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Ineffective esophageal motility and bolus clearance. A study with combined high-resolution manometry and impedance in asymptomatic controls and patients

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Abstract

Background: The definition and relevance of ineffective esophageal motility (IEM) remains debated. Our aim was to determine motility patterns and symptoms associated with IEM defined as impaired bolus clearance.

Methods: To define altered bolus clearance, normal range of swallows with complete bolus transit (CBT) on high-resolution impedance manometry (HRIM) was determined in 44 asymptomatic controls. The results were then applied to a cohort of 81 patients with esophageal symptoms to determine the motility patterns which best predicted altered bolus clearance. Subsequently, in a cohort of 281 consecutive patients the identified motility patterns were compared with patients' customary symptoms.

Key Results: In asymptomatic controls, the normal range of swallows with CBT was 50%-100%. In patients, altered bolus transit (<50% CBT) was only associated with 30% or more failed contractions ($P < .001$). Neither weak peristalsis nor absence of contraction reserve (CR) was associated with altered bolus clearance. The patterns which best predicted altered bolus clearance were failed contractions ≥30% (specificity 88.2% and sensitivity of 84.6%), and ≥70% ineffective (failed + weak) contractions (sensitivity 84.6% and specificity 80.9%). No motility pattern was correlated to symptom scores.

Conclusions and Inferences: Based on bolus clearance assessed by HRIM, ≥30% failed contractions and ≥70% ineffective contractions have the best sensitivity and specificity to predict altered bolus clearance. Weak contractions and absence of CR are not relevant with respect to bolus clearance.

KEYWORDS

esophageal bolus clearance, esophageal motility, high-resolution esophageal manometry, high-resolution impedance manometry

1 | INTRODUCTION

The definition of ineffective esophageal motility (IEM) has evolved during the last decades and remains a matter of debate. Indeed, IEM as diagnosed by high-resolution manometry (HRM) is considered as a minor motility disorder as it can be observed in a significant proportion of healthy subjects[1] and is not clearly correlated to symptoms.[2-6]

In the current Chicago classification (version 3.0), IEM is defined as more than 50% ineffective contractions (ie, distal contractile integral [DCI] <450 mm Hg.cm.s), together with a normal relaxation of the esophagogastric junction (EGJ),[7] without any distinction between failed (DCI < 100 mm Hg.cm.s) and weak contractions (100 mm Hg.cm.s < DCI < 450 mm Hg.cm.s) as it was in the previous version of the classification.[8] Even though these changes have been made to simplify the definition, they do not consider the implications of these motility patterns in terms of bolus transit since, by contrast to weak contractions, failed contractions have been consistently shown to be associated with incomplete bolus transit (IBT).[9,10] Some authors recently proposed to consider "severe" IEM when 70% or more ineffective contractions were observed,[11] because this pattern is associated with abnormal esophageal acid burden.[12] Finally, the absence of a contraction reserve (CR) after multiple rapid swallows (MRS) has been associated with IBT,[3] more severe acid reflux[13] and occurrence of late post-fundoplication dysphagia[14] and therefore may be an additional criterium included in the definition of IEM.[11]

To our best knowledge, only one study with HRM proposed to phenotype IEM based on intraluminal impedance as the primary indicator of impaired bolus clearance.[10] However, this study did not determine normal values of altered bolus clearance and used a threshold of 20% obtained with conventional combined manometry and impedance.[15] The aim of the present study was to determine the motility patterns associated with altered bolus clearance. The normal range of bolus clearance was assessed in asymptomatic controls by the means of combined high-resolution impedance manometry (HRIM). Subsequently, the motility patterns which predict abnormal bolus clearance were determined in patients with esophageal symptoms. Finally, symptoms scores were compared in patients with and without esophageal motility abnormalities associated with altered bolus clearance.

Key Points

- The definition of ineffective esophageal motility (IEM) remains debated. Bolus clearance is an objective assessment of esophageal motility which can be used for the definition of IEM.
- Using combined high-resolution manometry and impedance in asymptomatic controls, the normal range of complete bolus clearance is 50%-100%.
- In patients, ≥30% failed contractions and ≥70% ineffective contractions have the best sensitivity and specificity to predict altered bolus clearance. These motility patterns should be part of the IEM definition. There was no correlation between motility patterns and symptoms.

2 | MATERIALS AND METHODS

2.1 | Participants

2.1.1 | Asymptomatic controls

Forty-four controls (22 women and 22 men; mean age 28.3 years, range 19-55 years) without esophageal symptoms were recruited from five different centers (Madrid/Spain, Veracruz/Mexico, Bogota/Colombia, Rio do Janeiro/Brazil, Santiago/Chile) between August 2012 and February 2014. Participants had no known disease, no history of previous surgery and were not on any medication that could affect esophageal motility.

2.1.2 | Patients

The tracings from 281 consecutive patients referred for high-resolution manometry from September 2018 to December 2019 to the Motility and Functional Gut Disorders Unit, University Hospital Germans Trias i Pujol (Badalona, Spain) (185 women and 96 men, mean age 57.8 years, range 19-93 years) were analyzed. Patients with previous history of esophageal and/or gastroduodenal surgery, EGJ outflow obstruction, achalasia distal esophageal spasm, and hypercontractile disorders according to Chicago Classification 3.0[7] were excluded. There were 84 patients with IEM and 197 with normal esophageal motility. Customary symptoms (dysphagia, chest pain, regurgitation, and heartburn) were registered in each participant using a 0 (never) to 5 (every meal) score scale. As part of the routine clinical workup, organic disease had been previously ruled out in all patients by endoscopic or radiologic examinations. Esophageal biopsies were only obtained when it was considered pertinent by the endoscopist. Table 1 describes the main demographic characteristics and symptoms of referral in the patient group. A subgroup of 81 consecutive (58 women and 23 men, mean age 61.5 years, range 19-93 years) had HRM combined with impedance.

The study protocol had been previously approved by the Institutional Review Board of the Germans Trias i Pujol University Hospital (PI-16-016), and all subjects gave written informed consent before participating in the study.

2.2 | High-resolution manometry protocol

High-resolution esophageal manometry was performed to all participants using a solid-state HRM assembly with 36 circumferential sensors spaced at 1-cm intervals (Manoscan 360°; Given Imaging,

Yoqneam, Israel). In the studies performed with simultaneous impedance and manometry, the HRIM catheter incorporated, in addition to the 36 solid-state circumferential pressure sensors, 19 metal rings spaced 2 cm apart to facilitate 18 impedance recordings (ManoScan ESO Z Catheter; Given Imagine, Duluth, GA, USA). On the day of the study, participants were intubated after a 6-hour fast. The manometric probe was introduced transnasally in a sitting participant and positioned to record from the hypopharynx to the stomach with at least three intragastric sensors. The catheter was fixed in place by taping it to the nose, and the participant was asked to lie down in supine position to start the recording. Once the standard HRM protocol (ten 5-mL water swallows at 30-seconds intervals) finished, subjects were asked to perform a MRS sequence consisting of at least four 2-mL water swallows performed in rapid succession, with ≤4-seconds interval between swallows.[14] At least two attempts were performed if the first one failed to show any CR. In the studies performed with HRIM, a 50% saline solution was used.

TABLE 1 Demographics and clinical characteristics of patients referred for high-resolution manometry

	n = 281 patients
Mean age (range)	57.8 y (19-93)
Gender (W/M)	185/96
Symptoms	
Dysphagia score, median (IQR)	3 (0-3)
Daily dysphagia (n)	67
Pain score, median (IQR)	0 (0-3)
Daily pain (n)	44
Regurgitation score, median (IQR)	2 (0-3)
Daily regurgitation	49
Heartburn score, median (IQR)	3 (0-4)
Daily heartburn	119

2.3 | Study design

This was a retrospective study to analyze motility patterns and clinical data prospectively collected in two cohorts of patients referred for esophageal manometry, compared with data obtained in asymptomatic controls.

2.4 | Data analysis

Manometric data were analyzed using the ManoView analysis software (ManoView 3.0; Given Imaging). All the tracings were analyzed by two investigators (FZ, JS) using the same procedure. The data obtained during the standard HRM protocol were analyzed following the parameters proposed by the Chicago consensus, and patients were diagnosed accordingly.[7] Briefly, each individual swallow was classified as failed if DCI was <100 mm Hg.s.cm, weak if DCI was between 100 and 450 mm Hg.s.cm. Weak contractions with breaks larger than 5 cm (with an isobaric contour 20 mm Hg) were also identified. Fragmented contractions were defined by a DCI >450 mm Hg.s.cm and breaks larger than 5 cm. The percentage of ineffective contractions in each individual subject was the sum of the percentage of failed and weak contractions. After MRS, the presence of a

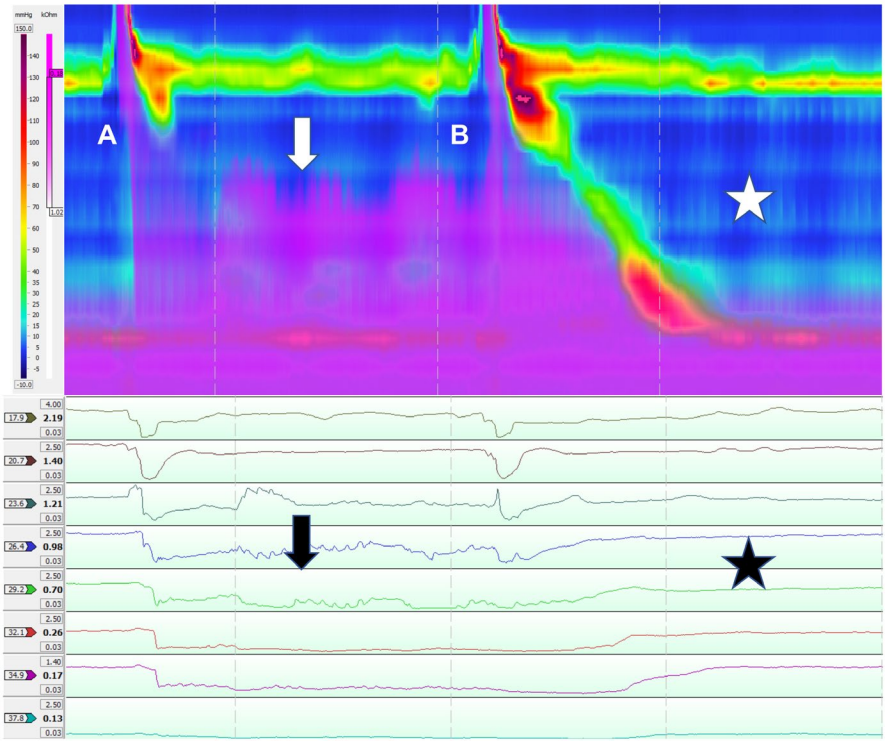

FIGURE 1 Example of combined high-resolution manometry and impedance in a patient referred for dysphagia. Upper panel shows the esophageal pressure topography and impedance data displayed as overlaid pink colorization. The lower panel shows corresponding impedance tracings. The first swallow (A) was failed and resulted in an incomplete bolus clearance as evidenced by the pink shading indicative of retained bolus (white arrow). Lower panel shows the corresponding impedance tracings without return to baseline values (black arrow). The second swallow (B) was normal and associated with complete bolus clearance as evidenced by disappearance of the pink color (white star) and an increase back to baseline of impedance values

TABLE 2 Esophageal motility patterns in controls and patients. Normal motility and ineffective contraction >50% refer to the Chicago classification 3.0[7]

	Normal motility	Ineffective contractions >50%	Ineffective contractions ≥70%	Failed contractions ≥30%
Controls (n = 44)	41 (93.2%)	3 (6.8%)	1 (2 0.3%)	3 (6.8%)
Patients (n = 281)	200 (71.2%)	81 (28.8%)	60 (21.4%)	65 (23.1%)

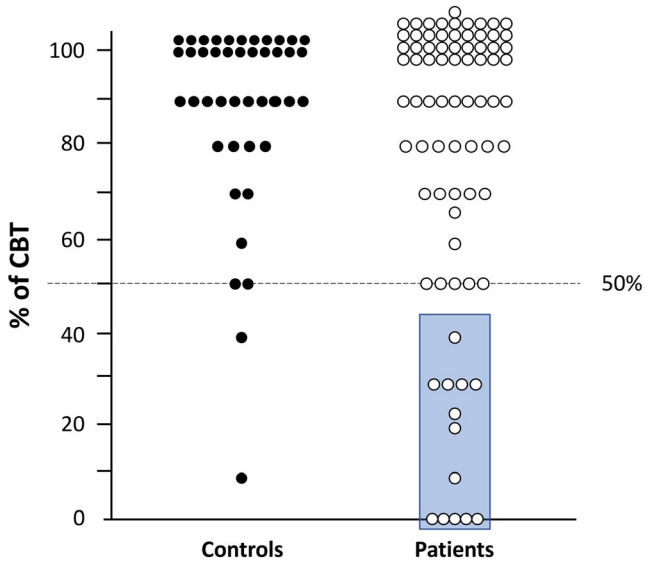

FIGURE 2 Percentage of swallows with complete bolus clearance in controls (n = 44) and patients (n = 81) on combined high-resolution manometry and impedance. According to 5-95 percentiles in healthy subjects, patients with less than 50% of swallows with complete bolus transit were considered to have impaired bolus transit

CR was defined by a DCI of the post MRS contraction superior to the mean DCI of single wet swallows.[14]

In studies with HRIM, bolus transit was assessed for each individual swallow using both colored contour function of the Manoview software and impedance tracings (Figure 1). To determine baseline impedance the color contrast was adjusted so that the contour showed an empty esophagus before the swallow. After color adjustment, bolus transit was considered complete if colorization was followed by color disappearance and incomplete if this was not the case. As the colored contour method has been shown to be well correlated to impedance tracings analysis,[10] tracings were reviewed only in doubtful cases to confirm IBT. Complete bolus transit (CBT) was defined as a >50% drop from baseline followed by an increase back to at least 50% from impedance nadir at two or more consecutive recording sites.[15]

2.5 | Statistical analysis

In patients, data were described as median (interquartile range). In controls, descriptive statistics (median, 5th, 95th centiles) were used to describe normality range for CBT and manometry findings. These data were then applied to patients in order to define the motility patterns associated with IBT, by using logistic regression. Receiver operating characteristic (ROC) curves were constructed for altered bolus clearance (as defined by normative values obtained in healthy subjects) based on rates of failed, weak and ineffective contractions, and CR.

Data between groups were compared using the chi-square test or the Fisher's exact test, as corresponded, for categorical data and the Mann-Whitney test for quantitative, non-parametric data. A *P* value <.05 was considered significant. The SPSS software (version 20) was used.

3 | RESULTS

3.1 | Esophageal motility and bolus clearance in asymptomatic controls

Most controls (93.2%) showed normal esophageal motility according to Chicago classification 3.0. Only 6.8% had IEM according to this definition (Table 2). For each subject, the median rates (5th-95th centiles) of failed, weak, and ineffective contractions were 0 (0-30), 0 (0-28.5) and 0 (0-58.5), respectively. Among a total of 438 swallows, 384 (87.7%) achieved CBT: 369/381 (96.9%) normal contractions, 0/24 (0.0%) failed, 15/30 (50%) weak (including 0/8 weak with large breaks), and 0/3 (0%) among fragmented. Regarding bolus clearance, the median rate of swallows with CBT was 95% with a normal range defined by 5th and 95th centiles of 50%-100% (Figure 2).

3.2 | Esophageal motility and bolus clearance in patients

Eighty-one patients were studied with HRIM. According the Chicago classification 3.0, there were 28 patients with IEM, and 53 with normal esophageal motility. In these patients, among a total of 807 swallows, 617 (76.5%) achieved CBT. Complete bolus clearance was achieved in 495/497 (99.6%) of normal contractions, 15/144 (10.4%) of failed contractions, 98/145 (67.6%) of weak contractions (including 8/27 (29.6%) weak contractions with large breaks), 9/10 (90%) of fragmented contractions, and 0/1 (0%) premature contractions.

According to the normal range (50%-100%) of swallows with CBT determined in normal subjects, 13/81 patients had less than 50% swallows with CBT and were considered to have significantly altered esophageal clearance. All patients with altered bolus clearance had IEM.

Contraction reserve was present in 46.5% of patients with altered bolus clearance, and 64.7% of patients with normal bolus clearance (NS).

3.2.1 | Motility patterns associated to altered bolus clearance

Multivariate analysis (logistic regression) showed that neither the rate of weak contractions nor the absence of CR was significantly associated with altered clearance. The only factor associated with altered esophageal clearance was the rate of failed contractions ($P < .001$).

A ROC analysis was performed to determine the motility patterns which best predict altered bolus clearance, that is, rate of CBT <50%. The ROC curves for altered bolus clearance are shown in Figure 3. The AUC for weak contractions was low (0.529). The highest AUC (0.887) was obtained for ineffective contractions (failed + weak). The cut-off value of 65% of ineffective contractions had a sensitivity of 84.6% and a specificity of 80.9%. The sensitivity and specificity of the threshold of 55% (corresponding to the Chicago 3.0 definition of IEM, in which the threshold is >50%) were 92.3% and 76.5%. The rate of failed contractions also demonstrated a high AUC (0.874) with a cut-off value of 25% having a sensitivity of 84.6% and a specificity of 88.2% (Table 3). Adding the absence of CR to ineffective motility resulted in a decreased AUC value (0.706) (curve not shown). It is of note that most patients (21/24, 87.5%) with ≥70% ineffective contractions had 10% or more failed contractions.

3.3 | Association between ineffective esophageal motility and customary symptoms

Table 4 shows symptoms scores at referral to manometry of the 281 patients with ≥30% failed (n = 65), ≥70% (n = 60) and >50% (n = 81) ineffective contractions. When total scores were considered, there was no significant difference between groups. Similar results were obtained when daily symptoms were considered (symptom score ≥4).

4 | DISCUSSION

Ineffective esophageal motility diagnosed by HRM is a heterogenous disorder which definition has evolved with time. In the current version of the Chicago classification, no distinction is made between failed and weak contraction to reach the threshold of more than 50% of ineffective contractions.[7] Recently, it has been proposed to consider severe IEM as defined by 70% or more ineffective contractions[11] as it has been shown to be associated with more severe gastro-esophageal reflux.[12] The aim of the present study was to determine motility patterns which best predict IEM, defined as impaired bolus clearance, using high-resolution esophageal motility combined with multichannel esophageal impedance recording, in a control group of healthy non-symptomatic subjects, and a cohort of consecutive patients referred for esophageal manometry.

In asymptomatic controls, the normal range of complete bolus clearance was equal or more to 50% of swallows. Different thresholds for normal bolus transit have been published so far. Tutuian et al have reported a value of 20% of incomplete bolus swallows, based on data obtained from combined conventional manometry (four pressure sensors) and impedance (four impedance channels), which may be less sensitive to detect IBT.[15] In a study with HRIM performed in 16 healthy subjects, Bulsiewicz et al considered abnormal bolus transit to be equal or more than 30%.[16] In the present study performed in 44 asymptomatic controls from different centers in Europe and Latin America, the normal range for complete bolus clearance was 50%-100%, as defined by 5th and 95th centiles (Figure 2). We therefore considered that having <50% of cleared bolus could reliably be considered as abnormal, and indicative of significantly altered esophageal motility.

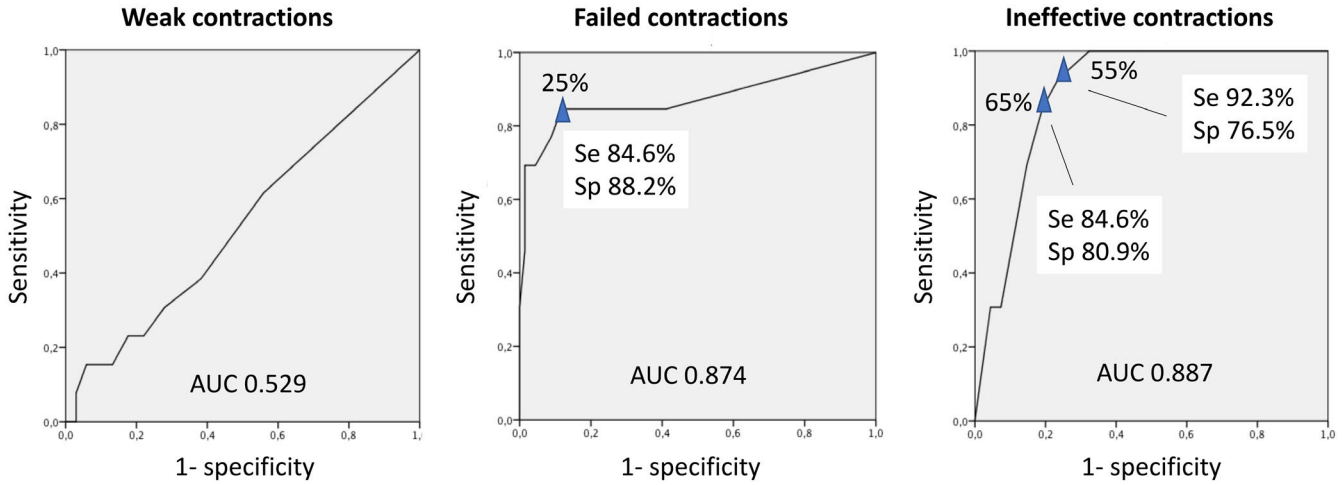

FIGURE 3 Receiver operating characteristic (ROC) curves showing altered bolus clearance in association with weak, failed, and ineffective swallows. AUC: area under the curve. Note that the best AUC was obtained for failed contractions, and the combination of failed and weak contractions (ineffective contractions)

Using this threshold, we have shown that 30% or more failed contractions and 70% or more ineffective contractions have the best sensitivity and specificity to predict altered bolus clearance. The current definition of IEM, that is, more than 50% of ineffective contractions, though very sensitive, was less specific.

As in most published studies, we found that most failed contractions were associated with IBT.[9,10,16] The presence of 30% or more failed contractions was the only pattern significantly associated with impaired bolus clearance. This threshold is relevant because it corresponds to the upper limit of normal observed in asymptomatic controls. Consequently, adding this criterium in the definition of IEM should be considered.

The presence of 70% or more ineffective contractions should also be considered in the definition, as recently suggested by a group of experts.[11] Indeed, in the present study, this pattern could predict impaired bolus clearance with a high sensitivity and a better specificity than the cut-off of more than 50% currently used in the Chicago classification.[7] It is of note that nearly 90% of the patients with 70% or more ineffective contractions had also at least 10% of failed contraction. Whether patients with 70% or more weak contractions without any failed contractions should be included is debatable, but our data clearly demonstrate that the impact of weak sequences in terms of bolus clearance is low, concordant with a recent study by Jain et al[10] Taken altogether, these results further confirm that only very poor esophageal contractility is associated with incomplete bolus clearance.

The absence of CR after MRS may also be taken into account in the definition of IEM because it has been shown to be a marker of severely impaired esophageal motility in systemic sclerosis.[17] A study by Min et al also reported an association between impaired bolus clearance and the absence of CR.[3] This was not confirmed in the present study showing that the absence of CR was not a good predictor of altered bolus clearance. This discrepancy may be related to a more stringent definition of impaired bolus transit in our study (<50% of swallows) as compared to the study of Min et al in which the threshold was 20%.[3] Considering how impaired bolus clearance was determined in the present study, the threshold of 50% is probably more specific. Our results may appear as counter intuitive because the presence of CR has been associated with less occurrence of severe post-fundoplication dysphagia; it may reflect some preserved esophageal contractility and therefore less postoperative symptoms. Moreover, an inaccurate evaluation of the CR cannot be ruled out because only two attempts of MRS were performed routinely, instead of three as previously suggested by Mauro et al[18]. However, these results need to be further confirmed, and the mechanisms of postoperative dysphagia may involve many other factors. Nevertheless, if CR may not be relevant in a definition of IEM focused on bolus clearance, we acknowledge that it may be useful as a complementary information if an anti-reflux procedure is considered.[14]

The clinical significance of IEM remains unclear because most studies failed to find any correlation with symptoms.[2-6,9,19] In the study by Jain et. al, failed peristalsis defined by a median DCI below 100 mm Hg.cm.s was associated with higher Eckardt scores.[10] As compared to symptom scores based on frequency of specific symptoms occurrence as we did in the present study, Eckardt score also takes into account weight loss, which may be an indirect marker of severity. If more severe symptoms may be encountered in patients with IEM, the observed associations remain weak and, to date, IEM, whatever its definition, remains a manometric diagnosis without demonstrated clinical significance regarding symptoms.

Our study has some limitations. Firstly, there was no systematic assessment of gastro-esophageal reflux either by pH or pH-impedance monitoring. However, if abnormal acid reflux has been consistently associated to IEM,[6,12,20] especially severe IEM,[12] our aim

TABLE 3 Sensitivity and specificity of esophageal motility abnormalities associated with altered bolus clearance as defined by a complete bolus clearance in less than 50% of swallows

	Sensitivity	Specificity
Failed contractions ≥30%	84.6%	88.2%
Ineffective contractions >50%	92.3%	76.5%
Ineffective contractions ≥70%	84.6%	80.9%

TABLE 4 Symptom scores (median IQR) and number of patients with daily symptoms according to motility patterns. No significant difference between groups

	Failed contractions			Ineffective contractions			Ineffective contractions		
	<30% (n = 216)	≥30% (n = 65)		≤50% (n = 200)	>50% (n = 81)		<70% (n = 221)	≥70% (n = 60)	
Dysphagia score	3 (0-3)	3 (0-4)	ns	3 (0-3)	3 (0-4)	ns	3 (0-3)	3 (0-4)	ns
Pain score	0 (0-3)	1 (0-3)	ns	0 (0-3)	1.5 (0-3)	ns	0 (0-3)	1 (0-3)	ns
Heartburn score	3 (0-4)	3 (1-4)	ns	3 (0-4)	3 (0-4)	ns	3 (0-4)	3 (0-4)	ns
Regurgitation score	2 (0-3)	1 (0-3)	ns	2 (0-3)	2 (0-3)	ns	2 (0-3)	2 (0-3)	ns
Daily dysphagia	49 (22.7%)	20 (30.8%)	ns	44 (21.9%)	24 (29.6%)	ns	52 (23.5%)	17 (28.3%)	ns
Daily pain	34 (15.7%)	15 (23.1%)	ns	30 (15.0%)	19 (23.4%)	ns	35 (15.8%)	14 (23.3%)	ns
Daily heartburn	89 (41.2%)	30 (46.2%)	ns	81 (40.5%)	38 (46.9%)	ns	91 (41.2%)	28 (46.7%)	ns
Daily regurgitation	40 (18.5%)	9 (13.8%)	ns	34 (17.0%)	15 (18.5%)	ns	38 (17.2%)	11 (18.3%)	ns

was to define IEM through its impact on bolus clearance. Secondly, among 81 patients in whom HRIM was performed, only 13 had impaired bolus clearance according to our definition. Nevertheless, ROC analysis provided good sensitivity and specificity values, and relevant thresholds for esophageal motility abnormalities. These numbers did not allow us to draw any conclusion about the role of fragmented contractions, which were very few (only 10 out of 807 swallow) and showed 90% of CBT. A huge number of patients would have been necessary to draw reliable conclusions for fragmented contractions. Finally, we did not evaluate bolus transit using other consistencies, like solid swallows. Nevertheless, standard protocol only uses liquid swallows. The use of provocative tests such as a rapid drink challenge[21] or a solid test meal[22] is probably more sensitive to unmask significant motility disorders (either hypercontractile or obstructive) and to correlate them with symptoms.

In conclusion, the definition of IEM should focus on its impact on esophageal bolus clearance. Studies with HRIM in asymptomatic controls provide the threshold of less than 50% swallows with cleared bolus to define impaired bolus clearance. In patients, 30% or more failed contractions and 70% or more ineffective contractions have the best sensitivity and specificity to predict altered bolus clearance. Although no association with customary symptoms could be demonstrated, adding these criteria in the definition of IEM should be considered in the future. By contrast, weak contractions and absence of CR are not relevant with respect to bolus clearance.

CONFLICT OF INTEREST

FZ: consultant/speaker for Takeda, Allergan, Biocodex, Vifor Pharma, Mayoli Spindler, Ipsen, Abbott, Reckitt Benckiser, Alfasigma. JS: acted as consulter/speaker or received research funding from ABbiotics, Allergan, Bayer, Cassen-Recordati, Norgine, Salvet, Reckitt Benkiser, and Zespri. IM, DC, LA, AH, AML, JRT, JPS, ARL: nothing to disclose.

AUTHOR CONTRIBUTIONS

IM, JS, and FZ were involved in acquisition of data, analysis, and interpretation of data, drafting of the manuscript, and statistical analysis; DC, LA, AH, AML, JRT, JPS, and ARL were involved in acquisition of data and critical revision of the manuscript for important intellectual content.

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