles indicate those show the discrepant result between the 2 criteria. Four data points in the upper right quadrant are outside the axis limits. DCI = distal contractile integral, MRS = multiple rapid swallow.

Comparison of HRIM Data

Subjects with IEM (0.0%, IQR 0.0–20.0) and IEM with abnormal MRS (10.0%, IQR 30.0–80.0 and 0.0%, IQR 0.0–20.0 for IEM-A and B, respectively) presented with less complete bolus transit than subjects with NEM (60.0%, IQR 30.0–80.0, all $P < 0.001$), resulting in higher IBT rates in subjects with IEM, IEM-A, and IEM-B than subjects with NEM (98.1%, 100%, and 100% vs 66.9%, $P < 0.001$, $P = 0.004$, and $P = 0.001$, respectively; Table 2). Subjects with IEM had lower integrated relaxation pressure (IRP) value than subjects with NEM (10.3 mm Hg, IQR 7.6–12.5 vs 11.9 mm Hg, IQR 9.7–13.9, $P = 0.003$), whereas IEM patients with abnormal MRS (IEM-A and B) had similar IRP values with subjects with NEM.

Subjects with IEM (373.2 mm Hg-s-cm, IQR 219.4–443.5) and IEM with abnormal MRS (389.0 mm Hg-s-cm,

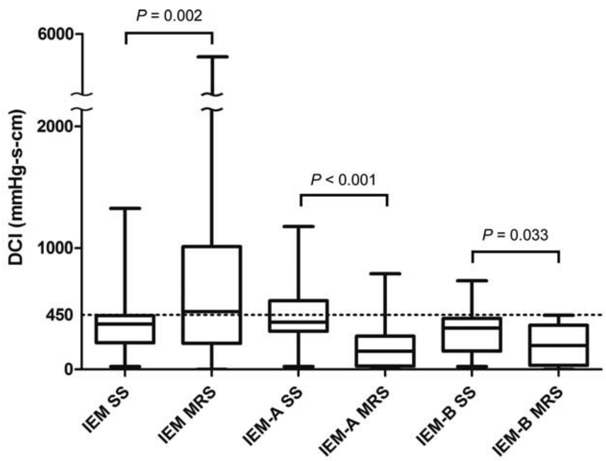

FIGURE 4. Distal contractile integral of average single swallow (SS) and MRS contraction in subjects with IEM and IEM with abnormal MRS contraction (IEM-A and B). Whisker extends to the minimum and maximum values. IEM = ineffective esophageal motility, MRS = multiple rapid swallow.

TABLE 1. Characteristics of Subjects With NEM, IEM, and IEM With Abnormal Multiple Rapid Swallow Contraction (IEM-A and B)

Variables	NEM (n = 133)	IEM (n = 53)	IEM-A (n = 18)	IEM-B (n = 23)	P^1	P^2	P^3
Age, y	55.0 (46.0–60.0)	53.0 (47.5–60.5)	53.5 (49.5–59.5)	54.0 (48.0–58.0)	0.905	0.938	0.954
Sex, male	58 (43.6%)	18 (34.0%)	6 (33.3%)	7 (30.4%)	0.227	0.408	0.237
Height, cm	160.0 (155.1–165.3)	163.0 (155.8–166.0)	163.6 (155.8–167.0)	161.4 (155.4–166.3)	0.301	0.470	0.710
Weight, kg	60.0 (52.8–66.0)	58.5 (54.0–69.9)	58.0 (52.6–63.6)	57.5 (51.7–61.4)	0.797	0.399	0.220
BMI, kg/m^2	23.5 (21.2–25.4)	23.3 (22.1–25.0)	21.6 (20.2–23.1)	21.9 (20.5–23.0)	0.877	0.111	0.107
Diabetes	8 (6.0%)	2 (3.8%)	0 (0.0%)	8 (6.0%)	0.727	0.597	1.000
Hypertension	24 (18.0%)	5 (9.4%)	1 (5.6%)	2 (8.7%)	0.144	0.310	0.371
Chief complaints					0.801	0.673	0.767
Chest pain/discomfort	60 (45.1%)	19 (35.8%)	8 (44.4%)	12 (52.2%)			
Globus	21 (15.8%)	12 (22.6%)	5 (27.8%)	6 (26.1%)			
Dysphagia	20 (15.0%)	10 (18.9%)	1 (5.6%)	2 (8.7%)			
Regurgitation	15 (11.3%)	6 (11.3%)	3 (16.7%)	2 (8.7%)			
Heartburn	10 (7.5%)	4 (7.5%)	1 (5.6%)	1 (4.3%)			
Others	7 (5.3%)	2 (3.8%)	0 (0.0%)	0 (0.0%)			
Reflux esophagitis	7 (5.6%)	6 (12.0%)	1 (6.3%)	3 (14.3%)	0.199	1.000	0.158

Data are shown as the median (interquartile range) or number (%) of patients.
BMI = body mass index, IEM = ineffective esophageal motility, NEM = normal esophageal motility.
$P^{1,2,}$and ^{3} for comparison between subjects with NEM and subjects with IEM, IEM-A, and B, respectively.

IQR 314.9–566.3 and 341.2 mm Hg-s-cm, IQR 151.5–421.1 for IEM-A and B, respectively) had lower mean DCI of single wet swallows than subjects with NEM (1541.3 mm Hg-s-cm, IQR 934.7–2449.2, all $P < 0.001$). In addition, IEM subjects with abnormal MRS could not increase DCI with MRS, whereas increased DCI was observed in the total subjects with IEM (Figure 3).

Comparison of 24-Hour MII-pH Data

Subjects with IEM presented with longer bolus clearance time than subjects with NEM (14.0 seconds, IQR 9.0–20.0 vs 10.0 seconds, IQR 7.0–14.0 $P < 0.001$), whereas there were no significant differences in acid exposure time, acid clearance time, presence of PAE, bolus exposure time, presence of PBE, reflux episode activity, and proximal extent. Although subjects with IEM-A showed similar results with subjects with IEM, those with IEM-B additionally showed significantly higher PBE rate than those with NEM (55.6% vs 29.3%, $P = 0.001$; Table 3).

Prevalence of GERD

Subjects with IEM had a similar prevalence of GERD as compared with subjects with NEM (10.5% vs 11.3%, $P = 0.583$). Although subjects with IEM-B (13.0%) had the highest prevalence of GERD among the subjects groups, that also did not show statistically significant difference from subjects with NEM ($P = 0.730$).

DISCUSSION

Although the terminology IEM for HRM revived in the CC v3.0, its clinical significance remains to be investigated. In addition, it is uncertain how MRS will be worked into IEM. Thus, we evaluated the clinical utility of IEM with optimally determined MRS. Subjects with IEM presented with longer bolus clearance time, less complete bolus transit, and more frequent IBT rate than those with NEM on 24-hour MII-pH; however, the presence of RE or the prevalence of GERD did not differ among subjects with IEM and NEM. When MRS was combined, IEM-A could not show more differences from subjects with NEM; however, IEM-B (IEM with DCI of MRS contraction <450 mm Hg-s-cm) subjects had a more frequent PBE rate than subjects with NEM. Taken together, for the first time according to the CC v3.0, the present study demonstrates that subjects with IEM have prolonged bolus clearance time and poor bolus transit as compared with subjects with NEM.

TABLE 2. Esophageal High-Resolution Impedance-Manometry Data of Subjects With NEM, IEM, and IEM With Abnormal Multiple Rapid Swallow Contraction (IEM-A and B)

Variables	NEM (n = 133)	IEM (n = 53)	IEM-A (n = 18)	IEM-B (n = 23)	P^1	P^2	P^3
Complete bolus transit, %	60.0 (30.0–80.0)	0.0 (0.0–20.0)	10.0 (30.0–80.0)	0.0 (0.0–20.0)	<0.001	<0.001	<0.001
Impaired bolus transit	88 (66.9%)	52 (98.1%)	18 (100%)	23 (100%)	<0.001	0.004	0.001
IRP, mm Hg	11.9 (9.7–13.9)	10.3 (7.6–12.5)	11.0 (8.7–13.9)	11.6 (8.3–13.8)	0.003	0.591	0.324
DCI, mm Hg-s-cm							
Single swallow	1541.3 (934.7–2449.2)	373.2 (219.4–443.5)	389.0 (314.9–566.3)	341.2 (151.5–421.1)	<0.001	<0.001	<0.001
Multiple rapid swallow	1379.0 (623.0–2447.0)	477.0 (216.0–1012.5)	150.5 (27.8–274.8)	197.0 (33.0–365.0)	<0.001	<0.001	<0.001

Data are shown as the median (interquartile range) or number (%) of patients.
DCI = distal contractile integral, IEM = ineffective esophageal motility, IRP = integrated relaxation pressure, NEM = normal esophageal motility.
$P^{1,2,}$ and ^{3} for comparison between subjects with NEM and subjects with IEM, IEM-A, and B, respectively.

TABLE 3. Twenty-Four Hour Multichannel Intraluminal Impedance-pH Monitoring Data of Subjects With NEM, IEM, and IEM With Abnormal Multiple Rapid Swallow Contraction (IEM-A and B)

Variables	NEM (n = 133)	IEM (n = 53)	IEM-A (n = 18)	IEM-B (n = 23)	P^1	P^2	P^3
Acid exposure time, pH <4.0, %	0.50 (0.00–1.70)	0.30 (0.00–1.50)	0.20 (0.00–2.00)	0.55 (0.08–2.10)	0.821	0.774	0.527
Mean acid clearance time, s	49.0 (16.0–97.0)	41.0 (12.0–94.0)	45.0 (12.0–101.0)	55.5 (19.5–103.3)	0.501	0.973	0.655
Pathologic acid exposure	8 (8.1%)	4 (10.3%)	1 (6.7%)	2 (11.1%)	0.740	1.000	0.651
Bolus exposure time, %	0.80 (0.40–1.50)	1.10 (0.70–1.90)	1.10 (0.70–1.90)	1.50 (0.98–2.13)	0.071	0.173	0.023
Pathologic bolus exposure	29 (29.3%)	16 (41.0%)	6 (40.0%)	10 (55.6%)	0.186	0.388	0.030
Bolus clearance time, s	10.0 (7.0–14.0)	14.0 (9.0–20.0)	16.0 (9.0–20.0)	15.5 (9.0–20.5)	<0.001	0.013	0.005
Reflux episode activity (n)	29.0 (16.0–42.0)	26.0 (18.0–49.0)	24.0 (18.0–60.0)	30.5 (20.3–58.5)	0.717	0.834	0.361
Proximal extent (n)	15.0 (6.0–23.0)	14.0 (8.0–24.0)	14.0 (10.0–28.0)	14.5 (11.0–37.0)	0.850	0.709	0.341

Data are shown as the median (interquartile range) or number (%) of patients.
IEM = ineffective esophageal motility, NEM = normal esophageal motility.
$P^{1,2,}$ and ^{3} for comparison between subjects with NEM and subjects with IEM, IEM-A, and B, respectively.

Furthermore, if DCI of MRS contraction is <450 mm Hg-s-cm, they also have an increased risk of PBE.

IEM appears to be linked with GERD. IEM has been found in 21% to 49.4% of patients with GERD.[20,21] In addition, IEM was more prevalent in patients with GERD-associated respiratory symptoms than GERD patients with no extraesophageal manifestations.[22] GERD has a complex and multifactorial pathogenesis.[23] Prolonged acid clearance from the esophagus of IEM seems the most relevant factor in the development of GERD.[24] Among GERD patients, longer esophageal acid exposure and clearance times have been shown in patients with IEM than those without.[20,21] Nevertheless, due to the limited diagnostic utility due to sensitivity or specificity issues, the guideline states that manometry is not indicated for making or confirming a suspected diagnosis of GERD.[25] In the present study, which employed the new criteria of IEM according to the CC v3.0, the prevalence of GERD and RE did not differ between subjects with IEM and those with NEM. Similar results have also been reported in a large cohort of patients with IEM according to its conventional criteria.[9] The presence or severity of IEM was not correlated with the presence of abnormal esophageal acid exposure. Thus, adjunctive tests of IEM seem still to be needed to increase clinical utility.

Patients with subtle or intermittent esophageal symptom often result in a normal manometry study. On the contrary, some patients might show IEM due to a relative weak stimulation produced by single water swallow during a manometry. In these cases, provocative maneuvers could increase the diagnostic yield and accuracy.[13,26,27] Weak contraction following the last swallow is predictive of impaired integrity of neural excitation and muscle.[10,11] As weak peristalsis is associated with ineffective bolus movement,[28,29] weak MRS contraction could predict postoperative dysphagia in patients undergoing antireflux surgery.[15,30] Thus, MRS is also expected to play a role in assessing esophageal peristaltic reserve in patients with IEM.

Although MRS has potential as an adjunctive test in assessment of esophageal motility, it has not been standardized. In the present study, subjects took 5 repetitive swallows of 2 mL normal saline within 10 seconds, injected into their mouths through a syringe while in the supine position. Among 53 subjects with IEM, only 1 could not follow the MRS protocol; however, most of the deglutitions occur in the sitting position, although weak peristalsis is associated with more reflux and delayed reflux clearance in the supine position.[21,31] Thus, the optimal subject posture in MRS according to the goal is the interesting topic to be established in the future.

In the present study, we applied 2 different criteria for abnormal MRS contraction to IEM subjects: DCI ratio between average 10 wet swallows and post-MRS contraction <1 and DCI of MRS contraction <450 mm Hg-s-cm. DCI ratio is associated with the occurrence of postoperative dysphagia in patients undergoing antireflux surgery.[15] Moreover, the authors reported that the optimal DCI ratio threshold of 0.85 had a sensitivity of 67% and a specificity of 64% in segregating patients with late postoperative dysphagia from those with no postoperative dysphagia; however, DCI ratio would not predict effective swallow, but could reflect the peristaltic reserve. Instead, we need to assess whether the swallow is effective when the peristaltic reserve is operative. DCI value <450 mm Hg-s-cm can be used to predict ineffective swallow.[8] Thus, we hypothesized that it would be reasonable to determine the criteria for abnormal MRS contraction as DCI of MRS contraction <450 mm Hg-s-cm. Subjects in the lower right quadrant may show ineffective swallow even though their DCI ratios exceed 1 (Figure 3). In these cases, high DCI does not indicate sufficient peristaltic reserve but just reflects the low average DCI of single swallows (Figure 2C). Conversely, those in the upper left quadrant may have effective swallow even though their DCI ratios are below 1. In addition, it would be technically easier to decide abnormal MRS contraction according to the DCI value than ratio. Indeed, in the present study, IEM patients with MRS contraction DCI <450 mm Hg-s-cm

(IEM-B) had increased risk of PBE, which could not be predicted by applying the DCI ratio (IEM-A) to define abnormal MRS. Furthermore, IEM-B (44.2%) segregated more subjects from those with IEM than IEM-A (34.6%). When applying DCI threshold of 0.85, only 1 subject was excluded from IEM-A, and the results did not change (data not shown).

Our HRIM results demonstrate that IEM is associated with ineffective bolus transit. Thus, diagnosing IEM on HRM could play a role in assessing patients with nonobstructive esophageal dysphagia. On the contrary, IEM patients irrespective of MRS results do not show significant differences in the presence of pathologic acid exposure, RE on endoscopy, and prevalence of GERD as compared with those with NEM. Thus, IEM cannot be a marker for the presence of GERD in a group of patients with esophageal symptoms, even when MRS is abnormal; however, IEM patients with abnormal MRS (MRS contraction DCI <450 mm Hg-s-cm) are likely to have PBE. Nonacid reflux also induces reflux symptoms.[32] In addition, defective activation of secondary peristalsis is shown in IEM patients with abnormal bolus transit.[33] Thus, MRS may be able to predict the presence of abnormal bolus exposure to esophagus contributed by esophageal hypomotility in patients with refractory GERD.

The present study had some limitations. Firstly, the control group consisted of subjects with esophageal symptoms; however, all control subjects were confirmed as having NEM on HRM. Moreover, MRS is usually performed as an adjunctive test to evaluate the esophageal motor function in symptomatic patients. Thus, our study population consisted of subjects with esophageal symptoms might be effective for determining optimal diagnostic criteria of MRS and assessing its clinical utility. Secondly, true clinical significance should be evaluated in the other population, preferably with outcome data. Finally, sample size was rather small to draw a concrete conclusion. Nevertheless, this is the first study recruiting IEM patients according to the CC v3.0, and the reasonable, simple definition of abnormal MRS contraction is suggested. In conclusion, IEM patients with weak MRS contraction <450 mm Hg-s-cm have an increased risk of prolonged bolus clearance, poor bolus transit, and PBE. Thus, IEM patients need to be assessed whether MRS contraction is <450 mm Hg-s-cm for segregating clinically relevant patients.

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